

QFTR-MYSORE



4814

Textbook of pedi







- 4814 ① infants ② children  
③ child development ⑪  
⑫ sick children  
⑬ prenatal disturbances  
⑭ nutritional disturbances  
⑮ infectious diseases  
⑯ child ~~tract~~ system  
⑰ digestive system  
⑱ respiratory system  
⑲ cardiovascular system

- ⑳ endocrine system  
㉑ metabolic disorders  
㉒ urine ㉓ neoplasms  
㉔ neoplastic like tissues  
㉕ skin  
㉖ bones ㉗ joints  
㉘ child disorders

TLM







# Textbook of PEDIATRICS

SEVENTH EDITION

EDITED BY

Waldo E. Nelson, M.D., D.Sc.

PROFESSOR OF PEDIATRICS, TEMPLE UNIVERSITY SCHOOL OF MEDICINE;  
MEDICAL DIRECTOR OF SAINT CHRISTOPHER'S HOSPITAL FOR CHILDREN

*With the Collaboration of*  
EIGHTY-ONE CONTRIBUTORS

W. B. SAUNDERS COMPANY

PHILADELPHIA

LONDON



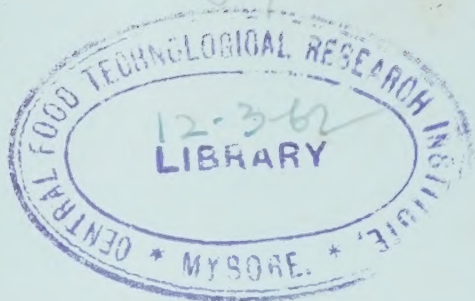
✓  
4814

L9C

59

L-9C54

N60



CFTRI-MYSORE



4814

Textbook of pedi.

Reprinted, October, 1959, and August, 1960

© 1959, by W. B. Saunders Company. Copyright, 1933, 1937, 1941, 1945, 1950, and 1954, by W. B. Saunders Company. Copyright under the International Copyright Union. All Rights Reserved. This book is protected by copyright. No part of it may be duplicated or reproduced in any manner without written permission from the publisher. Made in the United States of America. Press of W. B. Saunders Company. LIBRARY OF CONGRESS CATALOG CARD NUMBER: 59-5963

TO THE MEMBERS OF MY DEPARTMENT,  
PAST AND PRESENT,

    this book is inscribed  
        in recognition of  
their good spirit,  
their kindly tolerance,  
their catalytic capacities





# Contributors

## **S. T. ACHAR, M.D., F.R.C.P. (C)**

Professor of Pediatrics, Madras Medical College; Director, Institute of Pediatrics, General Hospital, Madras, India.

## **JOHN A. ANDERSON, M.D., Ph.D., F.A.A.P.**

Professor and Head of the Department of Pediatrics, University of Minnesota Medical School.

## **JAMES B. AREY, M.D., Ph.D.**

Professor of Pathology, Temple University School of Medicine; Pathologist, St. Christopher's Hospital for Children.

## **HARRY E. BACON, M.D., Sc.D., LL.D., F.A.C.S., F.R.S.M.**

Professor and Head of the Department of Proctology, Temple University Medical Center; Consultant in Proctology, Douglass, Shriners, St. Mary's, St. Christopher's, Frankford, Northeastern, National Stomach, Veterans, Mercy and Paul Kimball Hospitals.

## **HENRY W. BAIRD, III, M.D., F.A.A.P.**

Assistant Professor of Pediatrics, Temple University School of Medicine; Associate Pediatrician (Neurology), Temple University Hospital and St. Christopher's Hospital for Children.

## **WILLIAM P. BARBA, II, M.D.**

Associate in Pediatrics, Temple University School of Medicine; Chief of Pediatrics, Memorial Hospital; Physician, St. Christopher's Hospital for Children and Germantown Hospital and Dispensary.

## **JOHN B. BARTRAM, M.D., F.A.A.P.**

Associate Professor of Pediatrics, Temple University School of Medicine; Director of Services for Handicapped Children, and Senior Attending Pediatrician, St. Christopher's Hospital for Children.

## **PAUL C. BEAVER, Ph.D.**

Professor of Parasitology, Department of Tropical Medicine and Public Health, Tulane University School of Medicine; Visiting Scientist, Charity Hospital; Consultant in Parasitology, U.S. Public Health Service Hospital.

## **JOSEPH B. BILDERBACK, M.D., F.A.A.P.**

Clinical Professor of Pediatrics, University of Oregon Medical School; Attending Pediatrician,

Doernbecher Memorial Hospital for Sick Children.

## **RUSSELL J. BLATTNER, M.D., F.A.C.P., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, Baylor University College of Medicine; Pediatrician-in-Chief, Jefferson Davis Hospital; Physician-in-Chief, Texas Children's Hospital; Chief of Pediatrics, Hermann Hospital.

## **WILLIAM L. BRADFORD, M.D., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-Chief, Strong Memorial and Rochester Municipal Hospitals.

## **W. EMORY BURNETT, M.D., F.A.C.S.**

Professor and Head of the Department of Surgery, Temple University School of Medicine; Chief of Surgery, Temple University Hospital; Consultant, Philadelphia General and Veterans Hospitals.

## **PHILIP L. CALCAGNO, M.D., F.A.C.P., F.A.A.P.**

Assistant Professor of Pediatrics, University of Buffalo Medical School; Attending Pediatrician, Children's Hospital; Pediatrician-in-Chief, Our Lady of Victory Hospital.

## **CHARLES C. CHAPPLE, M.D., F.A.A.P.**

Associate Clinical Professor of Pediatrics, Howard University; Chief, Research-in-Aging Division, Research and Education, Veterans Administration, Washington, D.C.

## **AMOS CHRISTIE, M.D.**

Professor of Pediatrics, Vanderbilt University School of Medicine; Pediatrician-in-Chief, Vanderbilt University Hospital.

## **DAVID B. CLARK, M.D., Ph.D.**

Associate Professor of Neurological Medicine and Pediatrics, Johns Hopkins University School of Medicine; Attending Neurologist, Johns Hopkins Hospital, Harriet Lane Home, Rosewood State Training School; Assistant Attending Neurologist, Baltimore City Hospital.

## **CHARLES DAVENPORT COOK, M.D., F.A.A.P.**

Assistant Professor of Pediatrics, Harvard Medical School; Associate Physician, Children's Hospital.



**ROBERT E. COOKE, M.D.**

Professor of Pediatrics, Johns Hopkins University School of Medicine; Pediatrician-in-Chief, Johns Hopkins Hospital; Director, Harriet Lane Home for Invalid Children.

**EDWARD C. CURNEN, M.D., F.A.A.P.**

Professor of Pediatrics, University of North Carolina School of Medicine; Chief of Pediatric Service, North Carolina Memorial Hospital.

**LOUIS K. DIAMOND, M.D., F.A.A.P.**

Associate Professor of Pediatrics, Harvard Medical School; Associate Chief of Medical Service, and Hematologist, Children's Hospital.

**ANGELO M. DI GEORGE, M.D., M.S. (Ped.), F.A.A.P.**

Assistant Professor of Pediatrics, Temple University School of Medicine; Associate Attending Pediatrician and Endocrinologist, St. Christopher's Hospital for Children; Assistant Chief of Pediatrics, Philadelphia General Hospital, Blockley Division.

**KATHARINE DODD, M.D., F.A.A.P.**

Professor of Pediatrics, University of Louisville School of Medicine; Staff, Louisville General and Children's Hospitals.

**ERNEST CARROLL FAUST, Ph.D.**

Professor of Parasitology, Tulane University School of Medicine. On leave since April, 1958—Field Coordinator, Tulane-Colombia Program in Medical Education, Facultad de Medicina, Universidad del Valle, Cali, Colombia.

**HARRY A. FELDMAN, M.D.**

Professor and Chairman of the Department of Preventive Medicine, State University of New York, Upstate Medical Center at Syracuse; Attending Physician, University and City Hospitals; Consultant, Veterans Administration Hospital.

**BENJAMIN GREELEY FERRIS, Jr., M.D.**

Associate Professor of Environmental Health, Harvard School of Public Health; Consultant in Physiology, Children's Medical Center.

**F. CLARKE FRASER, M.D., C.M., Ph.D.**

Associate Professor of Genetics and Demonstrator in Pediatrics, McGill University; Director, Department of Medical Genetics, The Montreal Children's Hospital.

**JACOB BERNARD FRIEDMANN, M.D.**

Associate Professor of Anesthesia, Temple University School of Medicine; Attending Anesthesiologist, St. Christopher's Hospital for Children.

**LYTT I. GARDNER, M.D., F.A.A.P.**

Professor of Pediatrics, State University of New York, Upstate Medical Center at Syracuse; At-

tending Pediatrician, Syracuse Memorial Hospital.

**SYDNEY S. GELLIS, M.D.**

Professor and Chairman of the Department of Pediatrics, Boston University School of Medicine; Lecturer on Pediatrics, Harvard Medical School; Director of Pediatrics, Boston City Hospital; Consultant, Children's Medical Center.

**ELI GOLD, M.D.**

Assistant Professor of Pediatrics, Western Reserve University School of Medicine; Visiting Pediatrician, Cuyahoga County Hospital; Assistant Pediatrician, University Hospitals.

**GEORGE M. GUEST, M.D., F.A.A.P.**

Professor of Research Pediatrics, University of Cincinnati College of Medicine; Attending Pediatrician, Cincinnati Children's and General Hospitals.

**ARILD E. HANSEN, M.D., Ph.D., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, University of Texas, Medical Branch.

**JEROME S. HARRIS, M.D., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, and Associate Professor of Biochemistry, Duke University School of Medicine; Pediatrician, Duke Hospital.

**ROBERT H. HIGH, M.D., M.S. (Ped.), F.A.A.P.**

Associate Professor of Pediatrics, Temple University School of Medicine; Director, In-Patient Services, St. Christopher's Hospital for Children; Consultant in Pediatrics, U.S. Naval Hospital.

**PAUL H. HOLINGER, M.D., F.A.C.S., F.A.C.P.**

Professor of Bronchoesophagology, Department of Otolaryngology, University of Illinois College of Medicine; Senior Attending Bronchoesophagologist, St. Luke's Hospital; Attending Bronchoesophagologist, Children's Memorial and Research and Educational Hospitals.

**CHEVALIER L. JACKSON, M.D., F.A.C.S.**

Professor of Laryngology and Bronchoesophagology, Temple University School of Medicine.

**CHARLES A. JANEWAY, M.D., F.A.A.P.**

Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School; Physician-in-Chief, Children's Hospital.

**JOSEPH A. JOHNSTON, M.D., F.A.C.P., F.A.A.P.**

Pediatrician-in-Chief, Henry Ford Hospital, Detroit.

**SAMUEL KAPLAN, M.D.**

Assistant Professor of Pediatrics and Internal Medicine, University of Cincinnati College of Medicine; Cardiologist, Children's and General



Hospitals; Consultant, U.S. Air Force, Wright Patterson Air Force Base, and Cardio-respiratory Unit, Jewish Hospital.

**NORMAN KENDALL, M.D., M.S. (Ped.), F.A.A.P.**  
Assistant Professor of Pediatrics, Temple University School of Medicine; Attending Pediatrician, St. Christopher's Hospital for Children.

**E. GILLET KETCHUM, M.A.**  
Director, The Reeducation Clinic, The Institute of the Pennsylvania Hospital.

**ANN G. KUTTNER, M.D., Ph.D.**  
Associate Professor of Pediatrics, New York University-Bellevue Medical Center; Member of the Medical Board, Irvington House.

**DEAN M. LIERLE, M.D., M.S., Sc.D.**  
Professor and Chairman of the Department of Otolaryngology and Maxillofacial Surgery, State University of Iowa Medical School.

**SHERMAN LITTLE, M.D., F.A.A.P.**  
Professor of Pediatrics and of Psychiatry, University of Southern California School of Medicine; Director of Psychiatric Service, Children's Hospital Society.

**ROBERT A. LYON, M.D., F.A.A.P.**  
Professor of Pediatrics, University of Cincinnati College of Medicine; Assistant Medical Director, Children's Hospital; Attending Physician, Cincinnati General Hospital.

**JOHN S. McGAVIC, M.D., M.S. (Surgery)**  
Professor of Ophthalmology, Temple University School of Medicine; Professor of Clinical Ophthalmology, University of Pennsylvania Graduate School of Medicine; Attending Ophthalmologist, Temple University Medical Center and Bryn Mawr Hospital; Civilian Consultant, Valley Forge Army Hospital.

**ROBERT JAMES McKAY, JR., M.D., F.A.A.P.**  
Professor and Chairman of the Department of Pediatrics, University of Vermont College of Medicine; Chief of Pediatric Service, Mary Fletcher Hospital; Attending Pediatrician, De Goesbriand Memorial Hospital.

**IRVINE McQUARRIE, M.D., Ph.D., F.A.A.P.**  
Director of Research, The Bruce Lyon Memorial Research Laboratory of the Children's Hospital of the East Bay. Formerly Professor and Head of the Department of Pediatrics, University of Minnesota Medical School.

**MAURY MASSLER, D.D.S., M.S.**  
Professor and Head of the Department of Pedodontics, University of Illinois College of Dentistry; Dental Consultant, Research and Educational Hospitals.

**ROBERT W. MILLER, M.D., M.P.H.**  
Chief of Pediatrics, Atomic Bomb Casualty Commission, Hiroshima, Japan.

**JOHN ROYAL MOORE, M.D.**  
Professor of Orthopedic Surgery, Temple University School of Medicine.

**DAVID MYERS, M.D., F.A.C.S., F.I.C.S.**  
Professor and Head of the Department of Otorhinology, Temple University Medical Center; Attending Otorhinologist, St. Christopher's Hospital for Children.

**WALDO E. NELSON, M.D., Sc.D., F.A.A.P.**  
Professor and Head of the Department of Pediatrics, Temple University School of Medicine and Hospital; Medical Director, St. Christopher's Hospital for Children.

**ROBERT H. PARROTT, M.D., F.A.A.P.**  
Clinical Professor of Pediatrics, Georgetown and George Washington University Schools of Medicine; Physician-in-Chief and Director of Research Foundation, Children's Hospital.

**DANE G. PRUGH, M.D., F.A.A.P.**  
Associate Professor of Psychiatry and Pediatrics, University of Rochester School of Medicine and Dentistry; Senior Associate Psychiatrist and Pediatrician, and Head, Child Psychiatry Division, Department of Psychiatry, Strong Memorial Hospital.

**MILTON RAPOPORT, M.D.**  
Professor of Pediatrics, University of Pennsylvania School of Medicine and Graduate School of Medicine; Senior Pediatrician, Children's Hospital of Philadelphia.

**JULIUS B. RICHMOND, M.D., F.A.A.P.**  
Professor and Chairman of the Department of Pediatrics, State University of New York, Upstate Medical Center at Syracuse; Attending Pediatrician, Syracuse Memorial Hospital.

**FREDERICK C. ROBBINS, M.D., F.A.A.P.**  
Professor of Pediatrics, Western Reserve University School of Medicine; Director, Department of Pediatrics and Contagious Diseases, Cuyahoga County Hospital; Associate Pediatrician, University Hospitals.

**HOWARD W. ROBINSON, Ph.D.**  
Professor of Physiological Chemistry, Temple University School of Medicine.

**ALBERT H. ROWE, M.D., M.S., F.A.C.P.**  
Lecturer (Emeritus) in Medicine, University of California Medical School; Allergist, Samuel Merritt Hospital; Consulting Allergist, Oakland Naval Hospital.

**MITCHELL I. RUBIN, M.D., F.A.A.P.**

Professor and Head of the Department of Pediatrics, University of Buffalo School of Medicine; Pediatrician-in-Chief, Children's Hospital.

**ISAAC SCHOUR, D.D.S., Ph.D.**

Professor and Head of the Department of Histology, and Dean, University of Illinois College of Dentistry.

**T. F. McNAIR SCOTT, M.D., F.R.C.P.**

Research Professor of Pediatrics, University of Pennsylvania School of Medicine; Senior Physician and Director of Research, Children's Hospital of Philadelphia.

**MILTON J. E. SENN, M.D., F.A.A.P.**

Sterling Professor of Pediatrics and Psychiatry, and Chairman of the Department of Pediatrics, Yale University School of Medicine; Pediatrician-in-Chief, Grace-New Haven Community Hospital.

**THOMAS E. SHAFFER, M.D., F.A.A.P.**

Professor of Pediatrics and of Preventive Medicine, Ohio State University College of Medicine; Attending Pediatrician, Children's and University Hospitals.

**ROBERT E. SHANK, M.D.**

Danforth Professor of Preventive Medicine, Washington University School of Medicine; Associate Physician, Barnes Hospital.

**HARRY C. SHIRKEY, M.D., F.A.A.P.**

Assistant Clinical Professor of Pediatrics and Associate Professor of Pharmacology, University of Cincinnati College of Medicine; Assistant Director (Pediatric Division), Cincinnati General Hospital; Attending Staff, Cincinnati, Children's, General, Christ and Good Samaritan Hospitals.

**CHARLES E. SMITH, M.D., D.P.H.**

Dean, School of Public Health, University of California; Member, California State Board of Health.

**CLEMENT A. SMITH, M.D., Sc.D. (Hon.), F.A.A.P.**

Associate Professor of Pediatrics, Harvard Medical School; Physician, Children's and Infants Hospitals; Director of Research on the Newborn, Boston Lying-in Hospital.

**NATHAN J. SMITH, M.D.**

Alfred Dorance Daniels Professor of Diseases of Children and Chairman of the Department of Pediatrics, University of Wisconsin School of Medicine.

**EARLE H. SPAULDING, Ph.D.**

Professor and Head of the Department of Microbiology, Temple University School of Medicine; Bacteriologist, Temple University Hospital.

**ALEX J. STEIGMAN, M.D., Sc.D. (Hon.), F.A.A.P.**

Professor and Head of the Department of Pediatrics, University of Louisville Medical School; Pediatrician, Children's and Louisville General Hospitals.

**STUART SHELTON STEVENSON, M.D., M.P.H., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, Seton Hall College of Medicine and Dentistry. Formerly Research Professor of Pediatrics, University of Pittsburgh School of Medicine; Senior Pediatrician, Children's Hospital.

**JOSEPH STOKES, JR., M.D., Sc.D. (Hon.), F.A.A.P.**

William H. Bennet Professor of Pediatrics and Chairman of the Department of Pediatrics, University of Pennsylvania School of Medicine; Physician-in-Chief, Children's Hospital of Philadelphia.

**HAROLD S. STUART, M.D., F.A.A.P.**

Professor (Emeritus) of Maternal and Child Health, Harvard School of Public Health; Consultant to Child Health Division, Children's Medical Center.

**VICTOR C. VAUGHAN, III, M.D., F.A.A.P.**

Professor and Chairman of the Department of Pediatrics, Medical College of Georgia; Chief Pediatrician, Eugene Talmadge Memorial Hospital; Pediatric Consultant, University Hospital.

**ARTHUR JUDSON WALKER, M.D., C.M., D.T.M.**

Associate Professor of Tropical Medicine, Tulane University School of Medicine. On leave as Medical Parasitologist to Malaria Eradication, Pan American Sanitary Bureau, World Health Organization.

**JOSEF WARKANY, M.D.**

Professor of Research Pediatrics, University of Cincinnati School of Medicine; Attending Pediatrician, Children's and Cincinnati General Hospitals.

**RALPH J. P. WEDGWOOD, M.D.**

Assistant Professor of Pediatrics and Preventive Medicine, Western Reserve University School of Medicine; Associate Pediatrician, University Hospitals; Visiting Pediatrician, Cuyahoga County Hospital; Pediatrician-in-Charge, Rainbow Hospital for Crippled Children.

**ARMINE T. WILSON, M.D.**

Chief of Bacteriology, Alfred I. du Pont Institute, Wilmington, Delaware.

**CARROLL S. WRIGHT, M.D.**

Professor of Dermatology, Temple University School of Medicine; Professor of Clinical Dermatology, University of Pennsylvania Graduate School of Medicine; Dermatologist, Temple University, Abington, Shriners, Skin and

Cancer Hospitals and St. Christopher's Hospital for Children.

**HERMAN YANNET, M.D., F.A.A.P.**

Associate Clinical Professor of Pediatrics, Yale University School of Medicine; Attending Pediatrician, New Haven Hospital; Director, Southbury Training School; Consultant in Pediatrics, Waterbury Hospital.





# Preface to the Seventh Edition

THE PREPARATION of a textbook which proposes something approximating complete coverage of a major division of medicine is a humbling endeavor. As with the previous editions, it must suffice to say that contributors and editor have again done their best to serve the student and practitioner in their search for a better understanding of the medical problems of infants and children.

This edition, without shifting from the pattern of a text to that of a compendium, is somewhat shorter than its immediate predecessor. The accomplishment of this goal has not been without "blood, sweat and tears." The tolerance of the individual contributors in permitting some reconstruction of their literary effort can be appreciated only by those who have known the joys of literary conception. The toil of tightening and "containing" will be known only to those who have made the effort to avoid the need for the closing remark, "I regret my letter is so long, I had not the time to be brief."

Again, the major portion of credit is to the contributors, and the majority of criticism must be borne by the editor.

It is not possible to enumerate the extent of change in the various divisions. In certain ones, including Clinical Appraisal of Infants and Children, Parenteral Fluid Therapy, Drug Therapy, Anesthesia, Prenatal Factors in Diseases of Children, The Newborn Infant, Tuberculosis, Rickettsial Diseases, Mycotic Infections, The Respiratory Tract, The Nervous System, Convulsive Disorders, Cerebral Palsy and Orthopedic Pediatrics, there are completely new chapters by new contributors or new hands working with the authors of the preceding edition. In addition, there are several new sections, including Tropical Eosinophilia, Kala-azar, Cirrhosis of the Liver in Indian Children, Pulmonary Ventilation in Health and Disease, Mesenchymal Diseases, Behavior Problems Associated with Organic Brain Damage, and The Physician and the Child with a Handicap. Throughout the book there has been a "word-by-word" revision or reappraisal. We can only hope that the result will justify the labor.

No attempt has been made to provide a comprehensive bibliography. We have, however, attempted to include references to articles containing extensive bibliographies for as many subjects as possible.

Many persons other than the contributors have participated in this revision, and, although we cannot mention them all, we recognize our indebtedness to them. These include the many who have given constructive criticisms, who have lent encouragement and have confessed to usage of this book. Our colleagues at St. Christopher's Hospital for Children and in other departments of Temple Uni-

versity School of Medicine have without intention placed us deeply in their debt. Specifically we acknowledge the help and guidance of Drs. Carroll F. Burgoon, Samuel L. Cresson, George E. Farrar, Daniel S. Fleisher, Joseph M. Garfunkel, Nancy Huang, John A. Kirkpatrick, John W. Lachman, Arthur E. McElfresh, Richard W. Olmsted, George P. Pilling, IV, Helen Reardon, Howard H. Steel and Robert E. Wells. Of those outside our medical school group, we must mention the help of Drs. Carroll F. Palmer and Phyllis Q. Edwards in the section on Tuberculosis. Dr. Richmond, likewise, acknowledges the assistance of Dr. Edward Lis.

Editorially, this book continues in the truest sense to be a family project. No person has participated to the extent Mrs. Nelson has. Her hand is evident on every page. Without her keen perceptiveness and deep devotion to detail this book would not exist in its present form. In the strictest sense she is co-editor.

Jane (Mrs. Edward F. Beatty, Jr.), now our "literary secretary," is constantly searching for increasing accuracy and adequacy of expression. Ann (Mrs. Richard E. Behrman) has found time in the midst of her own pediatric activities to continue to participate, and Bill, although "Uncle Sam" has temporary control of him, has not reneged when on leave.

To the members of the Saunders Company who have shared in the construction of this book, we acknowledge the pleasure of working with them and the stimulus they provide in their capacity to see a new edition as a new offspring and not just as a new dress for an existing one.

To the reader whose faith deserves more, we only wish we might have measured up in every detail; we can only acknowledge in real humility the support and confidence as expressed not only by use of previous editions, but also by expressions in word.

WALDO E. NELSON



# Contents

<b>THE FIELD OF PEDIATRICS</b>		
AN INTRODUCTION TO THE MEDICAL PROBLEMS OF INFANTS AND CHILDREN .....	1	
<i>Waldo E. Nelson</i>		
Problems of Various Age Periods ....	4	
The Pediatrician and His Patient ...	10	
<b>GENERAL FACTORS IN THE CARE AND EVALUATION OF CHILDREN</b>		
PHYSICAL GROWTH AND DEVELOPMENT .....	12	
<i>Harold C. Stuart and Stuart S. Stevenson</i>		
Growth of the Body as a Whole ....	13	
Osseous (Skeletal) Development ...	20	
Age Periods of Life before Maturity .	27	
Evaluation of Physical Status; Progress of Growth and Development .....	42	
TABLES OF NORMS FOR USE AS REFERENCE STANDARDS IN THE EVALUATION OF BODY MEASUREMENTS ....	47	
Techniques for Taking Measurements .....	48	
MENTAL AND EMOTIONAL DEVELOPMENT .....	62	
<i>Milton J. E. Senn</i>		
Heredity and Environment .....	62	
Reflex Actions and Learning .....	63	
Sensory Development .....	64	
Speech .....	65	
Emotional Development .....	65	
Intellectual Growth .....	66	
Mental Hygiene .....	67	
Play .....	71	
Sex Education .....	71	
PSYCHOLOGIC DISORDERS .....	73	
General Considerations .....	73	
NEUROTIC TRAITS .....	75	
"Nervousness" .....	75	
Thumb-Sucking .....	77	
Nail-Biting .....	77	
Teeth-Grinding .....	77	
Picking, Pulling, and Rubbing Habits .....	78	
Rhythmic Movements .....	78	
Breath-Holding .....	79	
Masturbation .....	80	
Compulsions .....	81	
Anxiety and Fear .....	82	
Hysteria .....	82	
Tics .....	83	
SCHOOL DIFFICULTIES .....	84	
CONDUCT DISORDERS .....	87	
PSYCHOSOMATIC ILLNESS .....	87	
Headache .....	88	
Eating Disorders .....	89	
Disorders of Sleep .....		
DISORDERS IN LANGUAGE FUNCTION ...	91	
<i>E. Gillet Ketchum</i>		
Speech Disorders .....	91	
Auditory Disorders .....	93	
Stuttering .....	93	
Reading Disorders .....	95	
NUTRITIONAL REQUIREMENTS .....	97	
<i>Arild E. Hansen</i>		
Water .....	97	
Calories .....	98	
Proteins .....	101	
Carbohydrates .....	101	
Fats .....	102	
Minerals .....	102	
Vitamins .....	107	
Miscellaneous Factors .....	111	
FEEDING OF INFANTS .....	112	
<i>John B. Bartram</i>		
Breast Feeding .....	113	
Artificial Feeding .....	119	
Other Foods .....	128	
First-Year Feeding Pattern and Problems .....	129	
Feeding during the Second Year of Life .....	132	
Feeding of Older Children .....	132	
HYGIENE .....	135	
PREVENTIVE PEDIATRICS .....	138	
<i>Thomas E. Shaffer</i>		
Primary Prevention of Disease ....	138	
Secondary Prevention of Disease ....	144	
Detection of Disease, and Health Education .....	145	
ADOLESCENCE .....	147	
PHYSICAL ASPECTS OF ADOLESCENCE ...	147	
<i>Joseph A. Johnston</i>		
PSYCHOLOGIC ASPECTS OF ADOLESCENCE .....	156	
<i>Milton J. E. Senn</i>		
<b>GENERAL FACTORS IN THE CARE OF SICK CHILDREN</b>		
CLINICAL APPRAISAL OF INFANTS AND CHILDREN .....	161	
<i>Dane G. Prugh</i>		
History .....	162	
Physical Examination of the Child ..	167	
Laboratory Diagnostic Studies ....	170	
Implementation of Results of the Clinical Examination .....	171	

<b>DISTURBANCES OF FLUID AND ELECTRO- LYTE EQUILIBRIUM</b> .....	172	<b>Inherited Disorders Involving Trypto- phane</b> .....	265
<i>George M. Guest</i> .....		<b>Disorders Involving Leucine, Isoleu- cine and Valine (Branched- Chain Amino Acids)</b> .....	267
Physiologic Considerations .....	172	<b>INBORN ERRORS IN CARBOHYDRATE ME- TABOLISM</b> .....	268
Clinical Disturbances .....	175	Defective Mucopolysaccharide Metabo- lism .....	268
<b>SHOCK</b> .....	181	Hurler's Syndrome .....	268
<b>PARENTERAL FLUID THERAPY</b> .....	183	Defective Glycogen Metabolism .....	268
<i>Robert E. Cooke</i> .....		Glycogen Disease .....	268
Deficit Therapy .....	183	Defective Disaccharide Metabolism ...	273
Maintenance Therapy .....	192	Sucrosuria .....	273
Abnormal Losses of Water and Elec- trolytes .....	195	Defective Hexose Metabolism .....	273
Supplemental Therapy .....	196	Essential Fructosuria .....	273
Parenteral Solutions .....	198	Hereditary Fructose Intolerance with Hypoglycemia .....	274
<b>ADMINISTRATION OF PARENTERAL FLUIDS</b> .....	198	Galactosemia .....	274
<i>Victor C. Vaughan, III</i> .....		Defective Pentose Metabolism .....	276
<b>TECHNICAL PROCEDURES</b> .....	203	Essential Pentosuria .....	277
<b>DRUG THERAPY</b> .....	205	<b>INBORN ERRORS OF LIPID METABOLISM</b> ..	278
<i>Harry C. Shirkey and</i> .....		Idiopathic Hyperlipemia .....	278
<i>William P. Barba, II</i> .....		<b>INBORN ERRORS OF PIGMENT METABO- LISM</b> .....	279
General Considerations .....	205	The Porphyrrias .....	279
Specific Considerations .....	205	Hereditary Defects Involving Biliru- bin .....	281
Table of Drugs and Doses .....	210	Hereditary Methemoglobinemias ...	281
<b>ANESTHESIA FOR CHILDREN</b> .....	227	Congenital Sulfhemoglobinemia ....	283
<i>Jacob Friedmann</i> .....			
<b>CONVALESCENT CARE</b> .....	231		
<i>Waldo E. Nelson</i> .....			
<b>PRENATAL DISTURBANCES</b>		<b>THE NEWBORN INFANT</b>	
<b>PRENATAL FACTORS IN DISEASES OF CHILDREN</b> .....	234	<b>PHYSIOLOGY OF THE NEWBORN INFANT</b> .....	286
<i>Josef Warkany and</i> .....		<i>Clement A. Smith and</i> .....	
<i>F. Clarke Fraser</i> .....		<i>R. J. McKay, Jr.</i> .....	
Genetic and Environmental Factors .	234	<b>THE HISTORY IN NEONATAL PEDIATRICS</b> .....	293
<b>CONGENITAL MALFORMATIONS</b> .....	243	<i>R. J. McKay, Jr., and</i> .....	
<b>ADVISABILITY OF PARENTHOOD</b> .....	247	<i>Clement A. Smith</i> .....	
<b>INBORN ERRORS OF METABOLISM</b> .....	250	<b>THE PHYSICAL EXAMINATION IN NEO- NATAL PEDIATRICS</b> .....	295
<i>Milton Rapoport</i> .....		<b>CARE OF THE NEWBORN INFANT</b> .....	301
<b>INBORN ERRORS IN PROTEIN METABOLISM</b> .....	253	<b>MULTIPLE PREGNANCIES</b> .....	304
Defective Synthesis of Plasma Proteins .	253	<b>PERINATAL MORTALITY</b> .....	306
Familial Idiopathic Dysproteinemia .	253	<b>PREMATURITY</b> .....	306
Idiopathic Hypoproteinemia .....	253	<b>POSTMATURITY AND PLACENTAL DYS- FUNCTION</b> .....	313
Congenital Defects in the Synthesis of Plasma Proteins Accompanied by Hemorrhagic Diathesis ....	253	Postmaturity .....	313
Agammaglobulinemia .....	255	Placental Dysfunction Syndrome ...	313
Beta-2-Globulin Deficiency Associated with Immunologic Paralysis ...	256	<b>DISEASES OF THE NEWBORN INFANT:</b>	
Haptoglobin Deficiency .....	256	<b>FULL TERM AND PREMATURE</b> ....	314
Hereditary Ceruloplasmin Deficiency	257	<b>CONGENITAL ANOMALIES</b> .....	314
Analbuminemia .....	257	<b>CLINICAL MANIFESTATIONS OF DISEASE DURING THE NEWBORN PERIOD</b> ....	314
Defective Hemoglobin Synthesis .....	257	<b>DISTURBANCES RELATED TO INTRAUTER- INE CONDITIONS OR TO DELIVERY</b> ..	315
Abnormal Hemoglobins .....	257	Birth Injury .....	315
Defective Amino Acid Metabolism ....	258	Anoxia .....	321
Errors in Phenylalanine and Tyrosine Metabolism .....	258	Respiratory Distress and Failure ...	322
Hereditary Clinical Syndromes of Tubular Insufficiency .....	261	Central Nervous System Failure ....	323
Molecular Diseases Involving Cystine and Glutathione .....	262	<b>DISTURBANCES OF ORGAN SYSTEMS</b> ....	323
		Disturbances of the Respiratory Tract .	323
		Atelectasis .....	324
		Congestive Pulmonary Failure .....	324
		Hyaline Membrane Disease .....	324
		Pneumonia .....	326

# CONTENTS

XV

Pneumothorax and Pneumomediastinum .....	328
Lobar Emphysema .....	329
Lung Cysts .....	329
Disturbances of the Digestive System ..	330
Vomiting .....	330
Thrush .....	330
Constipation .....	330
Meconium Plugs .....	331
Meconium Bodies .....	331
Meconium Ileus .....	331
Meconium Peritonitis .....	332
Jaundice in the Newborn Infant ...	332
Disturbances of the Blood .....	335
Anemia in the Newborn Infant ....	335
Hemorrhage in the Newborn Infant	336
Disturbances of the Genitourinary System .....	337
Bilateral Renal Agenesis .....	337
Urinary Tract Infections .....	338
Disturbances of the Cranium .....	338
Craniotabes .....	338
Disturbances of the Skin .....	338
Localized Skin Defects .....	338
Erythema Toxicum .....	338
Milia .....	339
Impetigo Neonatorum .....	339
Pemphigus Neonatorum .....	339
Paronychia .....	339
Mastitis Neonatorum .....	340
Disturbances of the Eye .....	340
The Umbilicus .....	340
Anomalies .....	340
Tumors .....	341
Hemorrhage .....	341
Granuloma of the Umbilicus .....	341
Infections of the Umbilicus .....	341
Umbilical Hernia .....	341
METABOLIC DISTURBANCES .....	342
Transitory Fever of the Newborn ...	342
Edema .....	342
Tetany .....	342
DISTURBANCES OF THE ENDOCRINE SYSTEM .....	343
INFECTIONS OF THE NEWBORN .....	344
Escherichia Coli Infections .....	344
Staphylococcal Infections .....	344
Diarrhea in the Newborn .....	346
Neonatal Infection Due to Listeria Monocytogenes .....	347
Coxsackie Virus Infection in the Newborn .....	348
Herpes Simplex of the Newborn Infant .....	348

## UNEXPECTED SUDDEN DEATH

UNEXPECTED SUDDEN DEATH .....	350
<i>Sydney S. Gellis</i>	

## NUTRITIONAL DISTURBANCES

Malnutrition .....	352
<i>Waldo E. Nelson</i>	
Obesity .....	354
Nutritional Edema .....	356

Kwashiorkor .....	357
Vitamin A Deficiency .....	360
<i>Josef Warkany</i>	
Vitamin B Complex Deficiency ....	363
Scurvy .....	368
Rickets of Vitamin D Deficiency ....	371
Tetany of Vitamin D Deficiency ....	378
<i>Waldo E. Nelson</i>	
Vitamin K Deficiency .....	379
<i>Sydney S. Gellis</i>	

## INFECTIOUS DISEASES

INFECTION, IMMUNITY AND ALLERGY IN RELATION TO PEDIATRICS .....	381
<i>Charles A. Janeway</i>	
Pediatric Immunology .....	382
CLINICAL USE OF THE MICROBIOLOGY LABORATORY .....	384
<i>T. F. McNair Scott and Earle H. Spaulding</i>	
SELECTION OF ANTIMICROBIAL AGENTS BY LABORATORY MEANS .....	395
<i>Earle H. Spaulding</i>	
ISOLATION MEASURES FOR INFECTIOUS DISEASES .....	397
<i>Waldo E. Nelson</i>	
BACTERIAL INFECTIONS .....	401
STREPTOCOCCAL INFECTIONS .....	401
General Considerations .....	401
<i>Armine T. Wilson</i>	
Scarlet Fever .....	404
<i>William L. Bradford</i>	
Erysipelas .....	410
Diphtheria .....	411
Pertussis .....	420
Parapertussis .....	424
Meningitis .....	424
Tetanus .....	432
Bacillary Dysentery .....	434
Typhoid Fever .....	437
Salmonella Infections .....	442
Brucellosis .....	445
Tularemia .....	447
Tuberculosis .....	449
<i>Robert H. High and Waldo E. Nelson</i>	
Intrathoracic Tuberculosis .....	453
Extrathoracic Tuberculosis .....	466

SPIROCHETAL INFECTIONS .....	472
Syphilis .....	472
<i>Katharine Dodd</i>	
Leptospirosis .....	480
Infections Transmitted by Rat Bites .	481



<b>VIRAL INFECTIONS AND THOSE PRESUMED TO BE CAUSED BY VIRUSES</b> . . . . .	483	<b>MYCOTIC INFECTIONS</b> . . . . .	562
Measles . . . . .	483	Actinomycosis . . . . .	562
<i>Joseph Stokes, Jr.</i> . . . . .		<i>Jerome S. Harris</i> . . . . .	
German Measles . . . . .	487	North American Blastomycosis . . . . .	562
Exanthem Subitum . . . . .	489	Cryptococcosis . . . . .	564
Herpes Simplex . . . . .	490	Mucormycosis . . . . .	565
<i>T. F. McNair Scott</i> . . . . .		Nocardiosis . . . . .	565
Varicella and Herpes Zoster . . . . .	494	Sporotrichosis . . . . .	566
Smallpox . . . . .	499	Histoplasmosis . . . . .	567
Vaccination against Smallpox . . . . .	501	<i>Amos Christie</i> . . . . .	
Mumps . . . . .	505	Coccidioidomycosis . . . . .	571
<i>Joseph Stokes, Jr.</i> . . . . .		<i>Charles E. Smith</i> . . . . .	
Epidemic Influenza . . . . .	508	<b>PARASITIC DISEASES</b> . . . . .	574
Rabies . . . . .	512	<b>HELMINTHIC AND ARTHROPOD DISEASES</b> . . . . .	574
Yellow Fever . . . . .	515	<i>Ernest Carroll Faust</i> . . . . .	
Lymphogranuloma Venereum . . . . .	518	Infections Produced by Roundworms	
<i>Sydney S. Gellis</i> . . . . .		(Nematoda) . . . . .	575
Infectious Mononucleosis . . . . .	518	Ascariasis . . . . .	575
Acute Infectious Lymphocytosis . . . . .	520	Toxocariasis and Visceral Larva Mi-	
<i>Waldo E. Nelson</i> . . . . .		grans . . . . .	578
Cat-Scratch Fever . . . . .	522	Oxyuriasis . . . . .	579
<i>Russell J. Blattner</i> . . . . .		Trichocephaliasis . . . . .	581
Cytomegalic Inclusion Disease . . . . .	524	Hookworm Infection . . . . .	582
<i>James B. Arey</i> . . . . .		Strongyloidiasis . . . . .	585
Infectious Neuritis . . . . .	525	Trichinosis . . . . .	587
<i>Sydney S. Gellis</i> . . . . .		Filariasis . . . . .	588
<b>INFECTIONS BY ENTERIC VIRUSES (ENTEROVIRUSES)</b> . . . . .	526	Dracunculosis . . . . .	589
Coxsackie Virus Infections . . . . .	526	Infections Produced by Tapeworms (Ces-	
<i>Edward C. Curnen</i> . . . . .		toidea) . . . . .	589
ECHO Virus Infections . . . . .	529	Teniasis . . . . .	589
Poliomyelitis . . . . .	531	Hymenolepiasis . . . . .	591
<i>Alex J. Steigman</i> . . . . .		Diphyllobothriasis . . . . .	591
<b>ACUTE ASEPTIC MENINGITIS SYNDROME</b> . . . . .	545	Hydatid Disease . . . . .	592
<i>Alex J. Steigman and</i> . . . . .		Infections Produced by Flukes (Trema-	
<i>T. F. McNair Scott</i> . . . . .		todes) . . . . .	593
<b>ENCEPHALITIS</b> . . . . .	547	Schistosomiasis . . . . .	593
<i>T. F. McNair Scott</i> . . . . .		Intestinal Fluke Infections . . . . .	596
<b>SUBACUTE SCLEROSING LEUKOENCEPHALITIS</b> . . . . .	552	Liver Fluke Infections . . . . .	596
<i>James B. Arey</i> . . . . .		Lung Fluke Infection . . . . .	597
<b>RICKETTSIAL DISEASES</b> . . . . .	553	Arthropods as Causative Agents and	
<i>Eli Gold and</i> . . . . .		Transmitters of Disease . . . . .	598
<i>Frederick C. Robbins</i> . . . . .		Venening Arthropods . . . . .	598
Typhus Fever . . . . .	555	Tissue-Invading Arthropods . . . . .	599
Murine Typhus . . . . .	556	Arthropods as Transmitting Agents of	
Brill's Disease . . . . .	557	Disease . . . . .	600
Scrub Typhus . . . . .	557	Tropical Eosinophilia . . . . .	602
Rocky Mountain Spotted Fever . . . . .	558	<i>Paul C. Beaver</i> . . . . .	
Fièvre Boutonneuse . . . . .	559	<b>PROTOZOAN DISEASES</b> . . . . .	604
Rickettsialpox . . . . .	559	Malaria . . . . .	604
Q Fever . . . . .	560	<i>A. J. Walker</i> . . . . .	
		Kala-azar in Children . . . . .	608
		<i>S. T. Achar</i> . . . . .	
		<b>INTESTINAL PROTOZOA</b> . . . . .	610
		Amebiasis . . . . .	610
		<i>Paul C. Beaver</i> . . . . .	
		Giardiasis . . . . .	613
		Balantidiasis . . . . .	614
		Toxoplasmosis . . . . .	615
		<i>Harry A. Feldman</i> . . . . .	

# THE DIGESTIVE TRACT

THE ORAL CAVITY .....	619
<i>Julius B. Richmond, Maury Mas-</i>	
<i>sler and Isaac Schour</i>	
DISTURBANCES OF THE TEETH .....	620
Disturbances in Growth .....	620
Disturbances in Calcification .....	622
The Teeth in Dietary Deficiencies ..	622
Disturbances in the Eruption of Teeth	623
Disturbances in Attrition of Teeth ..	625
Dental Caries .....	625
Periapical Infection .....	626
DISTURBANCES OF THE FACE AND JAWS ..	627
Malocclusions of the Teeth .....	627
Facial Asymmetry .....	628
Fractured Incisors .....	628
Cleft Lip and Cleft Palate .....	628
Palatopharyngeal Incompetence ....	630
Hypoplasia of the Mandible .....	631
DISEASES OF THE GUMS AND GINGIVAE ..	632
Lateral Abscess .....	632
DISEASES OF THE ORAL MUCOSA .....	633
Herpetic Stomatitis .....	633
Other Aphthous Lesions .....	633
Thrush .....	633
Noma .....	634
DISTURBANCES OF THE LIPS .....	634
Fissures .....	634
Herpes Simplex .....	635
Allergic Eruptions .....	635
Mucous Retention Cyst .....	635
THE TONGUE .....	635
Fissured Tongue .....	635
Black Hairy Tongue .....	635
Geographic Tongue .....	635
Tonguetie .....	636
Macroglossia .....	636
The Tongue in Systemic Disturbances	636
Trauma .....	637
SALIVARY GLANDS .....	637
Enlargements of the Salivary Glands	637
Suppurative Parotitis .....	637
Recurrent Parotitis .....	638
Ranula .....	638
Mikulicz's Disease .....	638
TUMORS OF THE NECK .....	639
<i>Julius B. Richmond</i>	
Thyroglossal Duct Cyst .....	639
Branchial Cleft Cyst .....	639
THE ESOPHAGUS .....	639
<i>Paul H. Holinger</i>	
Congenital Anomalies .....	640
Acquired Diseases .....	643
Foreign Bodies in the Esophagus ...	645
THE GASTROINTESTINAL TRACT .....	647
DIGESTIVE DISTURBANCES .....	647
Anorexia .....	647
<i>Waldo E. Nelson</i>	
Vomiting .....	647
Normal and Abnormal Stools .....	650
Constipation .....	652
Encopresis .....	654
Diarrheal Disorders .....	655

THE STOMACH AND INTESTINES .....	658
DISORDERS OF THE STOMACH .....	658
Malformations and Malpositions of	
the Stomach .....	658
Inflammation of the Gastric Mucosa .	662
Gastric Dilatation .....	662
Gastric Hemorrhage .....	663
Neoplasms of the Stomach .....	663
Foreign Bodies in the Stomach and In-	
testines .....	663
Gastric Perforation .....	663
Bezoars .....	664
INTESTINAL DISORDERS .....	664
Malformations and Malpositions of	
the Intestines .....	664
Intestinal Obstruction .....	665
Diverticulosis and Diverticulitis ....	669
Peptic Ulcer .....	671
Regional Enteritis .....	671
Pneumatosis Intestinalis .....	672
Megacolon .....	673
<i>Norman Kendall</i>	
Appendicitis .....	676
<i>W. Emory Burnett</i>	
Mesenteric Lymphadenitis .....	678
<i>Waldo E. Nelson</i>	
Chronic Colitis .....	679
ANUS, RECTUM AND SIGMOID .....	680
<i>Harry E. Bacon</i>	
Malformations of the Anus .....	680
Malformations of the Rectum .....	681
Fissure in Ano .....	682
Pruritus Ani .....	683
Prolapse and Procidentia of the Rec-	
tum and Sigmoid .....	683
Anorectal Abscesses .....	683
Fistula .....	684
Hemorrhoids .....	684
Neoplasms .....	684
Congenital Dimples, Sinuses, Cysts	
and Tumors of the Sacrococcy-	
geal Region .....	685
PERITONEUM AND ALLIED STRUCTURES	686
Malformations of the Peritoneum ...	686
<i>Waldo E. Nelson</i>	
Ascites .....	686
Peritonitis .....	686
<i>W. Emory Burnett</i>	
Tumors of the Peritoneum and Mes-	
entery .....	689
<i>Waldo E. Nelson</i>	
Hernias and Hydrocele .....	690
THE LIVER .....	693
<i>Milton Rapoport</i>	
TESTS OF LIVER DISTURBANCES AND	
FUNCTION .....	697
Tests not Measuring Derangement of	
Liver Function .....	697
Tests Measuring Functional Capacity	697
Biopsy of the Liver .....	700

HEPATIC DISORDERS .....	700	Retropharyngeal Abscess .....	753
Circulatory Disturbances .....	700	Peritonsillar and Retrotonsillar Abscesses .....	754
Jaundice .....	700	Sinusitis .....	754
Infections .....	704	General Considerations of Chronic Infections of the Upper Respiratory Tract .....	756
Indian Childhood Cirrhosis .....	711	Chronic Rhinitis .....	756
<i>S. T. Achar</i> .....		Chronic Pharyngitis .....	757
Cysts of the Liver .....	712	Tonsils and Adenoids .....	757
<i>Milton Rapoport</i> .....		THE EAR .....	762
Poisoning .....	712	<i>David Myers</i> .....	
Fatty Infiltration .....	713	Malformations .....	762
THE GALLBLADDER .....	714	Foreign Bodies .....	762
Cholecystitis .....	714	Otitis Externa .....	762
Cholelithiasis .....	714	The Tympanic Membrane .....	763
THE BILE DUCTS .....	714	Otitis Media .....	763
Cystic Dilatation .....	714	DISTURBANCES OF THE INNER EAR, MENINGES, LATERAL SINUS AND FACIAL NERVE .....	765
Congenital Atresia .....	714	Mastoiditis .....	765
THE PANCREAS .....	717	Impaired Hearing .....	766
Tests of Pancreatic Function .....	719	<i>Dean M. Lierle</i> .....	
Causes of Steatorrhea .....	720	THE LARYNX .....	770
CELIAC DISTURBANCES .....	721	Congenital Malformations .....	771
True or Idiopathic Celiac Disease .....	721	<i>Chevalier L. Jackson</i> .....	
Cystic Fibrosis of the Pancreas .....	726	Trauma of the Larynx .....	772
Pancreatic Dysplasias Simulating Cystic Fibrosis of the Pancreas .....	730	Laryngeal Stenosis .....	772
Acute Pancreatitis .....	730	Neoplasms of the Larynx .....	773
Involvement of the Pancreas in Systemic Disease .....	731	Foreign Bodies in the Larynx, Trachea and Bronchi .....	773
Neoplasms and Cysts of the Pancreas .....	731	ACUTE INFECTIONS OF THE LARYNX .....	777
THE RESPIRATORY SYSTEM		<i>Waldo E. Nelson</i> .....	
RESPIRATORY PHYSIOLOGY AND ITS APPLICATION TO PULMONARY DISEASE .....	733	General Considerations .....	777
<i>Benjamin Greeley Ferris, Jr., and Charles Davenport Cook</i> .....		Acute Spasmodic Laryngitis .....	777
Control of Respiration .....	733	Acute Nondiphtheritic Infections .....	778
Muscles of Respiration .....	733	THE THORACIC CAVITY .....	781
Pulmonary Subdivisions .....	734	Malformations of the Trachea, Bronchi and Lungs .....	781
Mechanics of Respiration .....	734	Bronchitis .....	785
Ventilation .....	736	Pneumonia .....	786
Partial Pressures of Gases .....	739	Bacterial Pneumonia .....	787
Initiation of Respiration .....	740	Viral or Probable Viral Infections .....	794
Artificial Respiration .....	740	Mycotic Pulmonary Infections .....	798
Inhalation Therapy .....	742	Aspiration Pneumonias .....	799
AGE AS A FACTOR IN RESPIRATORY DISTURBANCES .....	743	Löffler's Syndrome .....	801
<i>Robert H. Parrott and Waldo E. Nelson</i> .....		Hypostatic Pneumonia .....	801
THE UPPER RESPIRATORY TRACT .....	744	Idiopathic Pulmonary Hemosiderosis .....	801
THE NOSE .....	744	Atelectasis .....	802
Malformations of the Nose .....	744	Emphysema .....	805
Foreign Bodies in the Nose .....	745	Pulmonary Edema .....	807
Neoplasms of the Nose .....	745	Pulmonary Embolism and Infarction .....	808
Epistaxis .....	745	Pulmonary Suppuration .....	808
ELONGATED UVULA .....	746	<i>W. Emory Burnett</i> .....	
INFECTIONS OF THE UPPER RESPIRATORY TRACT .....	746	DISEASES OF THE PLEURA .....	812
General Considerations of Acute Infections .....	746	Pleurisy .....	812
Etiologic Considerations of Newly Isolated Viruses .....	746	Pneumothorax .....	816
Acute Nasopharyngitis .....	748	<i>Waldo E. Nelson</i> .....	
Acute Pharyngitis .....	750	Hydrothorax .....	817
		Hemothorax .....	818
		Chyllothorax .....	818



# THE CARDIOVASCULAR SYSTEM

THE HEART AND CIRCULATION IN HEALTH AND DISEASE .....	819
<i>Samuel Kaplan and Robert A. Lyon</i>	
CONGENITAL HEART DISEASE .....	839
CONGENITAL CARDIAC DISEASE WITH CYANOSIS .....	842
Tetralogy of Fallot .....	842
Pulmonary Atresia .....	848
Tricuspid Atresia .....	848
Eisenmenger Syndrome .....	849
Transposition of the Great Vessels (Arteries) .....	851
Ebstein's Disease .....	852
Truncus Arteriosus .....	853
Single Ventricle .....	854
Aortic Atresia .....	854
Dextrocardia with Situs Inversus ...	855
Isolated Dextrocardia .....	855
Levocardia with Situs Inversus .....	855
Pulmonary Arteriovenous Fistula ...	855
Ectopia Cordis .....	856
Diverticulum of the Left Ventricle ..	856
CONGENITAL HEART DISEASE WITH LITTLE OR NO CYANOSIS .....	856
Ventricular Septal Defect .....	856
Atrial Septal Defect .....	859
Patent Ductus Arteriosus .....	863
Aorticopulmonary Septal Defect ....	866
Fistula of a Coronary Artery .....	866
Ruptured Sinus of Valsalva .....	866
Pulmonary Stenosis (with Normal Aortic Root) .....	866
Coarctation of the Aorta .....	870
Anomalous Pulmonary Venous Return ..	874
Congenital Aortic Stenosis .....	875
Congenital Mitral Stenosis .....	876
Anomalies of the Aortic Arch .....	877
Anomalous Origin of Coronary Arteries .....	877
Primary Pulmonary Hypertension ..	879
Marfan's Syndrome—Cardiovascular Manifestations .....	880
PRINCIPLES OF TREATMENT IN CONGENITAL HEART DISEASE .....	880
DISTURBANCES OF RATE AND RHYTHM OF THE HEART .....	883
Sinus Arrhythmia .....	883
Extrasystoles .....	883
Paroxysmal Tachycardia .....	884
Atrial Flutter .....	885
Atrial Fibrillation .....	885
Ventricular Fibrillation .....	886
Bradycardia .....	886
Heart Block .....	886
DISEASES OF THE ENDOCARDIUM .....	888
Acute or Malignant Endocarditis ...	888
Subacute Bacterial Endocarditis ....	888
Rheumatic Endocarditis .....	889
DISEASES OF THE MYOCARDIUM .....	893
Conditions Causing Myocardial Damage .....	893
Congenital Anomalies .....	895
Other Myocardial Diseases .....	896
Treatment of Cardiac Failure .....	897

DISEASES OF THE PERICARDIUM .....	899
Pericarditis .....	899
DISEASES OF THE BLOOD VESSELS .....	902
Aneurysms and Fistulas .....	902
Frostbite .....	902
Embolism .....	902
Thrombosis .....	903

RHEUMATIC FEVER .....	903
<i>Ann G. Kuttner</i>	

## DISEASES OF MESENCHYMAL TISSUES

RHEUMATOID ARTHRITIS .....	915
<i>Ralph J. P. Wedgwood</i>	
ANAPHLACTOID PURPURA .....	920
DERMATOMYOSITIS .....	922
SYSTEMIC LUPUS ERYTHEMATOSUS ....	925
PERIARTERITIS NODOSA .....	927
SCLERODERMA .....	928
MORPHEA .....	928

## DISEASES OF THE BLOOD

DISORDERS OF RED BLOOD CELLS .....	930
<i>Nathan J. Smith, Victor C. Vaughan, III, and Louis K. Diamond</i>	
THE ANEMIAS .....	933
Anemias Due to Inadequate Production of Erythrocytes or Hemoglobin ...	934
Congenital Hypoplastic Anemia ....	934
The Aplastic Anemias .....	935
Anemia of Chronic Infection .....	937
Anemia of Chronic Azotemia .....	938
The Megaloblastic Anemias .....	938
Anemia of Iron Deficiency .....	941
Anemias Due to Excessive Loss of Erythrocytes .....	943
Anemia Due to Acute Hemorrhage ..	943
Anemia Due to Chronic Hemorrhage ..	944
Hemolytic Anemias .....	944
POLYCYTHEMIA, ERYTHROCYTOSIS AND ERYTHREMIA .....	962
DISORDERS OF THE LEUKOCYTES .....	963
Agranulocytosis .....	964
Periodic Neutropenia .....	965
Chediak-Higashi Syndrome .....	965
The Leukemias .....	966
DISEASES OF THE BLOOD ASSOCIATED WITH DEFECTS IN HEMOSTASIS ...	970
Laboratory Tests Useful in the Study of Patients with a Bleeding Tendency .....	972
DEFECTS OF HEMOSTASIS IN SMALL VESSELS .....	973
Other Vascular Defects Associated with Bleeding Tendency .....	973
Idiopathic Thrombocytopenic Purpura .....	974
Thrombotic Thrombocytopenic Purpura .....	976
Thrombocytopenia in the Newborn ..	976
Thrombocytopenia and Giant Hemangioma .....	977

DISTURBANCES OF THE MECHANISM FOR CLOTTING .....	977
The Hemophilias .....	977
Deficiencies in Prothrombin and Accessory Factors .....	980
Disorders Involving Fibrinogen and Fibrin .....	982

### THE SPLEEN

THE SPLEEN .....	985
<i>Nathan J. Smith</i>	
Congestive Splenomegaly .....	986
Splenic Cytopenia .....	988
Infarction of the Spleen .....	989

### THE LYMPHATIC SYSTEM

DISEASES OF THE LYMPH VESSELS .....	990
<i>Nathan J. Smith, Victor C. Vaughan, III, and Louis K. Diamond</i>	
DISEASES OF THE LYMPH NODES .....	991
Lymphadenitis .....	991
Neoplasms of Lymph Nodes .....	992
Hodgkin's Disease .....	994

### THE THYMUS GLAND

THE THYMUS GLAND .....	997
<i>Waldo E. Nelson</i>	

### DISTURBANCES OF CELLULAR LIPID METABOLISM AND RELATED CONDITIONS

DISTURBANCES OF LIPID METABOLISM:	
THE LIPIDOSES .....	999
<i>Sydney S. Gellis</i>	
Gaucher's Disease .....	999
Niemann-Pick Disease .....	1000
Xanthomas of the Skin .....	1001
DISEASES OF THE RETICULOENDOTHELIAL SYSTEM: THE RETICULOENDOTHELIOSES .....	1002
Hand-Schüller-Christian Syndrome ..	1002
Letterer-Siwe Disease .....	1003
Eosinophilic Granuloma .....	1004

### THE GENITOURINARY SYSTEM

CLINICAL ASPECTS OF RENAL PHYSIOLOGY .....	1005
<i>Philip L. Calcagno</i>	
Glomerular Filtration .....	1006
Tubular Reabsorption .....	1007
Tubular Excretion .....	1008
Special Clearances .....	1008
Acid-Base Regulation .....	1008
Renal Function in Young Infants ...	1009

URINE AND URINATION .....	1010
<i>Mitchell I. Rubin</i>	

DIAGNOSTIC TESTS USED IN THE STUDY OF KIDNEYS .....	1012
DISORDERS OF URINARY SECRETION ...	1014
DISTURBANCES IN QUANTITY OR EXCRETION OF URINE .....	1014
Oliguria .....	1014
Retention of Urine .....	1015
Polyuria .....	1015
Frequent Urination .....	1015
Incontinence of Urine .....	1015

Enuresis .....	1015
<i>Sherman Little</i>	

ALTERATIONS IN COMPOSITION OF URINE .....	1018
<i>Mitchell I. Rubin</i>	

Albuminuria .....	1018
Glycosuria .....	1019
Pentosuria .....	1020
Galactosuria .....	1020
Lithuria .....	1020
Indicanuria .....	1020
Lipuria .....	1020
Acetonuria .....	1020
Hematuria .....	1020
Ammoniacal Urine .....	1021

ABNORMAL PIGMENTS IN THE URINE ...	1021
Abnormally Colored Urine .....	1021
Hemoglobinuria .....	1021
Paroxysmal Hemoglobinuria .....	1022
Melanuria .....	1022
Bile Pigments in the Urine .....	1022

MALFORMATIONS OF THE URINARY TRACT .....	1022
--	------

MALFORMATIONS OF THE KIDNEY, URETERS AND BLADDER .....	1023
Renal Agenesis and Hypoplasia ....	1023
Polycystic Disease of the Kidneys ...	1024
Solitary Renal Cyst .....	1024
Exstrophy of the Bladder .....	1024
Patent Urachus and Urachal Cyst ..	1025
Malformations Producing Obstruction to the Urinary Flow .....	1026
Displacement of the Kidney .....	1030

INFECTIONS OF THE URINARY TRACT ..	1030
Pyelonephritis, Pyelitis .....	1030
Perinephritis .....	1034

DISTURBANCES OF THE KIDNEY .....	1035
Nephritis .....	1035
Nephrotic Syndrome .....	1044
Tuberculosis of the Kidney .....	1052
Hemorrhagic Infarction of the Kidney	1053
Renal Calculus .....	1054

DISTURBANCES OF THE URINARY BLADDER .....	1055
Vesical Calculus .....	1055
Foreign Bodies in the Bladder .....	1055
Cystitis .....	1055
Tuberculosis of the Bladder .....	1055
Spasm of the Bladder .....	1056

MALFORMATIONS AND DISEASES OF THE MALE AND FEMALE GENITAL ORGANS .....	1056
Adherent Prepuce .....	1056
Phimosis .....	1056
Paraphimosis and Strangulation of the Penis .....	1056

Abnormal Size of the Penis ..... 1057

Balanoposthitis ..... 1057

Malformations of the Urethra ..... 1057

Inflammation of the External Urethral  
Orifice ..... 1058

Urethritis ..... 1058

Foreign Bodies in the Urethra, Includ-  
ing Urethral Calculus ..... 1058

Inflammation of the Scrotum ..... 1058

Genital Edema of the Newborn Infant ..... 1058

Undescended Testes ..... 1058

Polyorchism and Anorchism ..... 1059

Orchitis and Epididymitis ..... 1059

Torsion of the Spermatic Cord ..... 1059

Tuberculosis of the Male Genital Or-  
gans ..... 1059

Malformations of the Vulva, Vagina  
and Clitoris ..... 1060

Vulvovaginitis ..... 1060

Abscess of the Vulva ..... 1061

Gangrenous Vulvitis ..... 1061

Genital Hemorrhage; Precocious Men-  
struation ..... 1062

Diseases of the Uterus and Fallopian  
Tubes ..... 1062

Diseases of the Ovaries ..... 1062

THE NERVOUS SYSTEM

DIAGNOSTIC STUDY OF NEUROLOGIC DIS-  
EASE ..... 1063

*David B. Clark*

History and Physical Examination .. 1063

Examination of Newborn and Young  
Infants ..... 1067

Examination of the Hysterical Patient ..... 1068

Examination of the Unconscious Pa-  
tient ..... 1069

Special Diagnostic Procedures ..... 1069

SYMPTOMATOLOGY OF NEUROLOGIC DIS-  
EASE IN CHILDHOOD ..... 1073

STATIC AND DEVELOPMENTAL LESIONS ..... 1075

ECTODERMAL DYSPLASIAS ..... 1079

CONGENITAL VASCULAR LESIONS ..... 1080

EXPANDING LESIONS AND INCREASED In-  
TRACRANIAL PRESSURE ..... 1082

Intracranial Pressure ..... 1082

Brain Tumor ..... 1084

Extracerebral Accumulations of  
Fluid ..... 1087

Brain Abscess ..... 1090

Increased Intracranial Pressure with-  
out Mass Lesions ..... 1091

Hydrocephalus ..... 1092

Hydranencephaly ..... 1093

DEGENERATIVE DISEASES ..... 1094

Lipidoses and Leukodystrophies .... 1094

Degenerative Diseases Involving Spe-  
cific Fiber Tracts and/or Neural  
Groups ..... 1097

Degenerative Diseases of Uncertain  
Classification ..... 1101

The Syndrome of Epilepsy, Cerebral  
Degeneration and Myoclonus .. 1101

NEUROLOGIC SYNDROMES PECULIAR TO  
CHILDHOOD ..... 1102

Spasmus Nutans ..... 1102

Acute Cerebellar Ataxia ..... 1103

Acute Infantile Hemiplegia ..... 1103

CRANIOCEREBRAL AND SPINAL TRAUMA ..... 1104

DISEASES OF THE SPINAL CORD ..... 1105

DISEASES OF THE AUTONOMIC NERVOUS  
SYSTEM ..... 1107

NEURITIS AND NEUROPATHIES ..... 1107

Chronic Polyneuritis ..... 1107

TETANY

TETANY ..... 1110

*Waldo E. Nelson*

CONVULSIVE DISORDERS

CONVULSIVE DISORDERS ..... 1114

*Irvine McQuarrie and  
Henry W. Baird, III*

ACUTE OR NONRECURRENT CONVULSIVE  
DISORDERS ..... 1116

CHRONIC OR RECURRENT CONVULSIONS ..... 1117

Epilepsy ..... 1117

Chronic Paroxysmal Disorders Simu-  
lating Epilepsy ..... 1127

MENTAL DEFICIENCY

Psychologic Considerations ..... 1129

*Herman Yannet*

Clinical Classification ..... 1129

Treatment ..... 1135

CEREBRAL PALSY

CEREBRAL PALSY ..... 1138

*John B. Bartram*

BEHAVIOR PROBLEMS ASSOCIATED  
WITH ORGANIC BRAIN DAMAGE

BEHAVIOR PROBLEMS ASSOCIATED WITH  
ORGANIC BRAIN DAMAGE ..... 1143

*John B. Bartram*

THE PHYSICIAN AND THE CHILD WITH  
A HANDICAP

THE PHYSICIAN AND THE CHILD WITH A  
HANDICAP ..... 1145

*John B. Bartram*

PSYCHOSES

PSYCHOSES ..... 1148

*Milton J. E. Senn*



## THE ENDOCRINE SYSTEM

DISORDERS OF THE PITUITARY GLAND ..	1150
<i>Angelo M. DiGeorge and</i>	
<i>Josef Warkany</i>	
Pituitary Dwarfism .....	1151
Progeria .....	1153
Simmonds' Disease .....	1154
Pituitary Gigantism and Acromegaly ..	1154
Diabetes Insipidus .....	1155
Precocious Puberty .....	1157
Adiposogenital Dystrophy Induced by	
Lesions of the Hypothalamus and	
of the Pituitary Gland .....	1162
DISORDERS OF THE THYROID GLAND ..	1163
General Considerations .....	1163
Congenital Hypothyroidism .....	1165
Acquired Hypothyroidism .....	1168
Goiter .....	1169
Carcinoma of the Thyroid .....	1173
DISORDERS OF THE PARATHYROID	
GLANDS .....	1175
Hypoparathyroidism .....	1175
Hyperparathyroidism .....	1177
DISORDERS OF THE ADRENAL GLANDS ..	1180
General Considerations .....	1180
Hypoadrenocorticism .....	1182
Hyperadrenocorticism .....	1185
Pheochromocytoma .....	1191
DISORDERS OF THE GONADS .....	1193
HYPOFUNCTION OF THE TESTES .....	1195
The Eunuchoid Syndromes .....	1195
PSEUDOPRECOCITY RESULTING FROM TU-	
MORS OF THE TESTES .....	1197
GYNECOMASTIA .....	1198
HYPOFUNCTION OF THE OVARIES .....	1198
Primary Hypogonadism .....	1198
Secondary Hypogonadism .....	1200
PSEUDOPRECOCITY DUE TO GRANULOSA	
CELL TUMORS OF THE OVARY ....	1201
OTHER ENDOCRINE TUMORS OF THE	
OVARY .....	1201
Stein-Leventhal Syndrome .....	1201
HERMAPHRODITISM .....	1202
Chromosomal Sex .....	1202
Embryonic Sexual Differentiation ..	1202
Female Pseudohermaphroditism ....	1202
Male Pseudohermaphroditism .....	1203
True Hermaphroditism .....	1203

## METABOLIC DISORDERS

DIABETES MELLITUS .....	1205
<i>Waldo E. Nelson</i>	
The Diabetes Mellitus Syndrome in	
the Newborn Infant .....	1213
Infants of Diabetic Mothers .....	1214
<i>Sydney S. Gellis</i>	
HYPOGLYCEMIA .....	1215
<i>Milton Rapoport</i>	
METABOLIC DISORDERS WITH OSSEOUS	
LESIONS .....	1221
<i>Lytt I. Gardner</i>	

Vitamin D-Refractory (Resistant)	
Rickets .....	1221
Rickets Associated with Amino-acid-	
uria .....	1222
Rickets Associated with Hydrophthal-	
mos, Organic Aciduria and De-	
creased Renal Ammonia Produc-	
tion .....	1223
Rickets of Chronic Renal Glomerular	
and Tubular Insufficiency ....	1223
Rickets Associated with "Base-Losing	
Nephritis" .....	1223
Rickets of Celiac Disease .....	1224
Hypophosphatasia .....	1224
Idiopathic Hypercalcemia with	
Growth Retardation .....	1224

## THE BONES AND JOINTS

SKELETAL DEFECTS .....	1226
<i>Josef Warkany</i>	
DEFECTS IN OSSIFICATION OF THE SKULL	
Craniosynostosis .....	1226
Platybasia .....	1228
Parietal Foramina .....	1229
Lacunar Skull .....	1230
DEFORMITIES OF THE EXTREMITIES ....	1230
Miscellaneous Disturbances .....	1230
DEFORMITIES OF THE VERTEBRAE, CLAV-	
ICLES, SCAPULAS AND STERNUM ...	1232
Cleidal and Cleidocranial Dysostosis .	1232
Klippel-Feil Syndrome .....	1233
Pterygium Colli .....	1233
Sprengel's Deformity .....	1233
Winged Scapulas .....	1233
Deformities of the Sternum .....	1233
Pectus Excavatum .....	1234
DISTURBANCES IN OSTEOGENESIS AND IN	
ENDOCHONDRAL OSSIFICATION ....	1234
Chondrodystrophy .....	1234
Atypical Chondrodystrophies .....	1237
Osteopetrosis .....	1239
Osteogenesis Imperfecta .....	1241
MISCELLANEOUS DISORDERS .....	1243
Arachnodactyly .....	1243
Multiple Exostoses .....	1244
Ollier's Disease .....	1245
Melorheostosis .....	1246
Fibrous Dysplasia of Bone .....	1246
Leontiasis Ossea .....	1246
Mandibulofacial Dysostosis .....	1247
Arthrogryposis .....	1247
Hemihypertrophy .....	1248
Hypertrophic Pulmonary Osteoar-	
thropathy .....	1248
ORTHOPEDIC PEDIATRICS .....	1250
<i>Charles C. Chapple and</i>	
<i>John Royal Moore</i>	
Response of Bone to Local and Gen-	
eral Disturbances .....	1250
Relation of Intrauterine Position to	
Orthopedic Disturbances .....	1250
The Foot .....	1252
The Leg .....	1254
The Hip .....	1254

CONTENTS

xxiii

The Spine .....	1257
Osteochondrosis .....	1258
Subluxation of Head of Radius .....	1259
Infections of the Bones and Joints ..	1259
Tuberculosis .....	1261

THE MUSCLES

CONGENITAL DEFECTS OF MUSCLE ....	1264
<i>Robert E. Shank; revised by</i>	
<i>Waldo E. Nelson</i>	
Torticollis .....	1264
INFLAMMATORY DISEASES OF MUSCLE	1265
Myositis Fibrosa .....	1265
Progressive Myositis Ossificans .....	1266
METABOLIC AND DEGENERATIVE DIS-	
EASES OF MUSCLE .....	1267
Amyotonia Congenita Syndrome ...	1267
Myotonia Congenita .....	1267
Myotonic Dystrophy .....	1268
Progressive Muscular Dystrophy ....	1268
Myasthenia Gravis .....	1271
Familial Periodic Paralysis .....	1272

THE SKIN

CONGENITAL AND HEREDITARY ANOM-	
ALIES AND DEFECTS .....	1274
<i>Carroll S. Wright</i>	
Nevi .....	1274
Ichthyosis .....	1275
Keratosis Palmaris et Plantaris .....	1275
Epidermolysis Bullosa .....	1275
Congenital Ectodermal Dysplasia ...	1276
Pachonychia Congenita .....	1276
Xeroderma Pigmentosum .....	1276
Cutis Hyperelastica .....	1277
PIGMENTARY CHANGES IN THE SKIN ...	1277
Albinism .....	1277
Freckles .....	1277
Vitiligo .....	1277
HYPERTROPHIES AND ATROPHIES .....	1277
Cicatrix .....	1277
Keloid .....	1277
Keratosis Follicularis .....	1277
DISTURBANCES IN THE SUBCUTANEOUS	
FAT .....	1278
Subcutaneous Fat Necrosis of the	
Newborn .....	1278
Sclerema Neonatorum .....	1278
Scleredema .....	1278
Lipodystrophy .....	1279
Relapsing Nodular Nonsuppurative	
Panniculitis .....	1279
DISEASES OF THE SEBACEOUS GLANDS ..	1280
Milium .....	1280
Adenoma Sebaceum .....	1280
Acne Vulgaris .....	1281
DISTURBANCES OF THE HAIR .....	1281
Alopecia .....	1282
DRUG ERUPTIONS .....	1282
DERMATITIS AND ECZEMATOID LESIONS	1283
Dermatitis Venenata .....	1283
Seborrheic Dermatitis .....	1283
Infectious Eczematoid Dermatitis ...	1284

Leiner's Disease .....	1284
Ritter's Disease .....	1285
ERYTHEMATOPAPULAR AND SQUAMOUS	
ERUPTIONS .....	1285
Psoriasis .....	1285
Pityriasis Rosea .....	1286
Keratosis Pilaris .....	1287
INFECTIONS OF THE SKIN .....	1287
BACTERIAL INFECTIONS .....	1287
Impetigo Contagiosa .....	1287
Ecthyma .....	1288
Furunculosis .....	1288
Tuberculosis of the Skin .....	1289
Lupus Vulgaris .....	1289
Tuberculosis Verrucosa Cutis .....	1289
Scrofuloderma .....	1289
Primary Tuberculous Lesions .....	1289
Lichen Scrofulosorum .....	1290
Tuberculides .....	1290
Lupus Erythematosus .....	1290
FUNGUS INFECTIONS .....	1291
Ringworm .....	1291
Favus .....	1293
Pityriasis Versicolor .....	1293
Moniliasis .....	1293
PARASITIC INFESTATIONS .....	1294
Scabies .....	1294
Pediculosis .....	1295
VIRAL INFECTIONS .....	1296
Verrucae .....	1296
Molluscum Contagiosum .....	1297
THE ERYTHEMAS .....	1298
Miliaria Rubra .....	1298
Intertrigo and Diaper Rash .....	1298
Erythema Multiforme .....	1299
Erythema Nodosum .....	1300
Urticaria Papulosa .....	1300
Urticaria Pigmentosa .....	1300
Prurigo .....	1301
Hydroa Aestivale .....	1301
FORMULARY FOR DISEASES OF THE SKIN	1301

BURNS

BURNS .....	1302
<i>Robert H. High</i>	

ALLERGIC DISEASES

General Discussion .....	1304
<i>Mitchell I. Rubin</i>	
Eczema .....	1312
Urticaria and Other Allergic Erup-	
tions .....	1318
Allergic Rhinitis .....	1319
Asthma .....	1321
Serum Sickness .....	1325
Gastrointestinal Allergy .....	1326

THE EYE

Eyes of the Newborn Infant .....	1329
<i>John S. McGavie</i>	
Examination .....	1329

Refractive Errors .....	1331
Structural Disturbances .....	1332
Cataract and Dislocated Lenses .....	1333
Glaucoma .....	1334
Strabismus .....	1334
Infections .....	1337
Injuries .....	1340
Tumors .....	1341
Retina .....	1342
Retrolental Fibroplasia .....	1343
Hygiene of the Eye .....	1343
Sight-Saving Classes and Schools for Blind Children .....	1343

### UNCLASSIFIED DISEASES

AMYLOIDOSIS .....	1345
<i>Sydney S. Gellis</i>	
SARCOIDOSIS .....	1346
<i>Robert H. High</i>	

### NEOPLASMS AND NEOPLASTIC-LIKE TISSUES

Tumors of the Nose, Sinuses, Phar- ynx, Ear and Oral Cavity .....	1347
<i>James B. Arey</i>	
Tumors of the Salivary Glands .....	1349
Tumors of the Neck .....	1349
Tumors of the Mediastinum .....	1349
Tumors of the Heart .....	1350
Tumors of the Lung .....	1350
Tumors of the Gastrointestinal Tract .....	1351
Tumors of the Liver .....	1352
Tumors of the Pancreas .....	1353
Tumors of the Kidney .....	1353
Tumors of the Adrenal .....	1355
Other Retroperitoneal Tumors .....	1356
Tumors of the Bladder and Prostate .....	1357
Tumors of the Testis .....	1357
Tumors of the Ovary .....	1358
Tumors of the Vagina and Uterus .....	1358
Tumors of the Skin and Soft Tissues .....	1358
Neoplasms of Bone .....	1365

### RADIATION INJURY

RADIATION INJURY .....	1371
<i>Robert W. Miller</i>	

### POISONING FROM FOOD, METALS, CHEMICALS AND DRUGS

FOOD POISONING .....	1374
<i>John A. Anderson</i>	
Botulism .....	1374
Staphylococcal Poisoning .....	1374
Streptococcal Poisoning .....	1375
Salmonella Poisoning .....	1375
LEAD POISONING .....	1375
CHEMICAL AND DRUG POISONING .....	1378
Chemical Poisoning .....	1382

ACRODYNIA .....	1398
<i>J. B. Bilderback</i>	

### APPENDIX

NORMAL BLOOD VALUES .....	1402
<i>Howard W. Robinson</i>	
NORMAL CEREBROSPINAL FLUID VAL- UES .....	1405
SODIUM AND POTASSIUM CONTENTS OF ORAL FLUIDS .....	1408
<i>Waldo E. Nelson</i>	
FOOD VALUES .....	1408
METHOD FOR DIET CALCULATION .....	1409
ELIMINATION DIETS (ROWE) FOR THE STUDY AND CONTROL OF FOOD AL- LERGY .....	1412
<i>Albert H. Rowe</i>	
CONVERSION TABLES OF APOTHECARY'S MEASURES TO METRIC EQUIVAL- ENTS .....	1413
<i>Waldo E. Nelson</i>	
EQUIVALENT CENTIGRADE AND FAHREN- HEIT TEMPERATURE READINGS ...	1413
INDEX .....	1415



# The Field of Pediatrics

## AN INTRODUCTION TO THE MEDICAL PROBLEMS OF INFANTS AND CHILDREN

No field of specialized medicine has a broader scope, greater responsibilities or greater possibilities than has pediatrics. One important fact sets it apart from other divisions of medicine: it is chiefly concerned with the *continued* growth and development of its subjects.

The goal in the medical management of the child is to permit him to come into adulthood at *his* optimal state of development, physically, mentally and socially, so that he can compete at *his* most effective level. The physician who cares for children must of course be familiar with the illnesses and psychologic disturbances peculiar to infants and children and their reactions to them. But he must also know what constitutes adequate achievement at successive age levels for children of different body types and capabilities, with or without obvious physical or mental handicaps. This, the individualization of the child, is the essence of pediatric practice.

In the span of years from birth to maturity, when growth is complete, the physician must deal with a subject who is so different at various stages that it might almost seem he had been several distinct individuals. The characteristics of these stages are not sharply demarcated time-wise, but blend from one into the next. Nevertheless the general pattern of each stage is sufficiently different from each of the others to consider them separately. These stages, the general characteristics of which are listed in Table 5 (p. 26), are (1) the intrauterine period; (2) the neonatal period, the first four weeks of life; (3) the period of infancy and of rapid growth, the first two years; (4) the preschool period, two to six years of age; (5) the period of mid-childhood or the so-called school period, six to ten years of age for girls and six to twelve years for boys; (6) the prepubescent period, ten to twelve years of age for girls and twelve to fourteen years for boys; and (7)

the pubescent and postpubescent periods (adolescence), twelve to eighteen years of age for girls and fourteen to twenty years for boys. In the strict sense the process of birth should also be considered a separate period, since injury of the infant at this time may have serious and even permanent effects.

A number of factors are responsible for variations in the clinical manifestations of disease caused by identical etiologic agents in infants or children and in adults. These differences are implied by the phrase that "the child is not a little man" and include variations in anatomic, physiologic, pathologic and immunologic patterns. In most instances there is a direct relation to age: the younger the child, the more marked are the differences; conversely, as the child approaches maturity, the more do physical disturbances simulate those of adults.

*Anatomic variants*, such as the relative thinness of the chest wall, the more horizontal position of the heart, and the open sutures of the cranial bones in infants, are responsible for physical findings which both in health and in disease differ from those related to the same structures in adults.

*Physiologically*, the relatively greater nutritional needs of infants (calories, proteins, minerals, vitamins and water) reflect the requirements for growth in excess of those for basal functions and physical activity. During illness the infant and small child have less capacity than the adult to maintain homeostasis. Thus the infant with a diarrheal disturbance is in a more precarious position than an older child because of the greater rapidity with which severe disturbances of water and electrolyte metabolism develop.

*Pathologically*, the differences appear to be mainly those related to the effects of injurious agents upon growing tissue in contrast to those upon mature tissue. Thus vitamin D-

deficient rickets and infantile scurvy have quite different clinical patterns in infancy than they do in later childhood.

*Immunologically*, the infant is, in general, more susceptible and less resistant to infection. There are exceptions: to a few infections the infant inherits a limited, short-lived immunity from the mother.

*Mental development and psychologic development* provide the most important measures of the adequacy of growth during infancy and childhood. Training, education and molding of the child's personality determine the level of ultimate achievement. It is understandable that parent education, child guidance and psychiatry have become increasingly important in the medical care of children.

Pediatrics as a specialty of medical practice had its inception in this country in the latter part of the nineteenth century. Since that time there have been great changes in the medical problems of children and consequently in pediatric practice. In 1900 the death rate for infants under one year of age was in the range of 200 per 1000 live births; in 1954 it was only 26.6 for the country as a whole, and in some areas significantly lower. The death rates in the subsequent years of childhood have been reduced to an even greater extent. The notable reduction in the incidence of serious illness is attributable to a number of factors, some general, some spe-

cific. Improvements in the socio-economic status of general populations as represented by better housing and more adequate diets have been factors in increasing resistance to disease. Specifically, prevention of such diseases as diphtheria and smallpox and modification of others such as measles have been accomplished by vaccines and immune serums. Educational measures have been highly effective in the prevention of other diseases; these include isolation of tuberculous patients and the sterilization of milk formulas for infant feeding; the latter is the most important factor in the reduction of infant mortality in the postnewborn period. More recently the availability of effective sulfonamides and antibiotics has made possible successful therapy of many otherwise fatal infections. Such nutritional disturbances as rickets, scurvy, pellagra and nutritional edema have been largely eradicated in this and many other countries by general and specific health measures and can be controlled by appropriate measures in the remainder. The differences in the mortality rates of infants and small children between countries with marked variations in living standards are shown in Figure 1. Much of the credit for the great improvement in child health must be given to research, and continued improvement can be expected from further investigation in the fields of microbiology, chemistry, genetics and child be-

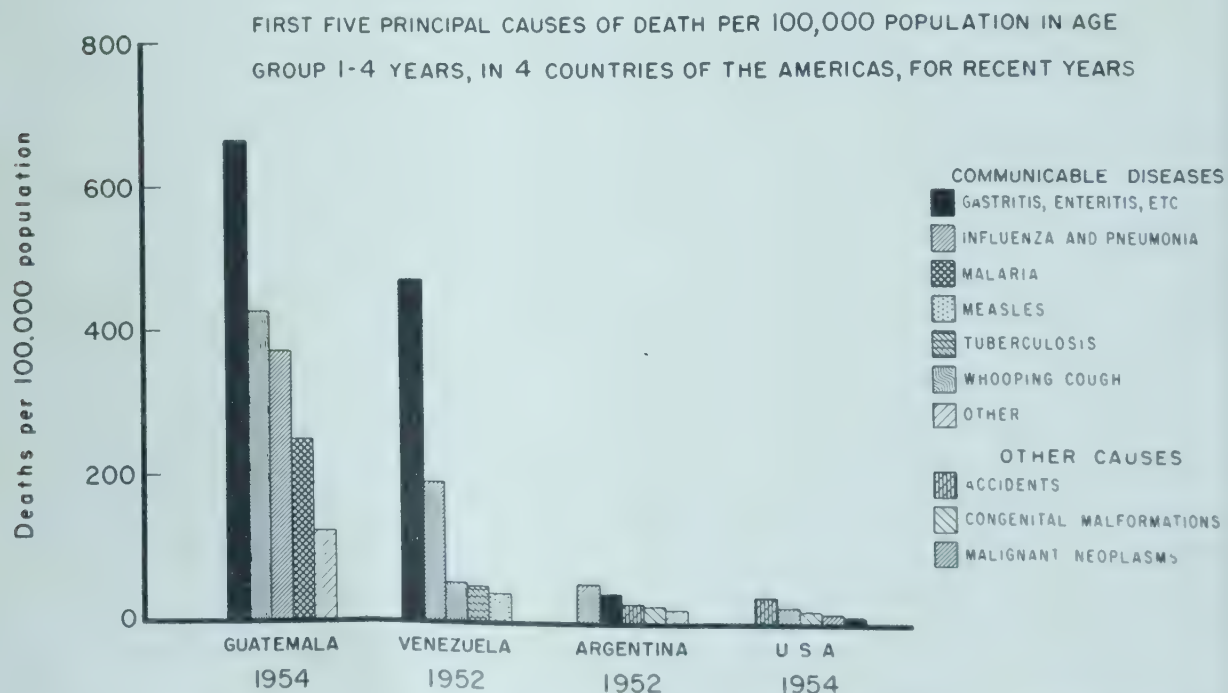


FIG. 1. (Child Mortality in the Americas, March 1957. Pan American Sanitary Organization—World Health Organization.)



Table 1. Leading Causes of Death among Children 1-4 Years of Age, United States, 1920, 1930, 1940, 1950 and 1955

Cause of Death	Rate per 100,000 Population 1-4 Years				
	1955	1950	1940	1930	1920
All causes.....	113.6	139.4	289.6	563.6	987.2
Leading causes:.....					
Accidents, except motor vehicle.....	83.9	98.0	198.4	409.7	794.4
Influenza and pneumonia.....	22.1	25.3	36.3	46.7	71.1
Congenital malformations.....	14.9	18.9	62.5	123.1	283.7
Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues.....	12.1	11.1	10.3	—	—
Motor vehicle accidents.....	11.1	11.7	—	—	—
Gastritis, duodenitis, enteritis and colitis, except diarrhea of newborn.....	10.5	11.5	12.4	14.5	—
Meningitis, except meningococcal and tuberculous.....	4.4	5.3	—	—	—
Bronchitis.....	2.5	2.8	—	—	—
Meningococcal infections.....	2.3	2.5	—	—	—
Tuberculosis, all forms.....	2.3	2.6	—	—	—
Diarrhea, enteritis, etc.....	1.7	6.3	12.3	25.9	45.4
Whooping cough.....	—	—	30.2	95.6	141.3
Diphtheria.....	—	—	9.7	23.4	57.7
Diseases of the ear, nose and throat.....	—	—	9.0	33.5	90.5
Appendicitis.....	—	—	8.9	15.2	12.3
Measles.....	—	—	6.8	—	—
Scarlet fever.....	—	—	—	21.9	56.4
Dysentery.....	—	—	—	9.9	23.2
All other causes.....	—	—	—	—	12.8
	29.7	41.4	91.2	153.9	192.8

Department of Health, Education, and Welfare, Social Security Administration, Children's Bureau. Based on Data from the National Office of Vital Statistics.

Causes of death listed are the 10 leading causes in any one of the years specified. Titles of the causes named are those of the Sixth Revision of the International Lists for 1950 and 1955; of the Fifth Revision for 1940; of the Fourth Revision for 1930; and of the Third Revision for 1920. All rates are unadjusted for differences in classification of causes of death in successive revisions of the Lists.

Table 2. Leading Causes of Death among Children 5-14 Years of Age, United States, 1920, 1930, 1940, 1950 and 1955

Causes of Death	Rate per 100,000 Population 5-14 Years				
	1955	1950	1940	1930	1920
All causes.....	48.4	60.1	103.7	171.7	263.9
Leading causes:.....					
Accidents, except motor vehicle.....	32.2	35.0	53.6	80.1	144.2
Motor vehicle accidents.....	12.1	13.8	17.1	21.4	31.3
Malignant neoplasms.....	7.9	8.8	11.5	14.7	—
Congenital malformations.....	7.0	6.7	—	—	—
Influenza and pneumonia.....	2.7	—	—	—	—
Acute poliomyelitis.....	2.5	3.2	9.0	18.8	45.1
Diseases of the heart.....	—	2.5	—	—	—
Appendicitis.....	—	—	8.0	12.1	17.4
Diphtheria.....	—	—	8.0	13.1	—
Tuberculosis, all forms.....	—	—	—	—	28.0
All other causes.....	—	—	—	—	22.4
	16.2	25.1	50.1	91.6	119.7
	Percentages of Deaths				
All causes.....	100.0	100.0	100.0	100.0	100.0
Leading causes.....	66.4	58.4	51.7	46.8	54.6
All other causes.....	33.6	41.6	48.3	53.2	45.4

Department of Health, Education, and Welfare, Social Security Administration, Children's Bureau. Based on Data from the National Office of Vital Statistics.

Causes of death listed are the 10 leading causes in any one of the years specified. Titles of the causes named are those of the Sixth Revision of the International Lists for 1950 and 1955; of the Fifth Revision for 1940; of the Fourth Revision for 1930; and of the Third Revision for 1920. All rates are unadjusted for differences in classification of causes of death in successive revisions of the Lists.



havior by persons dedicated to a more adequate understanding of the child and of his environment.

The concept of the field of pediatrics which certain persons hold, even some closely connected with medical circles, is a limited one. To some the practice of pediatrics is essentially infant feeding; to others it is the management of the ills of the first two or three years of life; to still others it is the practice of preventive medicine; and to a few it is simply the management of behavior disorders. It is all these and more. Concern for the child must antedate conception and extend through the final phases of growth in the period of adolescence. Care of the unborn child is provided by adequate supervision of the pregnant woman, and obstetric care at the time of delivery is directly reflected in the welfare of the infant. The neonatal period is the most hazardous period of life and presents problems that never arise again. Infancy represents the period of most rapid growth. This is the time when the infant is completely dependent on others for all phases of his care; when he is not only more susceptible to infections and nutritional disturbances, but often has a pattern of response to them which differs from that of later years. As the age of infancy is passed and the pre-school, prepuberty and adolescent ages are attained, the child assumes increasing responsibility for his own care, but intelligent and understanding pediatric supervision can continue to be an important aid. Surveys of children in all economic strata reveal a high incidence of nutritional and physical disturbances and of psychologic difficulties which are remedial and, more important, preventable.

## PROBLEMS OF VARIOUS AGE PERIODS

**Advisability of Parenthood** (see also pp. 247 and 1136). Young persons contemplating marriage, and couples who have had one or more defective offspring, often seek advice concerning the advisability of future parenthood. The increasing tendency for some degree of civil control over physical and mental fitness for marriage and parenthood will probably result in more frequent consultations. The physician who assumes such a responsibility must be well informed concerning the medical and legal aspects of fitness for parenthood. The problem involves the factors of genetic patterns and of physical, mental and moral fitness of the prospective parents. Moral fitness constitutes the most difficult

problem and, unless legal measures can be taken, is not controllable beyond the cooperation of the prospective parents.

**Prenatal Factors.** During pregnancy the mother's health is the most important factor determining whether the fetus will be carried to term and delivered in a viable, healthy condition. Adequate nutrition, properly balanced rest and exercise, and freedom from worry are essential to ensure this goal. Specific disturbances of the mother may affect the fetus, such as German measles during the first trimester, syphilis, toxoplasmosis, isoimmunization and diabetes mellitus. Regular prenatal visits to the physician have had a distinct effect in the reduction of both maternal and infant mortality. These visits should also be used to counsel the parents concerning the care of the newborn infant. Many problems of early infancy could be averted if prospective parents had a more adequate concept of infant care and especially of how simple and natural it can and should be.

**Natal Factors.** Every infant should be delivered by an adequately trained physician. The fact that more than 10,000 infant deaths a year are directly attributable to birth injuries and that many other infants are crippled for life illustrates the need for improvement in the technique of obstetric care. The choice and use of sedatives and anesthetics, the mechanics of delivery, including the improper use of forceps as well as failure to use them at appropriate times, and the management of the infant immediately after birth are factors which affect the offspring. Failure to clear the air passages of mucus and amniotic fluid contents, damage resulting from manual and mechanical attempts at resuscitation, failure to prevent chilling the infant, and nonantiseptic technique are also important factors.

**Neonatal Factors** (p. 28). During the neonatal period the infant must make adjustments to extrauterine existence. The difficulties are illustrated in part by the exceedingly high mortality rate and by the multiplicity of physical disturbances, many of them characteristic of this period.

Prematurity (pp. 286 and 306) is the most important problem of the neonatal period. During the first month of life infants born prematurely account for almost half of the total number of deaths. The smaller the infant, the less his chance of survival. However, weight of the infant at birth is not the sole factor determining survival. Toxemia or other

illness of the mother, the physical condition of the infant and the quality of his care beginning immediately after birth are of the greatest importance.

Injuries at birth and congenital malformations are important causes of crippling and death. Although certain injuries appear to be unavoidable, and others justifiable to save the mother's life, better obstetric care should result in a further reduction in neonatal mortality. Many congenital malformations are incompatible with life, but early recognition and treatment of certain ones will result in an increased saving of life.

Though acquired disease is relatively less important as a cause of death in the neonatal period, some idea of its actual importance may be obtained from the fact that in 1949 almost 4000 deaths of newborn infants were

attributed to respiratory and gastrointestinal diseases. This number represents more than one fifth of all deaths due to these causes in the first year of life.

The mortality rates of any age period do not completely reflect the relative importance of its various medical problems. Some deaths in age periods beyond the neonatal and many instances of prolonged illness and of persistent physical and mental disabilities have their origin in the perinatal period.

**Infancy Factors.** Infancy is the period of most rapid extrauterine growth. Adequate growth and development, both physical and mental, are essential to normal infancy, and the rates of development constitute the best measures available for evaluation of the infant's status. During most of this period the infant is dependent on others for mainte-

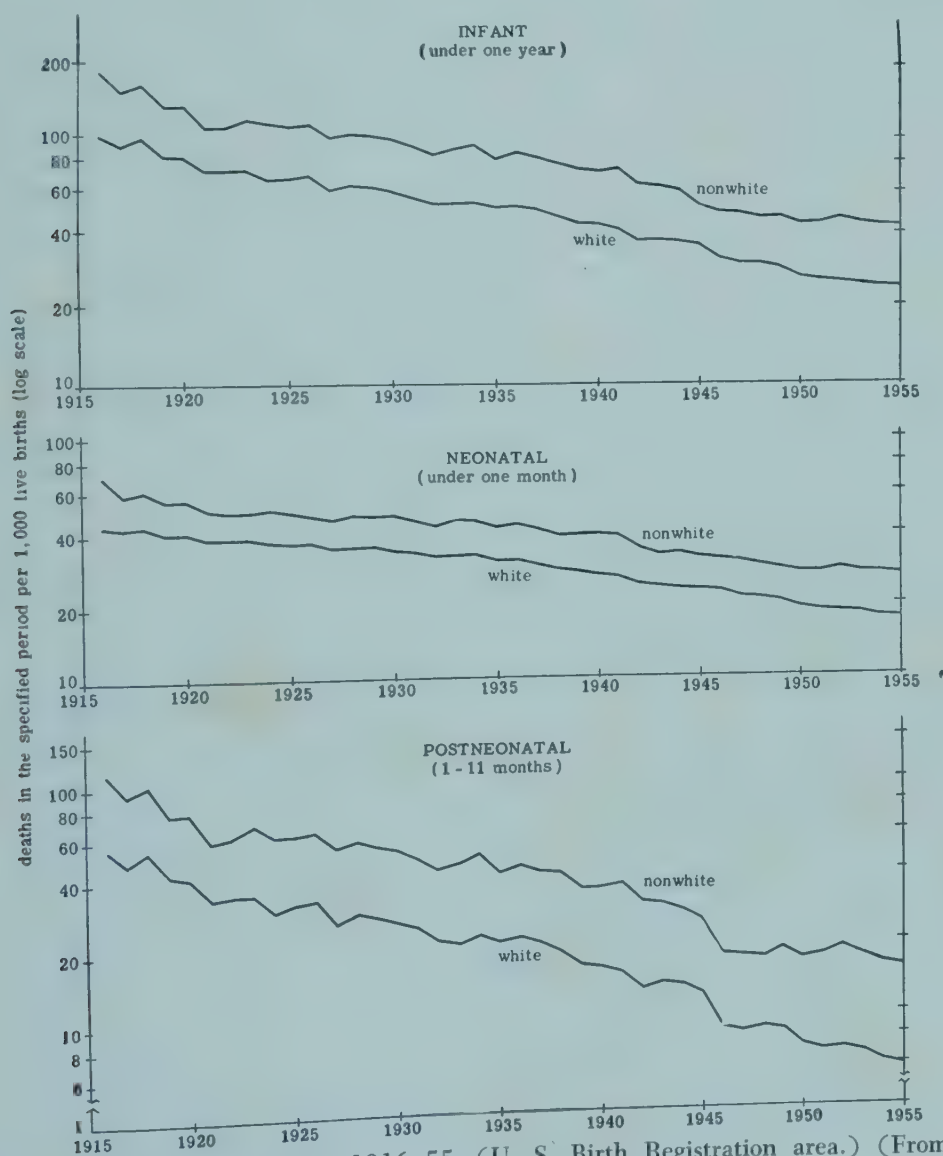


FIG. 2. Infant mortality rates by age, 1916-55. (U. S. Birth Registration area.) (From Children's Bureau Statistical Series No. 50.)

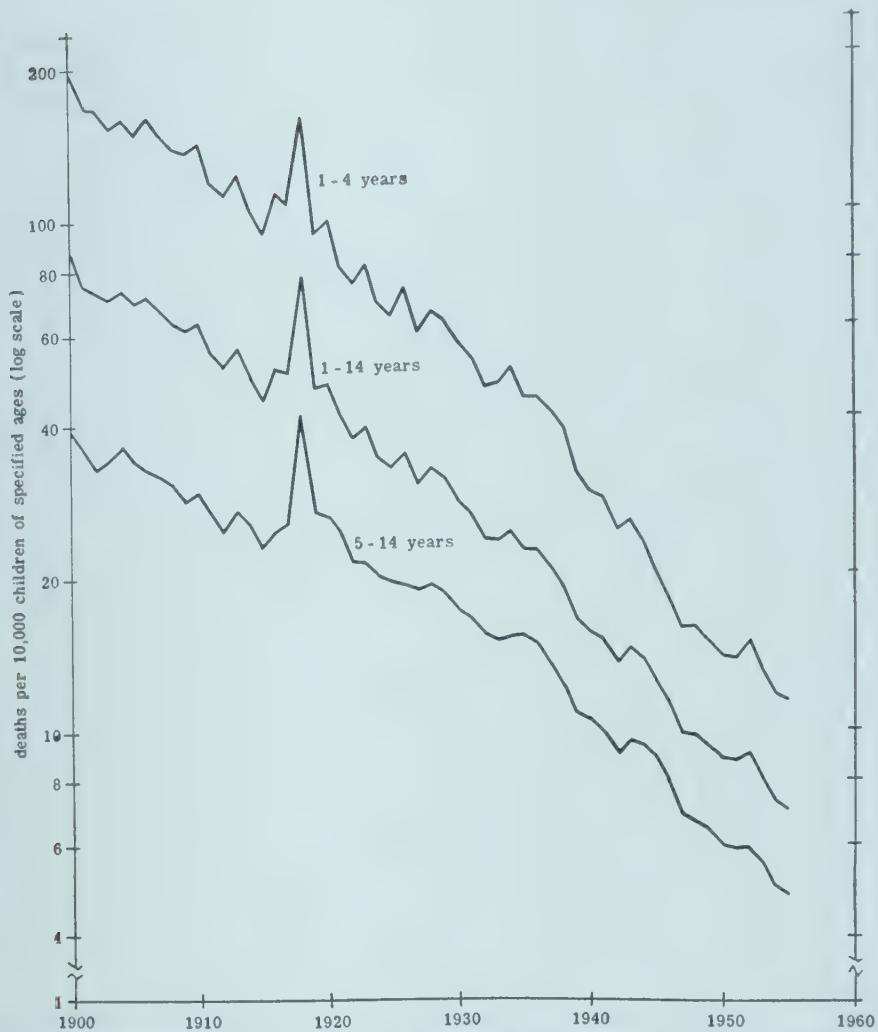


FIG. 3. Childhood Mortality, 1900-55. (U. S. Death Registration area.) (From Children's Bureau Statistical Series, No. 50.)

nance. Walking and eating alone are usually achieved by the latter part of this period. Nutritional deficiencies are thus particularly likely to be the fault of the person who designs the diet or feeds the infant. Likewise, infections are brought to the infant in contrast to his going to them, as he is more likely to do in the toddler and school years. These factors are important, since they make preventive measures more effective and simpler to apply during infancy. The infant is not only more susceptible to infections and nutritional disorders, but also in general has less resistance to them, and for many of them has clinical patterns which are distinctive. He has some degree of passive immunity during the first four to six months of life for measles, diphtheria, scarlet fever and poliomyelitis if the mother has had them, but not for the other common contagious diseases or for pneumococcal, staphylococcal, streptococcal or influenza infections.

The mortality rate for the second to the twelfth months of the first year of life is less than that for the first month alone (Fig. 2).

Analyses of the mortality rates reveal that infant death rates are consistently higher for males than for females in all races, higher in the other races than in the white race, higher for infants born in the winter months than in other seasons of the year, and higher for infants born in rural areas than in cities. It has been demonstrated that the high rate of infant mortality among families of low economic status can be reduced by education of the mother in the technique of infant care. So-called well-baby clinics or stations have been significant in dispensing such information and may be one of the factors responsible for the mortality rate being lower for infants in urban than in rural areas. Intelligence, education, housing, and economic level are probably more important than racial factors.



**Preschool Age Factors.** This period, the earlier part of which is termed the toddler age, is a safer one than infancy. The preschool age is important because the health of the child at this period is definitely reflected in the school years. Emphasis should be placed on normal living, with ample opportunity for the child to explore and become acquainted with his expanding world. The "guiding hand," which seems to be a necessity in the complexity of modern living, must lead and restrain, but should not prohibit the child from developing his own natural pattern.

Adequate nutrition, immunization against the preventable diseases, education in the avoidance of the nonpreventable ones and in the prevention of accidents, early and adequate medical care for disease, and counseling in family living are the important factors. The goal is a physically sound, mentally alert,

socially adjusted candidate for entrance to school.

**School Age Factors.** The total mortality for the period from five through fourteen years of age is less than for the period of one through four years of age. Of particular interest is the reversal in recent years of the relative positions of infectious and cardiovascular diseases and cancer as causes of death (Fig. 6).

The expanding environment of the child during these years provides him with increasing opportunities for mental and social growth. Wise parents will permit their child the sense of self-determination without eliminating the sense of a haven at home where support will always be available when needed and, of equal importance, where confidence and love are continually present. Many of the preventable cases of juvenile delinquency

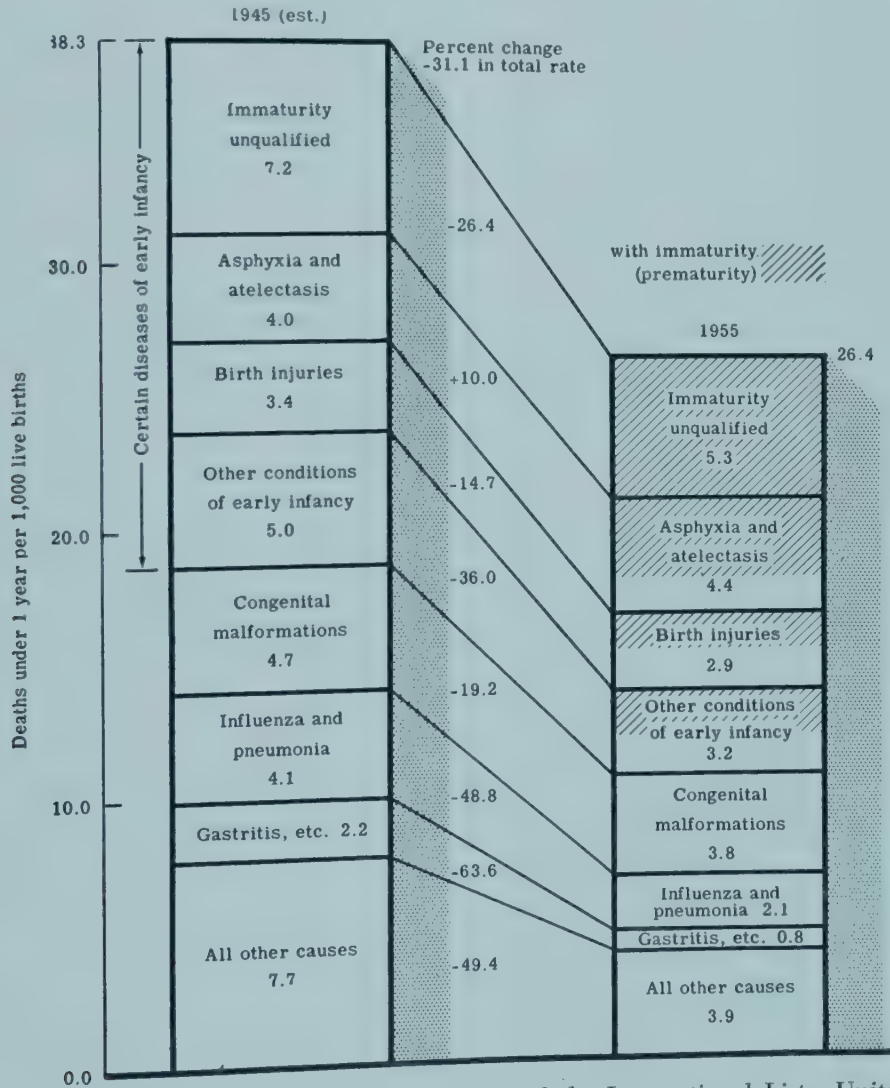


FIG. 4. Infant mortality. Main causes by Sixth Revision of the International Lists, United States, 1945 and 1955. (From Children's Bureau Statistical Series, No. 50.)

## INFANT MORTALITY, BY AGE, UNITED STATES, 1954

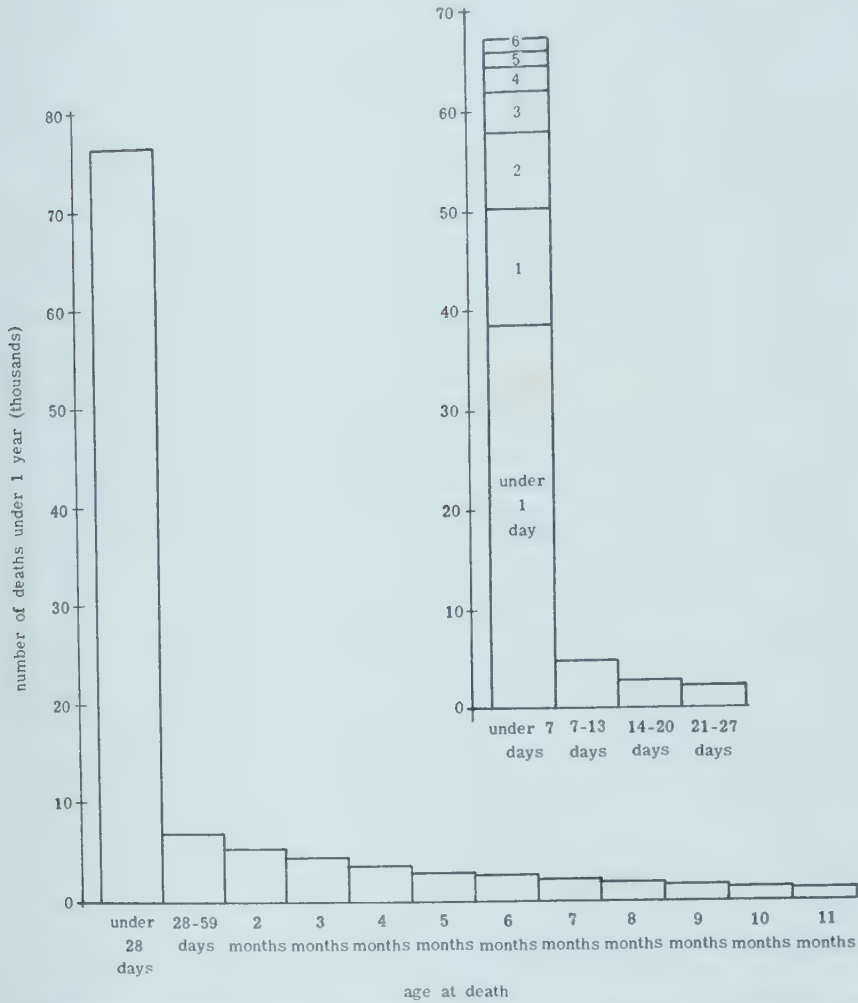


FIG. 5. Infant mortality by age, United States, 1954. (From Children's Bureau Statistical Series, No. 42.)

have their inception during these years. It is the wise physician who can assist in the problems of adjustment within the child's various groups—his family, school and playmates.

The goal is a physically sound, mentally alert, socially adjusted preadolescent child.

**Adolescent Factors** (see also p. 147). During this period there are tremendous physical and psychologic changes which under natural situations should occasion no difficulties. Unfortunately, "natural situations" prevail too infrequently. The physician who guides a child through the preadolescent years and understands him should have distinct advantages as the medical advisor for the adolescent years. But this can be true only if he understands the problems of this period and will give the necessary time to each of his adolescent patients.

The physical disturbances include such

chronic infections as dental caries, otitis media, tuberculous and nontuberculous pulmonary infections, rheumatic carditis, osteomyelitis, gonorrhea and syphilis; nutritional disturbances which range from undifferentiated malnutrition through the various specific nutritional deficiency diseases; and endocrine disturbances.

The onset of puberty and the rate of development during adolescence vary considerably from child to child. The rapidity of growth at this time makes the child especially vulnerable to detrimental influences, and one may expect that physical disturbances will have more significant effects upon growth and development than they do in the years of relatively slower growth between infancy and puberty.

The working adolescent child presents special problems. In part these are being met

by special legislation; but many factors center in the home and in recreational and educational facilities, besides those concerned with the type and place of work.

Health education, which should include adequate sex education, may be more effective at this age than at any other time of life. Behavior and social problems constitute a large part of adolescent care. Though emphasis should be placed on preventive measures in the preadolescent period, many maladjusted children will continue to require treatment. The problem of juvenile delinquency is especially urgent. Special clinics for adolescent children are doing much to meet the needs of this age group, and their extension is to be encouraged, as are increased provisions for vocational guidance.

**Handicapped Children.** Children with physical and mental handicaps present special

problems. The term "handicapped" implies a physical or mental defect not compatible with normal activity or achievement. Formerly much attention was centered on the orthopedic cripple, but in recent years interest has broadened to include almost all types of defects. Special attention is required for children with hearing, speech and sight defects, with cardiac disease, with tuberculosis, with orthopedic defects of peripheral and central origin, with mental retardation and with psychotic disorders. In addition to specialized medical attention, there is need for special classes, schools and institutions.

Initially, the problem is one of detection. Then the child must be thoroughly evaluated physically, mentally and psychologically. The family situation must also be appraised. All this usually requires a "team" approach. But the child and his family must have a single

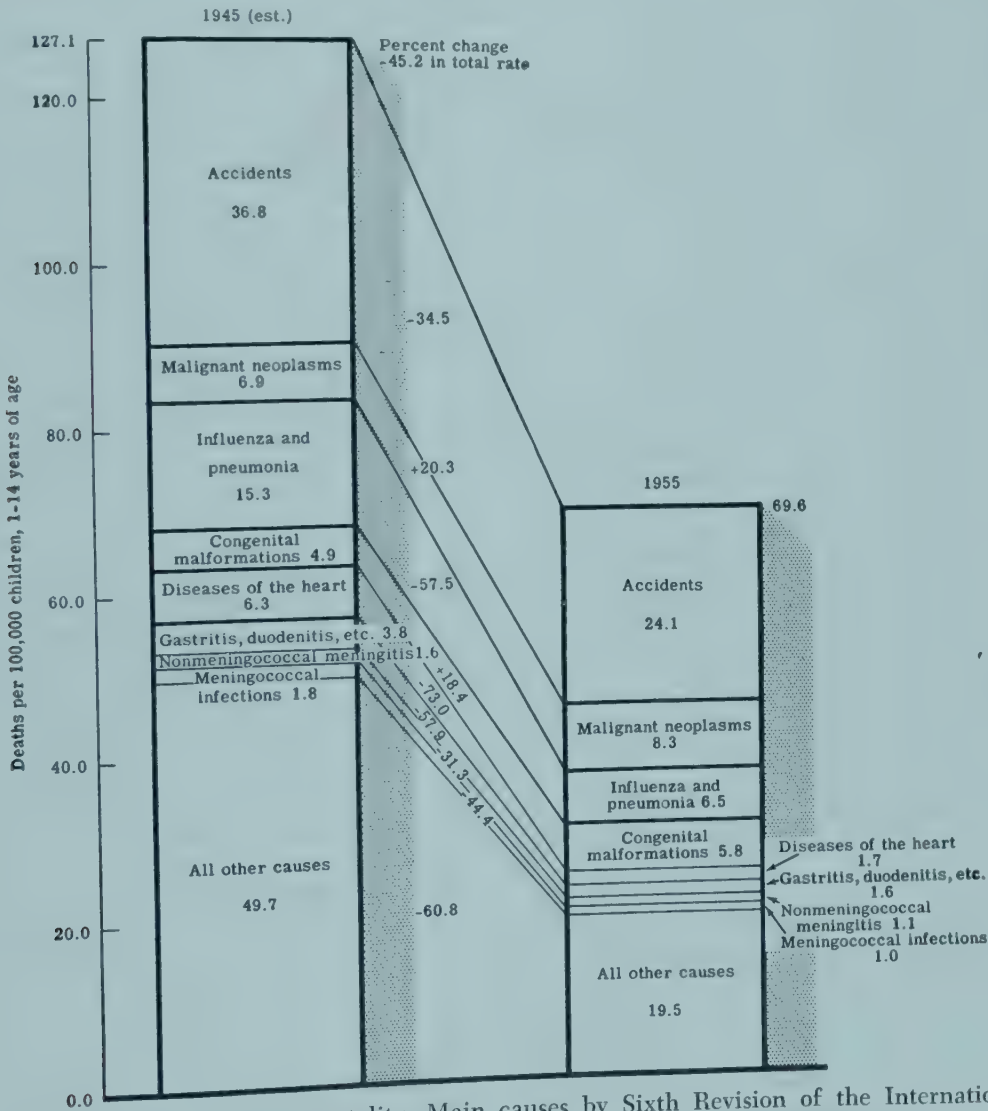


FIG. 6. Childhood (1-14 years) mortality. Main causes by Sixth Revision of the International Lists, United States, 1945 and 1955. (From Children's Bureau Statistical Series, No. 50.)



physician who assumes over-all responsibility and directs the program for the child. "Handicapped" children and their families must be treated realistically. Everything should be done which will provide the child with his optimal opportunities, but neither the child nor his family should be led to expect something which is impossible. Only to the extent that the "handicapped" child can be brought to a stage of independence compatible with his handicap can success be said to have been attained.

**Community Responsibility.** Health is a community problem. This does not imply that the individual must not assume personal responsibility or that the practice of medicine should not be a private enterprise. Certain aspects of health, such as control of communicable diseases, become the responsibility of the community merely for the protection of the uninfected. But other aspects are humanitarian ones. In a true democracy, health services should be the right of each child.

In his presentation before the White House Conference on Children in a Democracy in 1940, A. Graeme Mitchell stated the problem simply and clearly:

... It is obvious that proper physical and mental health cannot be expected unless there are good housing, proper clothing, satisfactory food, happy family life, facilities for recreation and education. . . . With heightened speed during the past decade, knowledge of the health needs of children has been acquired. . . . There is an obvious inequality in distribution of medical care in economic groups and in communities.

... Some families are able through their own resources to furnish good housing, clothing, food, recreation, education, and medical care to their children. Other families must face . . . unpredictable emergencies . . . which [cause] health as well as other essentials of family life to suffer. Then there is the group who are unable through their own resources to provide even the minimum needs.

... These inadequacies and many others constitute failure to protect the children of this democracy. All these inequalities are the concern of all of us—of the local community, the State, and the Nation.

**Individuality of the Child.** In the enthusiasm of solving a medical problem the physician often fails to recognize that he is dealing with a child who is sick rather than with a physical illness per se. Often the psychic disturbances of illness are as great as or greater than the physical ones. This situation is as true for infants and children as for adults. Thus in pediatric practice, interest should be primarily in the child and secondarily in his disease. Every disturbance should be viewed from the standpoint of its

effect upon the child and why it has such an effect.

## THE PEDIATRICIAN AND HIS PATIENT\*

Every child is an actor in a play; each phrase or deed is understood only as a part of his total role, and that role is meaningless except as a part of the total drama.

This role was pressed into his tiny hands long before he stepped upon the stage. Months before he was born, parents, relatives and neighbors "hoped it would be a boy" or "hoped it would be a girl"—lacking the courtesy to wait upon his arrival before deciding the part he must play. Indeed, his role goes farther back to the dreams, the tragedies, the triumphs of the early years of his parents. Who of us has not mended the disappointments of youth and adulthood with the promise that this child "will live it differently"? The role he is to play is often cast down to the last dotting of the "i" or crossing of the "t."

Children as actors differ markedly in what they do with their roles. Many, in comfortable security, accept and play the role as given to them. Many are tragically unsuited for the part they are expected to play—of the wrong sex, too intelligent, too retarded, too individualistic, too dependent, too frail for the titanic struggle or too eagerly adventuresome for a part that calls for docility. Some children forever grope in confusion to find the meaning of their roles, whereas others in ritualistic manner grow, go to school, work, marry, have children, amass a fortune, die—without ever having had the slightest idea of what it is all about. The pediatrician must understand these things and carefully assay the child's fitness to do what he is supposed to do.

Time should be taken to think of the family in its total setting. If the parents are over-anxious, mere irritation toward them accomplishes nothing. If the child is driven physically and mentally beyond his powers, the answer does not lie in exasperated denunciation, but rather in getting the family to assay its goals and values with more care. Every illness may be complicated—seriously so—by the family's call upon the child to be the Spartan or the dependent one. These compelling attitudes have a natural cause just as surely as do fever and pain.

It is important to know what the child means to each parent. Sometimes anxious

\* Originally written for the fourth edition by the late James S. Plant.

concern over his illness is a sort of emergency repair patch for a precariously thin marital situation. Just as often the physician will find a growing jealousy in one parent as the child absorbs the interest of the other. Some carry the care and expense of the child with poor grace; others glory in this and unwisely lavish too much in their joy of self-denial. An endless number of complaints about a child may mean that he has rudely broken in upon a "career" or the building of family fortunes.

The pediatrician may feel that these matters are none of his concern. But they are serious "complications" of every illness, and the basis of all sorts of pressing problems of child rearing that are brought to his office.

The pediatrician must also cultivate the practice of seeing the child alone and having him feel that his confidences are respected. The technique of the "own story" should be developed. This is a brief recapitulation of events, starting well behind the event under consideration. If one asks a child (or adult, for that matter) why he stole or played truant, he usually does not know. Many things we do are inexplicable as we look back upon them, but seemed reasonable when we did them. Thus the pediatrician must approach events as the child approached them. It is only as one sees what an act meant to the child at the time it was carried through that it can be understood.

The language of intelligence is words; the language of the emotions is the psychomotor tensions. One can tell a child that he has a fever; one has to show a child equanimity, courage, faith. The pediatrician cannot anxiously tell the parent to be calm, or hurriedly tell the child to be patient. We depend so much upon the written and spoken word that we fail to realize how utterly inadequate it is in the important field of the emotions. It is in the way that we talk, stand, walk, give advice that we transmit our most important messages.

In order to understand the activities and

reactions of a child, the pediatrician must have or acquire three fundamental attributes:

1. *Everlasting patience.* The "ortho" tendency, the fundamental drive to right the ship, is strong in all of us. Giving the child time and freeing him from adult anxieties and meddlesomeness are extremely important.

2. *Faith in the child's ability to solve his own problems.* Enuresis is the child's problem, as is petty stealing, lying and a legion of other matters that the parents or teachers are feverishly trying to solve for the child. When once the pediatrician has really won the child's confidence, he must persistently show his faith in that child's own ability to work out whatever his problem may be. It is not so much the pediatrician's task to stop the child's temper tantrums as to give him a fair and objective picture of what happens if they are continued.

3. *Ability to see the problem through the child's own eyes.* This is not to excuse—but to understand. Until the pediatrician has seen what the child is trying to do, he is working in the dark. Problem children are not trying to create problems—but to solve them. As fever and pain are normal reactions of normal people to abnormal conditions, so lying and stealing and persistent bed-wetting and temper tantrums may be normal reactions of normal children to unusual or abnormal conditions. In each instance the child is trying in his own way to solve a problem in human relationships.

In all these matters the pediatrician is in a peculiarly difficult position. His age and position of authority lead the child to feel that he is "just another adult." Thus he invites those same reticences, rebellions and bombastic aggressions that forced the parents to bring the child to him. Yet unless he resolutely attempts to approach the problems of childhood on this broader and natural basis, he remains a specialist in the diseases of children, rather than a specialist for children.

WALDO E. NELSON



# General Factors in the Care and Evaluation of Children

## PHYSICAL GROWTH AND DEVELOPMENT

### GENERAL CONSIDERATIONS

A knowledge of the growth and development of the human organism from conception to maturity is of basic importance to the physician who would attempt to care for infants and children and to advise parents as to the normality of their progress. The basic goal of the fetus, the infant and the child is to grow and develop toward an adult maturity which will represent for him optimal health and physical and mental fitness. Success, even survival, is dependent upon continuous though diminishing parental care and guidance and a protective environment. This care and protection should be adapted to each child's needs and capabilities.

The term "growth and development" as used in pediatrics applies to all aspects of progress of the human organism from conception to maturity. "Growth" refers to the changes in size resulting from multiplication of cells or increase in intercellular substances, whereas "development" refers to the maturation of structures and functions associated with this progress. It is not possible to distinguish sharply between the terms "growth" and "development," but the conjoined expression suggests a broader scope and a more complex set of factors than either term alone. Furthermore, it is now widely accepted as denoting all the chemical, physical and psychologic processes responsible for the closely inter-related changes in the forms and functions of all the body tissues, as well as the increasing capacities and purposeful adaptations acquired in the progress toward maturity. Growth is more readily evaluated than is development, because physical measurements are easier to apply and interpret than functional tests, but the latter must not be neglected. They progress together, but at times there may be development with little increase in size, or rapid growth with little differentiation in structure or function. The cortical function-

ing of the brain, for example, progresses in complexity long after measurable growth has ceased.

The rapidity of development and growth of the fetus magnifies the effects of unfavorable environment during gestation. The first two to three months after conception, during which organic differentiation is accomplished from a single-celled ovum, is a particularly critical time when adverse influences may result in congenital malformations. An understanding of the etiology of congenital malformations thus demands knowledge of the growth and development of the fetus.

Almost all disease processes and many congenital defects may affect some phase of growth and development. Some diseases simply retard growth or delay development, and natural adaptations make possible full recovery of lost ground. Others cause local or widespread tissue damage, arresting or permanently ending growth in certain parts. For example, poliomyelitis may affect only an extremity; encephalitis may affect the brain and, through it, the entire organism. Deficiencies of specific nutrients, notably vitamin D, distort growth in a characteristic manner, leading to deformities and disproportions which may not be fully compensated after the deficiency has been corrected. Deficiencies or excesses of specific hormones lead to delayed growth, overgrowth or disproportionate growth, to retarded or advanced maturation, to mental retardation and physiologic aberrations, or to various combinations of these.

In planning for the needs of a child, whether for food, sleep, activity or psychologic management, it is important to know not only what he is like as an individual, but also to understand how rapidly and in what ways he is changing. A general outline can be given for the care of the average child at a given age, but the details of the advice for a particular child should be determined after study of his physical and mental attributes,



the course of his development, and the way in which he has responded to the care and feeding already provided.

Proper assessment of a child's growth and development is essential as a guide for treatment of disease or disability. The best possible progress for the child who has genetic or acquired handicaps is promoted in various ways, but principally by helping the parents to understand the particular needs of their child at each age and to protect him from unfavorable environmental influences.

Thus the infant or child must be considered in respect to norms which are specifically applicable only to a given age or stage of development and which have wide ranges of individual variability. The many attributes, weaknesses and needs which are especially important and often peculiar to children of a given age, but which differ from those of the preceding and following ages, must also be taken into account. The changing characteristics and needs are understandable only after study of the main trends of growth and development throughout infancy and childhood, and of the patterns of variability encountered among normal children.

## GROWTH OF THE BODY AS A WHOLE

Although growth occurs continuously from conception to full maturity, it is by no means uniform from period to period, nor does it progress haphazardly by frequent spurts and rests. There are minor irregular fluctuations, especially in gains in weight, but for the most part increments of growth in any dimension or part of the body occur at predictable periods in accord with a characteristic pattern. This pattern for most parts of the body involves two periods of rapid growth separated by one of relatively uniform and slower increase. Each period is characterized by an accelerating rate of increase to a maximum, followed by rapid deceleration and a leveling off to a relatively slow increase, or terminating altogether in the part or parts concerned. The first of these cycles of rapid growth completes its accelerating phase during fetal life, and the decelerating phase extends throughout much of the preschool age period. The second cycle starts in the prepuberal stage and spans much of the second decade, or the years during which adolescent changes are taking place, and tapers off to a cessation of growth at maturity.

Most tissues and parts of the body participate in the cycles of rapid growth, so that

the increases in any measurement tend to reflect the general pattern. Nevertheless there are notable differences in the magnitudes of growth increments and in the timing of changes in the different parts or tissues. The peak of growth in length in the fetal cycle, for example, occurs about the end of the second trimester of pregnancy, whereas the peak of gain in weight occurs just before term (Fig. 7). The accelerating phase of the adolescent cycle, in contrast, begins earlier and is relatively greater in magnitude for weight than for height (Fig. 8).

The period of relatively uniform and slow growth which separates the two cycles of rapid growth has certain characteristics of interest, as shown in Figure 8. The increments in weight tend to increase slightly during this

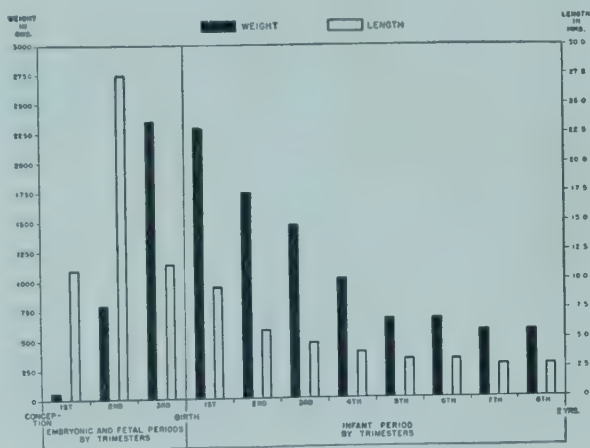


FIG. 7. Average increments in weight and length by trimesters during the prenatal and infant periods.

The data on growth in weight during the prenatal period are from Jackson (*Prenatal Growth of the Human Body*, Am. J. Anat., Vol. 9), and those on length from Hiss (*Unsere Körperform*, Leipzig, 1874), all adapted for this chart from figures by Feldman (*Ante-natal and Post-natal Child Physiology*, New York, Longmans, Green and Co., 1920). These data were obtained from a few cases at each age and from various sources, usually fixed specimens of calculated fetal age. They are used here since more accurate data do not appear to be available, and must be viewed from the standpoint of relative magnitude only.

The data on growth during infancy, in contrast, are from repeated measurements of the same group of living children studied in recent years by Stuart and his associates in Boston (derived from Table 9, p. 50). The columns for the fifth, sixth, seventh and eighth trimesters represent half of the 6 months' increments rather than actual 3 months' values. Although the true values for the prenatal increments of the latter group of infants would doubtless be higher than those portrayed, especially during the last trimester, it is clear that maximum growth in length occurs during the middle trimester of pregnancy, whereas that in weight occurs during the late fetal period.

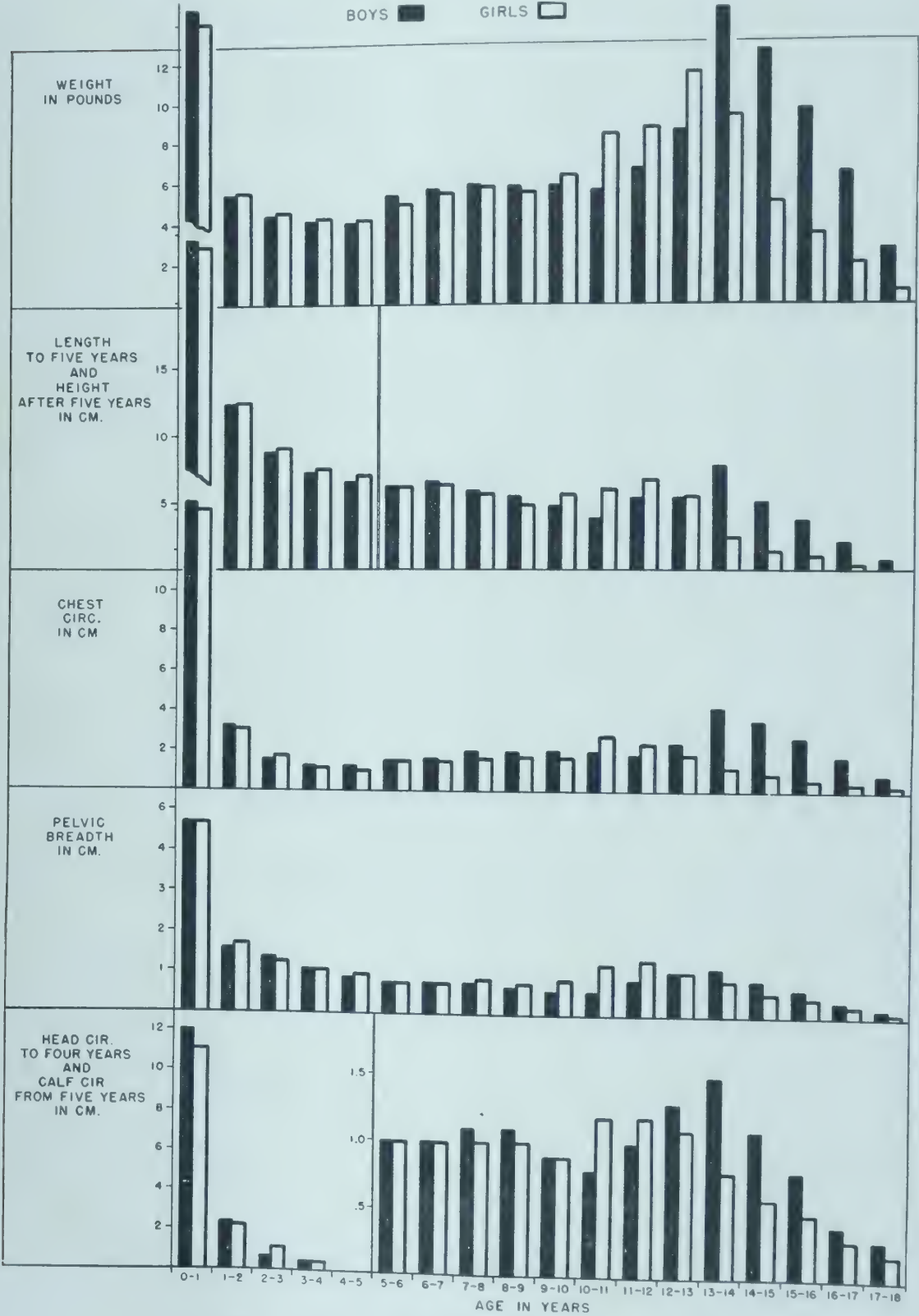


FIG. 8. Average increments by years in principal body measurements.

All increments were derived by the difference between the medians at succeeding ages. Measurements were obtained from one group of children under 5 years of age in Boston, and from another after 5 years of age in Iowa. The data from which these increments were obtained and further information regarding their source are given in Tables 10 and 11 (pp. 52 to 56).



period, while those in height continue to decrease. This is due in large measure to a relative enlargement in certain parts of the skeleton as shown in chest circumference and, to some extent, to an increase in muscle mass and subcutaneous tissue. The changes are so gradual that they are not readily recognized, but the total effect is to make the ten-year-old child appear more robust than the five-year-old one. This change is reflected in improvement in muscle tone and ligamentous support and hence in posture and other features of body mechanics. The child who matures slower than the average causes concern to parents because he stands out in sharp contrast to the majority of his classmates.

Some parts or tissues of the body participate in only one of the two periods of rapid growth, and some follow a different pattern altogether (Fig. 9). For example, the brain grows rapidly during the first cycle and ceases growth before the second cycle begins. It has attained about 25 per cent of its adult size at the time of birth, when total body weight represents only about 5 per cent of adult weight. About 50 per cent of its postnatal growth occurs during the first year of life and nearly 20 per cent in the second year: hence the importance of damage to the brain in infancy and the interest in head circumference as a measure of progress at this period. The genital organs, by contrast, grow relatively slowly during the first ten years and rapidly during the second ten years. They increase considerably in size after growth of the body as a whole has ended. The rate of increase of lymphoid tissue is relatively rapid throughout the first decade; at ten years of age there is normally nearly double the amount of this tissue that there is at maturity. This unique pattern must be kept in mind when assessing tissues such as tonsils and lymph nodes in childhood.

The data on the weights of organs at various ages are inadequate to define individual growth curves. The standards used to represent normality are based of necessity on post-mortem measurements and hence are of doubtful reliability for normal living structures. The growth of the eye follows the neural pattern; the ovary, testes and, to some extent, the uterus, the genital pattern. The spleen appears to follow the lymphoid pattern, but the liver grows in closer conformity with that of the body as a whole. The heart appears to deviate from this general pattern, as does skeletal muscle. The thymus gland is an exceptionally labile organ, increasing and de-

creasing rapidly in size within short periods. It appears to follow the general pattern of growth during the first five years of life. Between five and fifteen years it changes little in size, and thereafter its weight diminishes, simulating the pattern followed by lymphoid tissue.

The subcutaneous tissue tends to increase rapidly in thickness during the first nine months after birth, while growth of the body as a whole is decelerating. Thereafter it tends to diminish, so that by five years it is approximately half as thick as at nine months. During prepubescence it again tends to increase in amount and then decreases as the growth impulse diminishes. In certain physical types the panniculus may become as thick during adolescence as it was in infancy. Girls have a greater tendency than boys to accumulate or hold fat in the subcutaneous tissues at all ages (Fig. 10). When considering nutritional status, a thickness of subcutaneous tissue which might be proper at six months would indicate obesity at six years.

The growth of muscle (Fig. 10) follows a pattern somewhat similar to that of the body as a whole, but lags behind general growth

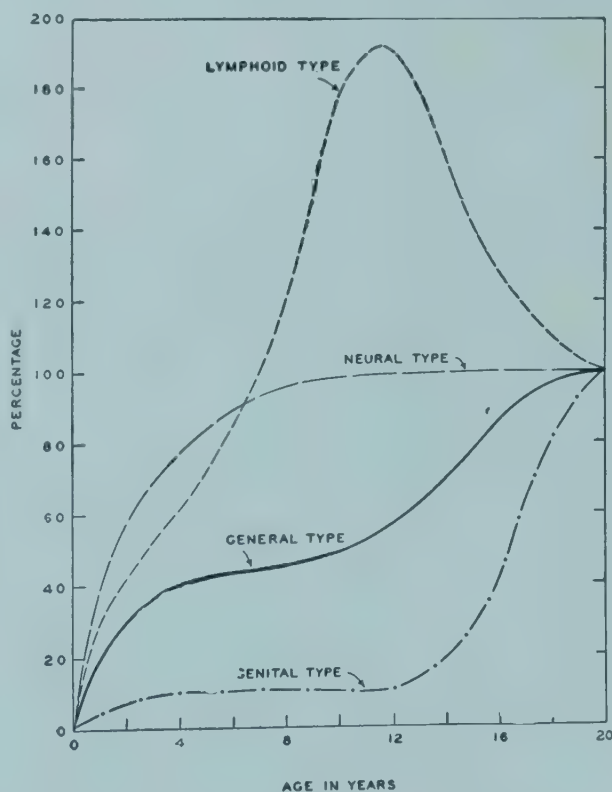


FIG. 9. Main types of postnatal growth of the various parts and organs of the body. (After Scammon: *The Measurement of the Body in Childhood, The Measurement of Man*. University of Minnesota Press.)



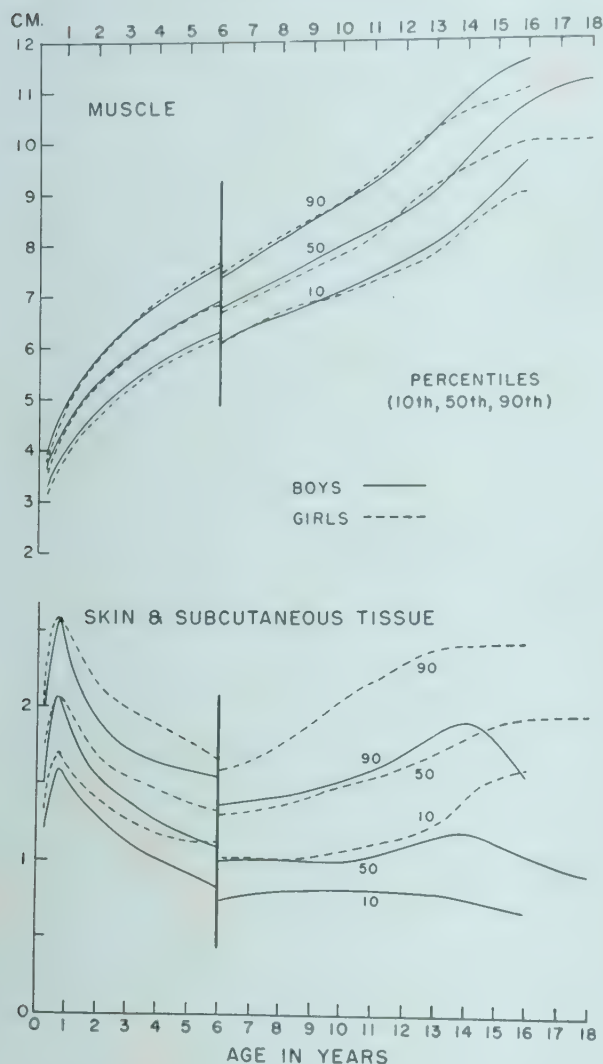
BREADTHS OF SOFT TISSUES IN CALF FROM  
A-P ROENTGENOGRAMS OF LEG

FIG. 10. Breadths of muscle and of double layers of skin and subcutaneous tissue at greatest width of calf by age and sex from 3 months to 18 years of age.

The graphs reveal the close similarity in pattern of the curves for muscle to those of general growth, but a unique pattern of increase and decrease and a marked sex difference in the skin and subcutaneous tissue. (For details, see Stuart and Sobel: *J. Pediat.*, Vol. 28, and Lombard: *Child Dev.*, Vol. 21. For distribution of subcutaneous fat in childhood and adolescence, see Reynolds: *Monographs Soc. Res. Child Dev.*, Vol. 15.)

during infancy and childhood and compensates by relatively rapid growth during the late stages of adolescence. Thus it appears to combine the pattern of general growth with that of the reproductive organs during the second decade. Growth of muscle, or its potential for growth, probably extends well into the third decade and is peculiarly dependent upon activity and nutrition. The bedridden or undernourished child may increase in stature

in a fairly normal manner, but muscles will not develop normally under these circumstances.

When increase in stature ceases, the adolescent is far from physically mature. His skeletal and cardiac muscular development is particularly short of its potentialities, and he does not have the strength or endurance usually attained during the last stage of development. Although he has reached his adult height, he has not attained the customary adult breadth of shoulders and robustness. The relative proportions of bone, muscle and subcutaneous tissue are shifting during this last stage of development, even though weight and height may be changing little. Furthermore, the boy or girl may appear fully mature from the standpoint of secondary sex characters and yet not be so in the primary sex organs and therefore not in reproductive capacity.

## CHANGES IN BODY PROPORTIONS

There is a general cephalocaudal progression of growth at successive age periods. This accounts for the relatively large head and short lower extremities at birth and the progressive changes in their relationships, as shown in Figure 11. From the second half of the first year of life to puberty the extremities grow more rapidly than the trunk, and both more rapidly than the head. At puberty the rates of growth of trunk and extremities are about equal, but the trunk continues to grow after the extremities have ceased their growth in the postpubescent period.

These differences in segmental growth rates cause changes in the ratio of the sitting height to the total height. The sitting height represents about 70 per cent of total height at birth, but falls rapidly to about 57 per cent at three years. By thirteen years in girls and fifteen years in boys this ratio has fallen to its lowest point of about 52 per cent and thereafter rises 1 or 2 percentage points. As with other measurements and indices, individuals differ considerably from the average, owing to their characteristics of build and the speed of their maturation, but they tend to be consistent in this index from stage to stage of development. Since the rapid linear growth of adolescence and the fusion of epiphyses in the lower extremities occur earlier in girls than in boys, girls tend to have a lower "sitting height-total height" ratio than do boys between eight and twelve years and a higher one between fourteen and eighteen years. This ratio is useful in confirming an impression of

unusual proportions in normal children and of gross deviations in abnormal ones. For example, in a boy with arachnodactyly this ratio fell steadily from 56 per cent at three years to 47.9 per cent at thirteen years of age, then rose to 48.8 per cent at sixteen years. Corresponding average ratios for normal boys are approximately 57, 52 and 52.3 per cent respectively. These data reveal the grossly abnormal overgrowth of the extremities in this disease. In contrast, the "sitting height-

total height" ratio of children with chondrodystrophy (achondroplasia) is abnormally high. One may recognize disproportions in this respect by comparing the percentile positions held by these two measurements in relation to their respective norms, without calculating the "sitting height-total height" ratio. For example, the boy with arachnodactyly maintained a sitting height in the range of the fiftieth percentile, whereas his total height was continually above the ninety-

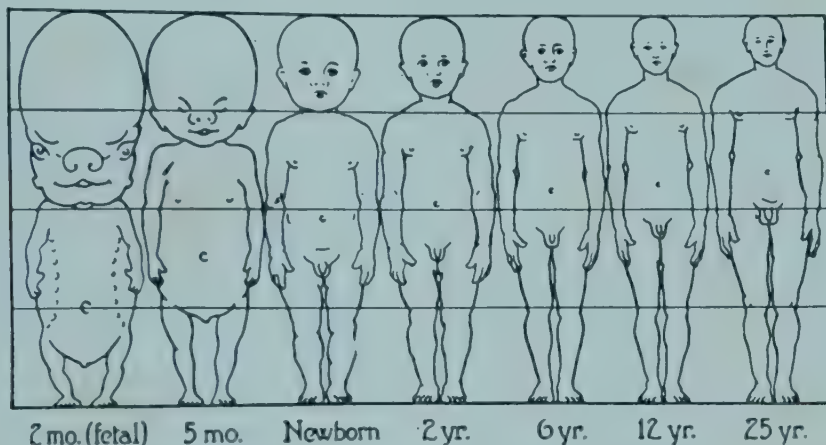


FIG. 11. Changes in body proportions from second fetal month to adulthood. (From Robbins et al.: *Growth*. New Haven, Yale University Press. By permission of publisher.)

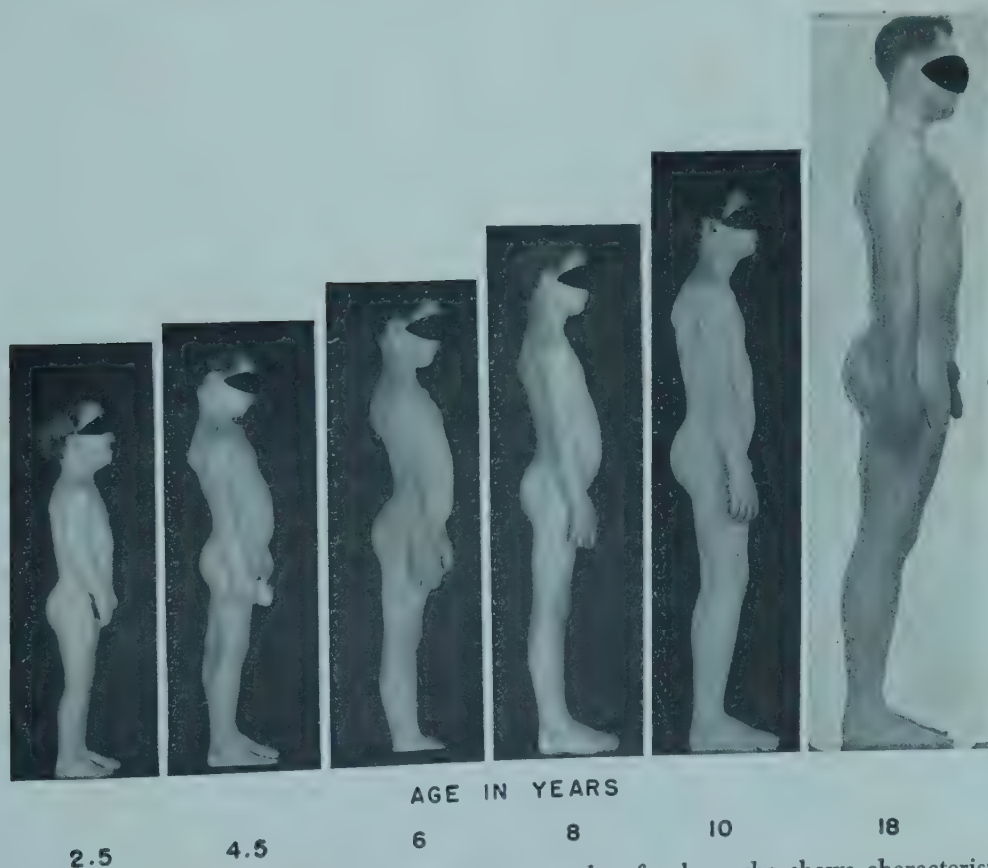


FIG. 12. Development of erect posture. Lateral photographs of a boy who shows characteristic developmental changes in posture. (From unpublished studies at Harvard School of Public Health.)



seventh percentile. Norms for sitting height are given in Table 13 (p. 60).

The normal development of erect posture involves a gradual transition from the primitive, four-footed relationships of spine, pelvis and lower extremities to their well balanced weight-bearing relationships in the adult. In the former the pelvis is tilted far forward on the femurs, and an erect posture is first attained in infancy by means of a lumbar curve, somewhat compensated by a developing dorsal curve. As a result of this lumbar curve combined with undeveloped abdominal muscles, lordosis and protuberant abdomen are characteristic of late infancy and the preschool years. Only gradually does the pelvis rotate upward and the mechanically more satisfactory adult posture become established. Appropriate erect posture is usually attained during adolescence (Fig. 12).

#### VARIABILITY IN GROWTH AND DEVELOPMENT

The range of difference of most human attributes varies widely in the several age periods of childhood. The extent of the differences encountered in the United States in individuals of the same age group in such physical attributes as size, build, rate of osseous development and age of sexual maturation is probably due in part to the heterogeneity of the population. Since race has much to do

with these and other physical characteristics, homogeneous groups would not be expected to show such extreme variations.

The curve produced by plotting the measurements of most biologic material comparable in regard to age or stage of development tends to simulate the so-called normal or bell-shaped distribution curve (Figs. 13, 14). The points of clinical interest in this natural phenomenon are as follows: (1) Normal children may be expected to deviate considerably from the average in either direction. (2) The greater this deviation, the more unusual is the child in respect to his colleagues,\* and the fewer there are like him. (3) There is no point in such a distribution at which one can say that normality ends and abnormality begins, but children in the extremes of the range or outside the range deserve careful study from this point of view.

Some measurements obtained from groups of children of the same age, however, tend to produce a distorted curve when plotted in this manner; the distortion usually takes the form of a skew to either the low or the high side of the average. Figures 15 and 16 show examples of normal deviations from the cus-

\* As used in this chapter, a child's colleagues refer to other children of the same sex, age, race or other grouping which might determine the distribution curve or extent of "normality" of any given part of the body or any attribute.

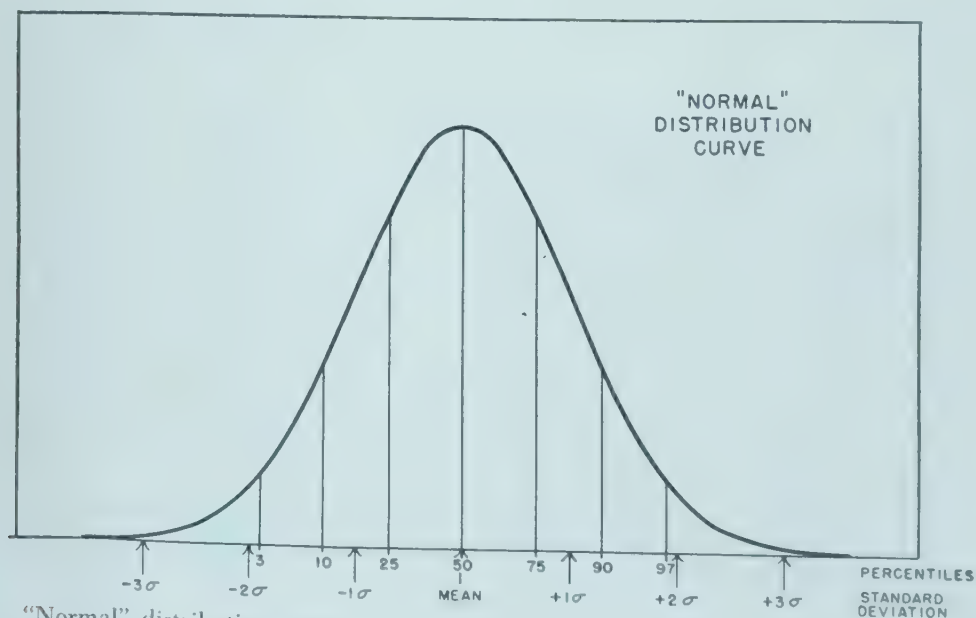


FIG. 13. "Normal" distribution curve. This theoretical curve represents a type of distribution characteristic of the range of variability between values for many measurements obtained from groups of children at a given age. The percentiles indicate certain positions within this distribution, as do the standard deviations with this curve in Figures 14 and 15.



tomary bell-shaped pattern. Hemoglobin values between nine and fifteen months show a skew toward low values and a sharp upper limit beyond which they do not progress. On the other hand, weights of boys of similar height at eleven years of age produce a curve with a skew toward the high side of the aver-

age. This indicates that at eleven years fatness is more common among boys than is thinness. Distributions of a variety of physical measurements obtained from large groups of children are available as standards of comparison for all ages. Whenever any of the measurements of a child deviate markedly from those

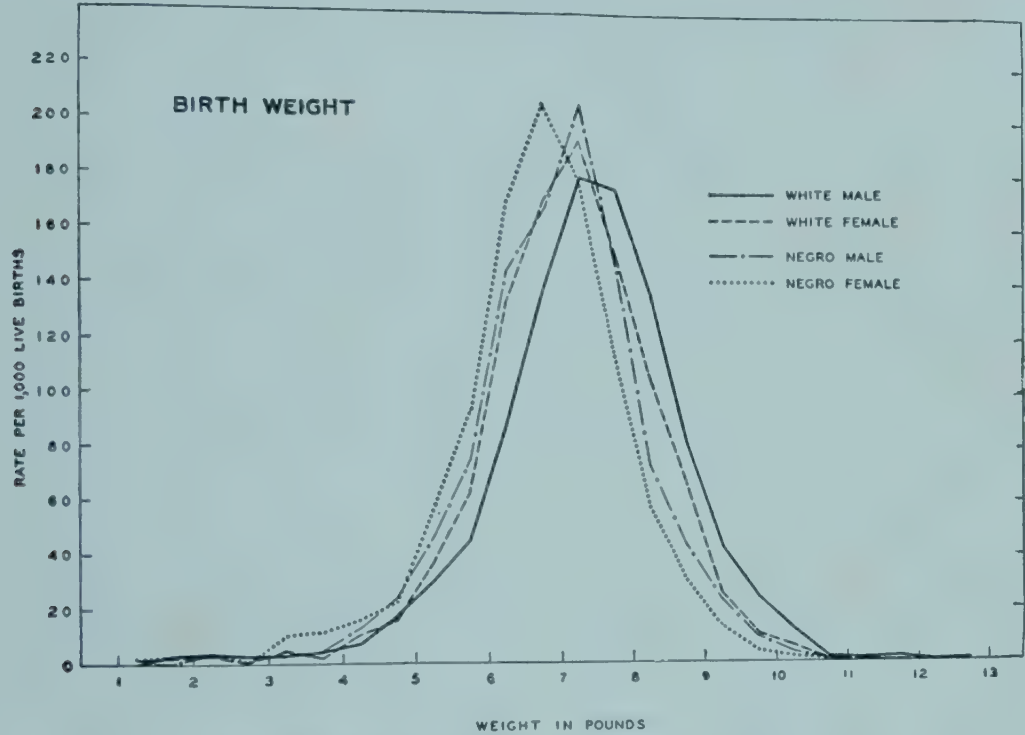


FIG. 14. Weight at birth; rates by color and sex per 1000 live births. (After Anderson, Brown and Lyon: Causes of Prematurity. III. Influence of Race and Sex on Duration of Gestation and Weight at Birth. Am. J. Dis. Child., Vol. 65.)

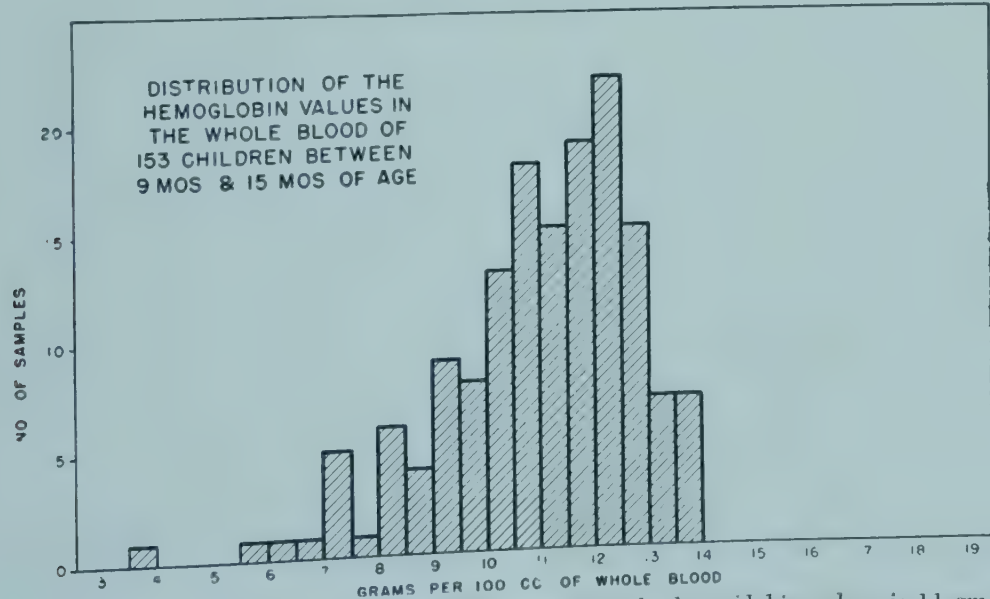


FIG. 15. Distribution of hemoglobin values. The mean for the hemoglobin values is 11 gm., somewhat below that of the greatest concentration of subjects. This is due in part to the inclusion of a few infants with anemia, causing a skew to the left, and in part to a physiologic limitation to the concentration of hemoglobin, causing an abrupt end to the graph on the right. (Values from Guest, Brown and Wing: Am. J. Dis. Child., Vol. 56.)

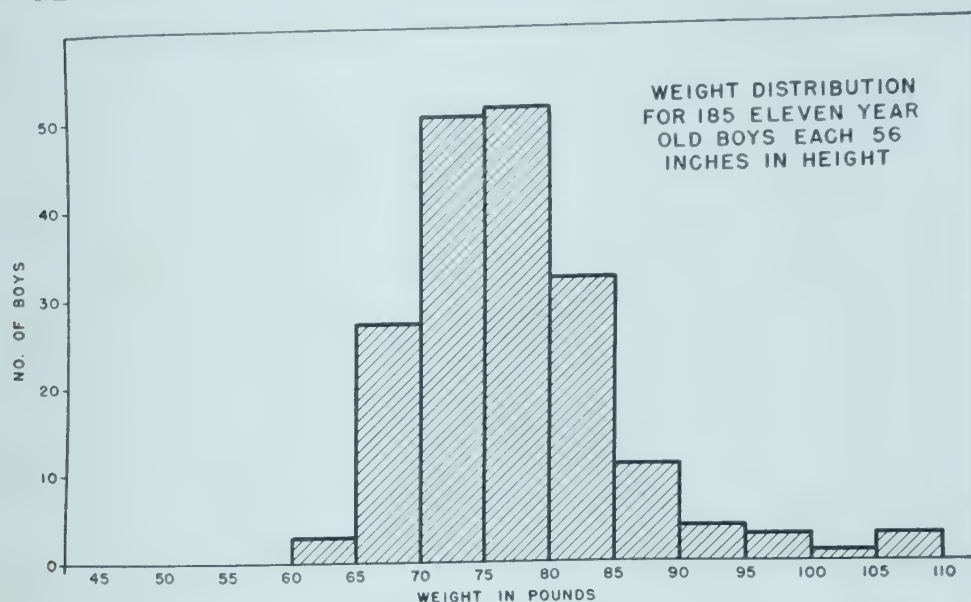


FIG. 16. Weight distribution of 185 boys. The mean for the distribution of weights is 77.2 pounds, within the range of the column of greatest concentration of values. There is a slight skew to the right of this curve, suggesting the inclusion of a few obese subjects. (Values from Franzen: School Health Research Monograph No. II. New York, American Child Health Association, 1929.)

of his sex and age group, an attempt should be made to discover the cause or causes.

Children also differ in the rate of development or maturation. This variability has particular importance during the adolescent years (p. 147), but it is present at all ages. For example, a baby may be small and immature at birth, either because pregnancy was shortened by premature delivery or because fetal growth and development was retarded, or the span of relatively slow growth which separates the infant and adolescent cycles of rapid growth may be longer or shorter than is customary. The variations in the duration of the several stages of development are often difficult to make clinically, but the need for recognizing them is constantly arising in the appraisal of children.

The principle of variability should also be recognized as applying to many aspects of development. Distribution curves based upon age of first sitting or walking, age of appearance of specific osseous centers, age of menarche, and the like, tend to show similar characteristics. Because of such variability, all norms of growth and development should be presented and regarded as ranges rather than averages.

### OSSEOUS (SKELETAL) DEVELOPMENT

There are normal sequences of developmental changes in the many centers of ossification in

the skeleton. The specific occurrences recognized in roentgenograms and significant in relation to the child's general level of development and normality of osseous maturation are as follows:

1. The centers of the small bones and the epiphyses and processes of the long bones begin to show calcification in a characteristic sequence and at fairly predictable ages.
2. The relative sizes of centers of ossification and particularly the interrelations between them.
3. The stage of development of a bone recognized by shape, contours and processes: so-called maturity indicators.
4. The sharpness of outlines of end zones or growth lines and the densities of shadows in these areas.
5. The relations between epiphyses and diaphyses: At first the breadth of the calcium-free zone between these parts is noted, but as the time of union approaches, the degree of fusion becomes significant.

The presence or absence of certain osseous centers is most significant in infancy; shapes and contours add much information in early childhood, and the relations between epiphyses and diaphyses are particularly noteworthy during adolescence. One can usually evaluate osseous development for clinical purposes from a roentgenogram of the hand and wrist.



Girls are more advanced than boys in osseous development at all ages, as in other aspects of maturation; this difference, slight at birth, is approximately two years at puberty. Thus separate norms for boys and girls are necessary. The variability among normal children of the same sex and age is so great, however, that at any given age some boys will be more advanced than some girls. In general, children tend to be average, retarded or advanced in osseous development to much the same extent at succeeding ages.

Advance or retardation in osseous development tends to correlate well with variations in other physical attributes. For example, the osseous developments of two girls, one of whom menstruates for the first time at eleven years of age and the other at fifteen years, will tend to be similar and more nearly that of the thirteen year average than that of girls of their own ages. Retarded osseous development during adolescence is closely associated with delay in the appearance of secondary sex characters, slow growth of sex organs, late occurrence of maximal adolescent growth and, in girls, late menarche. Retardations or advances in these respects during adolescence usually do not indicate pathologic disturbances in endocrine functions, but rather normal variability in the age of occurrence of physiologic changes.

Two features of osseous development should be considered: the general stage of advance or retardation for age, and the uniformity of pattern, indicative of orderly or uninterrupted progress. General growth is affected principally by endocrine abnormalities, as, for example, general retardation in cretinism and advancement with pituitary or adrenal cortical tumors and occasionally with hyperthyroidism. Minor general retardation or advance may be related to genetic factors, but retardation is often indicative of ill health or faulty nutrition. Therefore environmental as well as intrinsic factors must be regarded as possible explanations for retarded osseous development.

The second feature of osseous development requiring evaluation has to do with irregularities in the stages of development between individual bones. Little is known about the significance of these variations, but some of the deviations in the age of appearance of individual centers are undoubtedly due to genetic factors. It also appears probable that delays in the appearance of individual centers may be caused by illnesses or other trauma at

the time when the matrix should normally be laid down.

When osseous development is grossly retarded, it is customary to assign a skeletal (osseous) age to the child which may be compared with chronologic age, mental age and expressions of abnormality in other aspects of development. Various methods of appraising skeletal age have been developed, the *Atlas of the Hand* by Greulich and Pyle now being in wide clinical use as a standard of reference. An *Atlas of the Knee* by Pyle and Hoerr is also available. None of these can be used effectively without study and experience.

#### DENTAL DEVELOPMENT

The primary and secondary teeth erupt in characteristic sequences and at ages predictable within rather wide ranges of variability. Advance or retardation in the *timing* of eruption of teeth shows definite consistency. If the first tooth erupts early, subsequent teeth will usually do so throughout both dentitions. Age at the time of eruption appears to have a strong genetic predetermination. Eruption of teeth may be greatly delayed, however, by nutritional disturbances and by other conditions which inhibit growth in general. Retardation in the growth of the jaws may also interfere with the sequence of eruption as well as with the alignment of the erupted teeth.

The calcification of the teeth also proceeds according to a characteristic time schedule and sequence, starting about the fifth fetal month in the first primary teeth and continuing until the last permanent tooth is fully calcified in early adult life.

The quality or structure of the teeth, and hence their resistance to decay or other acquired defects, in some measure depends upon genetic factors, but internal and external environmental factors unquestionably play an important part. For example, maternal health and diet may exert considerable influence upon the fetal calcification of the primary teeth. Dental defects originating in utero are usually not recognized until the teeth have erupted. So, also, nutritional disturbances in infancy, particularly celiac disease, may scar permanent teeth being formed at the time, and these scars are not observed until after eruption during the school-age period. Although it is impossible to assign a specific cause to many of the dental defects, there is evidence that lack of vitamins A and D, of calcium and of ascorbic acid interferes with normal tooth development in fairly character-



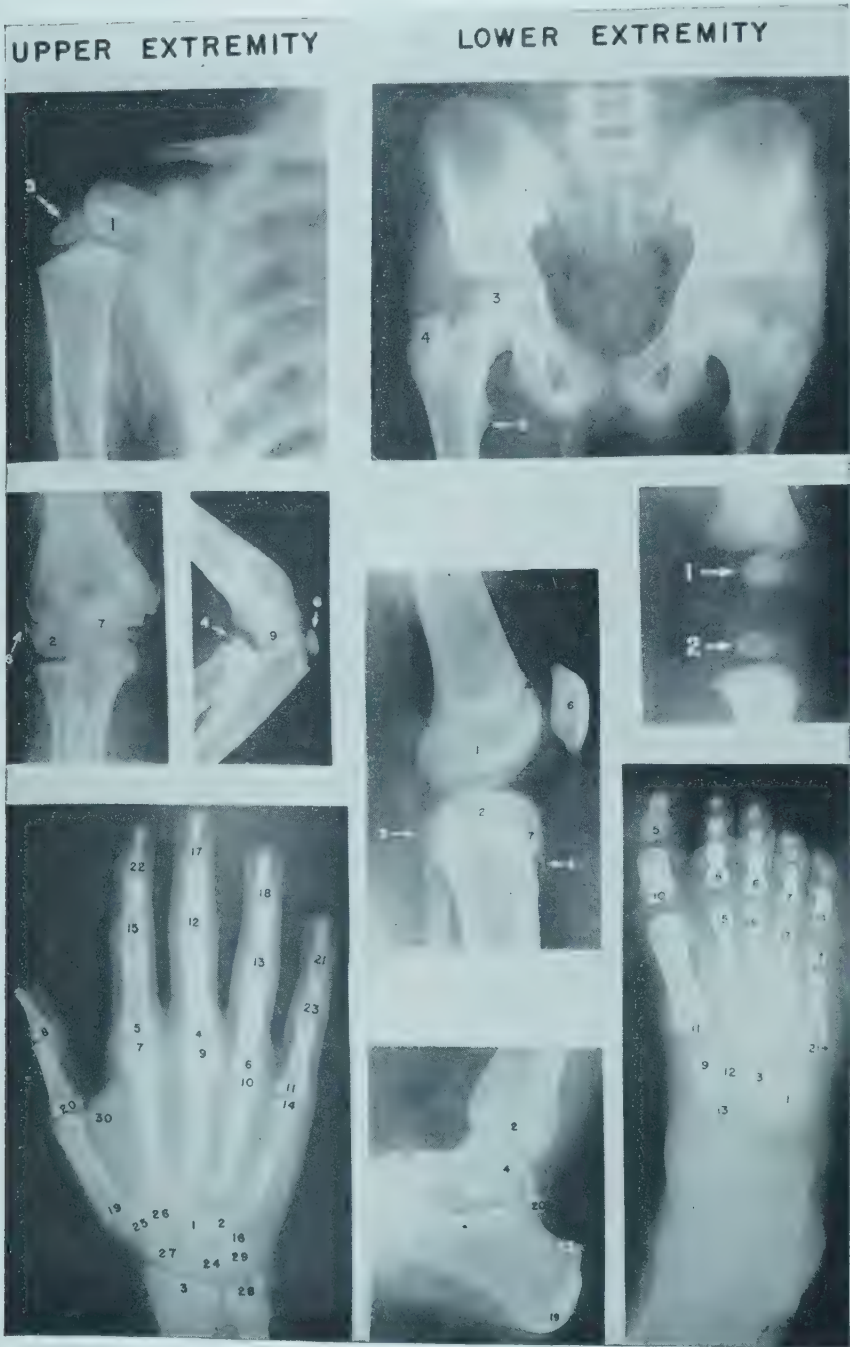


FIG. 17. Centers of ossification in the extremities for use in referring to Table 3.

Roentgenograms of children of different ages selected to show as clearly as possible the epiphysial centers of interest in each view and to identify them by the numbers which correspond to those in Table 3. (Figure prepared by I. Pyle, D. G. Shields, and W. H. Golden.)

Table 3. Ages at Onset of Ossification, Recognized by Appearance of Centers in Roentgenograms Useful as Maturity Indicators during Infancy and Childhood

BOYS			NO. CORRESPONDING TO CENTER IN FIG. 17	BONE AND OSSIFICATION CENTER	GIRLS		
Mean		Standard Deviation*			Mean		Standard Deviation*
Yrs.	Mos.	Mos.			Yrs.	Mos.	Mos.
Shoulder and Elbow							
3 weeks		—	1	Humerus, head	3 weeks		—
0	7	4	2	Humerus, capitellum	0	4	2
1	1	7	3	Humerus, greater tuberosity	0	6	3
5	5	15	4	Radius, proximal epiphysis	4	1	14
6	1	15	5	Humerus, medial epicondyle	3	7	12
—	—	—	6	Ulna, olecranon, 1	—	—	—
—	—	—	7	Humerus, trochlea	—	—	—
—	—	—	8	Humerus, lateral epicondyle	—	—	—
—	—	—	9	Ulna, olecranon, 2	—	—	—
Hand and Wrist							
0	2	2	1	Capitate	0	2	2
0	3	2	2	Hamate	0	2	2
1	1	5	3	Distal epiphysis, radius	0	10	4
1	4	4	4	Proximal epiphysis, 3rd finger	0	10	3
1	4	4	5	Proximal epiphysis, 2nd finger	0	11	3
1	5	5	6	Proximal epiphysis, 4th finger	0	11	3
1	6	5	7	Epiphysis of metacarpal II	1	0	3
1	7	7	8	Distal epiphysis, 1st finger	1	0	4
1	8	5	9	Epiphysis of metacarpal III	1	1	3
1	11	6	10	Epiphysis of metacarpal IV	1	3	4
1	9	5	11	Proximal epiphysis, 5th finger	1	2	4
2	0	6	12	Middle epiphysis, 3rd finger	1	3	5
2	0	6	13	Middle epiphysis, 4th finger	1	3	5
2	2	7	14	Epiphysis of metacarpal V	1	4	5
2	2	6	15	Middle epiphysis, 2nd finger	1	4	5
2	6	16	16	Triquetral	1	9	14
2	4	6	17	Distal epiphysis, 3rd finger	1	6	4
2	4	6	18	Distal epiphysis, 4th finger	1	6	15
2	8	9	19	Epiphysis of metacarpal I	1	6	5
2	8	7	20	Proximal epiphysis, 1st finger	1	8	5
3	1	9	21	Distal epiphysis, 5th finger	1	11	6
3	1	8	22	Distal epiphysis, 2nd finger	1	11	6
3	3	10	23	Middle epiphysis, 5th finger	1	10	7
3	6	19	24	Lunate	2	10	13
5	7	19	25	Greater multangular	3	11	14
5	9	15	26	Lesser multangular	4	1	12
5	6	15	27	Navicular (hand)	4	3	12
6	10	14	28	Distal epiphysis of ulna	5	9	13
—	—	—	29	Pisiform	—	—	—
12	8	18	30	Sesamoid in adductor pollicis	10	1	13
Hip and Knee							
(Usually at birth)			1	Femur, distal epiphysis	(Usually at birth)		
(Usually at birth)			2	Tibia, proximal epiphysis	(Usually at birth)		
0	4	2	3	Femur, head	0	4	2
3	6	10	4	Femur, greater trochanter	2	5	5
3	9	12	5	Fibula, proximal epiphysis	2	9	11
3	10	11	6	Patella	2	5	7
—	—	—	7	Tibia, tuberosity, 1	—	—	—
—	—	—	8	Tibia, tuberosity, 2	—	—	—

\* Standard deviation adjusted to nearest month. The range included between minus 1 and plus 1 standard deviation from the mean for any center will usually include about 68 per cent of a population of healthy children.

Note. The norms presented in this table represent a composite of published data from the Fels Research Institute, Yellow Springs, Ohio (Pyle and Sontag: *Am. J. Roentgenol.*, Vol. 19), and unpublished data from the Brush Foundation, Western Reserve University, Cleveland, Ohio, and the Harvard School of Public Health, Boston, Massachusetts. Compiled by Lieb, Buehl and Pyle.

Table 3 (Continued)

BOYS			NO. CORRESPONDING TO CENTER IN FIG. 17	BONE AND OSSIFICATION CENTER	GIRLS		
Mean		Standard Deviation*			Mean		Standard Deviation*
Yrs.	Mos.	Mos.			Yrs.	Mos.	Mos.
				Foot and Ankle			
2 weeks			1	Cuboid	2 weeks		
0	4	2	2	Tibia, distal epiphysis	0	4	1
0	4	4	3	Lateral cuneiform	0	4	4
1	1	4	4	Fibula, distal epiphysis	0	9	3
1	4	6	5	Distal epiphysis, great toe	0	9	3
1	7	5	6	Proximal epiphysis, 3rd toe	0	11	4
1	8	5	7	Proximal epiphysis, 4th toe	1	1	4
1	9	5	8	Proximal epiphysis, 2nd toe	1	1	4
2	1	10	9	Medial cuneiform	1	4	7
2	4	5	10	Proximal epiphysis, great toe	1	6	4
2	5	5	11	Metatarsal I	1	7	3
2	5	9	12	Middle cuneiform	1	7	7
2	7	13	13	Navicular (foot)	1	9	10
2	7	7	14	Proximal epiphysis, 5th toe	1	8	5
2	10	7	15	Metatarsal II	2	0	5
3	5	8	16	Metatarsal III	2	5	5
3	11	8	17	Metatarsal IV	2	9	7
4	5	10	18	Distal epiphysis, Metatarsal V	3	2	8
7	5	11	19	Calcaneus, epiphysis, 1	5	0	11
—	—	—	20	Accessory talus	—	—	—
—	—	—	21	Proximal epiphysis, metatarsal V	—	—	—
—	—	—	22	Calcaneus, epiphysis, 2	—	—	—

Age at Onset of Fusion in Skeletal Regions Useful as  
Maturity Indicators during Adolescence

BOYS	SKELETAL REGION	GIRLS
Modal Skeletal Age in Years*		Modal Skeletal Age in Years*
13.0 — 13.5	Elbow	
15.0 — 15.5	Begins in humerus	11.0 — 11.5
	Completed in ulna	12.5 — 13.0
14.0 — 14.5	Foot and Ankle	
15.5 — 16.0	Begins in great toe	12.5 — 13.0
	Completed in tibia and fibula	14.0 — 14.5
15.0 — 15.5	Hand and Wrist	
17.5 — 18.0	Begins in distal phalanges	13.0 — 13.5
	Completed in radius	16.0 — 16.5
15.0 — 15.5	Knee	
17.5 — 18.0	Begins in tibial tuberosity	13.5 — 14.0
	Completed in fibula	16.0 — 16.5
15.5 — 16.0	Hip and Pelvis	
after 18.0	Begins in greater trochanter	14.0 — 14.5
	Completed in symphysis	17.5 — 18.0
15.5 — 16.0	Shoulder and Shoulder Girdle	
after 18.0	Begins in greater tuberosity	14.0 — 14.5
	Completed in clavicle	17.5 — 18.0

\* Modal skeletal age is given for onset of fusion because satisfactory means and standard deviations are not available for these ages.



Table 4. Chronology of Human Dentition  
Primary or Deciduous Teeth

	CALCIFICATION		ERUPTION		SHEDDING	
	Begins at	Complete at	Maxillary	Mandibular	Maxillary	Mandibular
Central incisors . . . . .	5th fetal month	18-24 months	6-8 months	5-7 months	7-8 years	6-7 years
Lateral incisors . . . . .	5th fetal month	18-24 months	8-11 months	7-10 months	8-9 years	7-8 years
Cuspids . . . . .	6th fetal month	30-36 months	16-20 months	16-20 months	11-12 years	9-11 years
First molars . . . . .	5th fetal month	24-30 months	10-16 months	10-16 months	10-11 years	10-12 years
Second molars . . . . .	6th fetal month	36 months	20-30 months	20-30 months	10-12 years	11-13 years

Secondary or Permanent Teeth

	CALCIFICATION		ERUPTION	
	Begins at	Complete at	Maxillary	Mandibular
Central incisors . . . . .	3-4 months	9-10 years	7-8 years	6-7 years
Lateral incisors . . . . .	Max., 10-12 months Mand., 3-4 months	10-11 years	8-9 years	7-8 years
Cuspids . . . . .	4-5 months	12-15 years	11-12 years	9-11 years
First premolars . . . . .	18-21 months	12-13 years	10-11 years	10-12 years
Second premolars . . . . .	24-30 months	12-14 years	10-12 years	11-13 years
First molars . . . . .	Birth	9-10 years	6-7 years	6-7 years
Second molars . . . . .	30-36 months	14-16 years	12-13 years	12-13 years
Third molars . . . . .	Max., 7-9 years Mand., 8-10 years	18-25 years	17-22 years	17-22 years

Adapted from chart prepared by P. K. Losch, who carried out roentgenographic assays of the jaws of 1000 children in metropolitan Boston in 1942 at the Harvard School of Dental Medicine and provided the data for this chart.

Table 5. Age Periods of Life before Maturity

NAME OF PERIOD (SYNONYMS)	AGES REPRESENTED (APPROXIMATE)	EXAMPLES OF FEATURES CHARACTERIZING
Embryonic.....	1st trimester of prenatal life	Rapid differentiation Establishment of systems and organs
Early fetal.....	2nd trimester of prenatal life	Accelerating growth Elaboration of structures Early functional activities
Late fetal.....	3rd trimester of prenatal life	Rapid increase in body mass Completion of preparation for postnatal existence
Parturient.....	Period of labor and delivery	Risk of trauma and anoxia Discontinuance of placental circulation
Neonatal (Early infant; new-born).....	1st month of postnatal life	Initiation of respiration and other functions Postnatal adjustments in circulation
Infant proper (Middle infant).....	1 month to 1 year	Rapid growth and maturation Increase in functions, especially of nervous system
Transition (Late infant).....	1 to 2 years	Decelerating growth Progress in walking and other voluntary motor activities and in control of excretory functions
Preschool (Early childhood; run-about child).....	2 to 6 years	Slow growth Increased physical activity Further coordination of functions and motor mechanisms Rapid learning
School (Midchildhood).....	Girls: 6 to 10 years Boys: 6 to 12 years	Steady growth Developing skills and intellectual processes
Prepubescent (Late school or early adolescent).....	Girls: 10 to 12 years Boys: 12 to 14 years	Accelerating growth—rapid gain in weight Early adolescent endocrine and sex organ changes
Pubescent (Adolescent proper)....	Girls: 12 to 14 years Boys: 14 to 16 years	Secondary sex character maturation Maximum growth increase
Postpubescent (Late adolescent or youth).....	Girls: 14 to 18 years Boys: 16 to 20 years	Decelerating, terminal growth Rapid muscle growth and increased skills Rapid growth and maturing functions of sex organs Need for self-reliance and independence

Reproduced from Stuart: Introduction to Pediatrics; in Brennemann: Practice of Pediatrics. W. F. Prior Co. Vol. 1, Chap. 2.

istic ways. The fluoride content of drinking water habitually taken during the growth period has an important relation to the structure of the teeth, and oral hygiene is an important factor in protecting developing teeth from caries. The calcification of the teeth may be regarded as a permanent health record; teeth commonly show manifestations of past disease by changes in morphology and color.

Table 4 gives the chronology of human dentition from the standpoints of calcification and eruption, and, for the primary teeth, of their shedding (see also p. 623). The wide variability in age at the time of these occurrences is correlated only to a limited degree with general advance or retardation in growth and development; it appears to be in large measure an independent attribute. The sex differences are not presented separately, because the variability is not great, though, on the average, girls are slightly advanced over boys.

### AGE PERIODS OF LIFE BEFORE MATURITY

The years before maturity may be divided into periods characterized by certain features of growth and development. Although these divisions are not sharply delimited and are somewhat artificial, they form a convenient pattern within which to discuss growth and development. Table 5 lists these periods and indicates the principal features of each.

#### PRENATAL PERIOD

Study of growth and development should begin with conception, because the child has passed through the most rapid and hazardous changes associated with these processes by the time of birth, or at least within a few days after it. The incident of birth is important because of the physiologic changes required for extrauterine existence.

In the first trimester, or *embryonic period*, organogenesis proceeds rapidly and is almost complete by the end of the third month. During the first few weeks the future fetus is a self-contained organism deriving its nutrition largely from its own yolk granules. Damage to the embryo or abortion during this period is likely to be due to mechanical faults of implantation or to embryonic defects. During the remainder of the first trimester maternal disease and malnutrition may exert their most damaging effects. Each body part arises at a definite moment in a rigid sequence of fetal development. If the embryo is damaged—by rubella, for instance—organs or

organ systems forming at the time may be malformed or completely arrested. Unfortunately, many women are not aware of the hazards of disease and malnutrition peculiar to this phase.

The second trimester of pregnancy, or *early fetal period*, is a safer time for the developing organism. By the beginning of this period the fetus is a fairly complete human being with its organs differentiated and is largely beyond the danger of malformation. Implantation is secure; dangers of infection and abortion are slight. Maximum growth in length occurs during this period (Fig. 7), and by the end of the period the fetus has attained 70 per cent of the length it is to be at birth. It has laid down almost no subcutaneous fat, however, and has achieved only 20 per cent of its birth weight.

In the last trimester, or *late fetal period*, the developing organism is again beset by the hazards of infection and of abortion. Syphilis may be acquired at this time, and a luetic mother should start antisyphilitic treatment well before this trimester begins. This trimester is characterized by increasingly rapid gains in weight. Thus the fetus, which weighed approximately 700 gm. at the end of the second trimester, is gaining at a rate of over 200 gm. a week by the middle of the third trimester, to achieve a birth weight of about 3500 gm. Since mortality rates of premature infants correlate directly with their birth weights, every week that a mother continues to carry her infant toward term increases his chances of survival.

Fetal growth follows the cephalocaudal law, and the central nervous system grows rapidly, constituting 25 per cent of the body weight by the end of the second month of pregnancy. The possibilities of damage to this rapidly growing organ early in pregnancy are obvious. Even at term the central nervous system accounts for 15 per cent of the body weight, and premature infants have relatively large heads.

#### PARTURIENT PERIOD

At the end of approximately the tenth lunar month in utero the infant must pass through one of the most dangerous experiences as he traverses the birth canal. However, his body has certain attributes which help to protect him from the trauma of birth. He is well padded with subcutaneous fat to protect his internal organs and shield him from the shock of a cold, extrauterine world. He is limp, and



his joints are pliable; he folds with facility into a position mechanically advantageous for delivery. The sutures of his skull are patent, and the component bones can override to some extent with safety to allow easier birth of the head. His skeleton is still somewhat flexible, and pressure on his bones tends to bend rather than fracture them. Perhaps most important of all, his brain is much less sensitive to oxygen lack than is that of an adult.

Unfortunately, certain physical characteristics of the newborn make him vulnerable to birth trauma: The skull bones may override to such an extent as to damage his brain; the resultant shock is mildly evident in most infants by their drowsy, dazed behavior in the first hours of life, and is tragically evident in some in their limp musculature, subnormal temperature and difficulty in initiating extrauterine respiratory movements. Indirect evidence of the fragility of blood vessels in the newborn, and the ease with which intracranial vessels are torn, is found in the fact that in about 50 per cent of all neonates the cerebrospinal fluid reveals evidence of fresh hemorrhage.

The fetus makes respiratory movements prenatally; when he leaves the uterus, these movements normally become stronger and deeper. The first effective gasp must expand the lung, stretching its elastic fibrils and separating the cohesive, cuboidal cells of the alveoli. The lung is collapsed at birth and has none of the potential of the adult lung to spring back to a semiexpanded position when applied external pressure is released; hence most attempts at artificial respiration fail. The infant who does not begin to breathe spontaneously frequently has damage of his central nervous system and is in shock.

The liver of the newborn infant may extend 2 or more cm. below the protective thoracic cage and is vulnerable to injury, especially if rough tactics of artificial respiration are used. The adrenal glands, which have highly vascularized androgenic zones at this stage, are easily damaged, particularly in a breech delivery; such damage is usually lethal. The limp neck muscles may allow the cervical or brachial plexuses to be stretched and torn, or the vertebrae to be dislocated, by an overzealous operator.

The clavicles are the first bones to calcify in utero; fractures of the clavicle occur more frequently during birth than all other fractures combined.

Immediately after birth the umbilical cord

can deliver approximately 100 additional ml. of blood to the baby as the contracting uterus squeezes it out of the placenta.

The firstborn infant tends to be lighter in birth weight than subsequent siblings. This may be important to bear in mind when a mother has difficulty because of cephalopelvic disproportion with her first infant: Her second infant may not be deliverable by the pelvic route. In general, white infants are heavier than Negro infants at birth. Figure 14 (p. 19) shows the range of birth weights usually encountered in this country. There are considerable differences in the weights for other countries. Birth weight is a significant index of the state of development of the organ system of the body and therefore is valuable as an index of viability. It also reflects differences in maternal nutrition and socio-economic status.

In this country a birth weight of less than 2500 gm. ( $5\frac{1}{2}$  pounds) is used as the statistical criterion of prematurity. However, it will be seen from the foregoing that a Negro infant of 2000 gm. might be less immature than a white infant of the same weight. Data concerning premature births must be analyzed with further caution when they are obtained from countries where varying indices of prematurity are used, such as body length, foot length or a birth weight of less than 2272 gm. (5 pounds).

#### NEONATAL PERIOD

During this period, usually defined as the first month of life, although its main characteristics relate principally to the first two weeks, the neonate must make profound adjustments to his new environment. About 72 per cent of all infant mortality occurs in the first month of life, and half of this occurs in the first twenty-four hours.\*

In the first three or four days of life the infant loses weight. He may lose up to 10 per cent of his birth weight without causing concern; small infants lose proportionately less than large ones. This weight reduction largely represents loss of excess body fluid, and it is illogical to try to prevent it by forced feedings. Usually, by the fifth day, the infant begins to gain; many infants regain their birth weight by the tenth day, and most by the fourteenth.

\* Infant mortality is expressed as a rate which states the number of deaths under one year of age for every 1000 live births, and neonatal mortality is a similar rate for the first month of life.

Generous bottle feedings in the first few days of life result in a more rapid gain, and, though the breast-fed infant will usually gain more slowly, this slow gain is not an indication for adding cow's milk feedings to his diet.

The newborn infant has a strong hunger drive and will "root" about with his lips and tongue for milk. His sucking reflex is present at birth; his strong masseter muscles and his fat-padded cheeks (the "sucking pads") help to make this reflex mechanically effective. But the strength of his sucking depends directly upon the degree of his hunger, so that it is not wise to feed the infant water or sugar solution in his first two or three days if it is desired that he stimulate his mother's milk flow by strong sucking. Rarely the infant becomes dehydrated during these first few days before his mother's milk appears in adequate quantity. A decided loss in weight about the third day, associated with fever, is presumptive evidence of dehydration and is an indication for additional fluid intake.

The normal newborn is tense and lies with arms, legs and fingers flexed. The most accurate method for measuring the infant's length is to flatten him out on a smooth, straight, graduated board equipped with one fixed and one sliding upright.

The skin of the newborn is covered with greasy vernix caseosa. About the end of the first week of life the fine hair called lanugo, which may cover large areas of the body at birth, will have been shed. For the next two weeks the epidermis tends to flake off, especially if the vernix has been left in place; the mother must be told that this desquamation is normal and temporary.

The neonate frequently has small, capillary clusters or nonelevated hemangiomas on the nape of his neck, over the bridge of his nose or on his eyelids. These usually disappear before he is a year old and never require treatment.

Because of overriding of the skull bones the circumference of the skull and the size of the anterior fontanel may be smaller in the first few days of life than they would be otherwise.

The scalp may be covered with thick black hair extending well down over the forehead. Neither this hair, which will largely be shed and replaced by permanent hair, nor an absence of hair has any prognostic value as to future color, amount or texture.

The face of the newborn is round; the

mandible is less well developed than the maxilla, appears to recede, and is frequently asymmetrical in the first few weeks of life as a result of intrauterine pressures; the forehead is high and may appear to bulge. Small ethmoid, maxillary and sphenoid sinuses are present at birth and appear cloudy and opaque on roentgenograms because of redundant mucous membrane linings. Although the sinuses can become infected, they do not have great clinical significance at this time. The short, relatively wide eustachian tube, which enters directly into the pharynx, may easily convey infection to the middle ear and mastoid antrum, which are well developed at birth. The resulting otitis media may be masked by the fact that the tympanic membranes are still thickened by an internal layer of connective tissue which hides signs of infection and allows the ear drum to bulge only under considerable pressure. The mucoid material which fills the middle ear cavities and mastoid antrums in the first few days must not be mistaken for inflammatory exudate if the ear drum is incised.

The eyes of the newborn cannot focus. Extraocular movements are not usually coordinated in this period and may not be for several months. The sclera is distinctly bluish, the iris is usually unpigmented and gray-blue, and the optic disk has a peculiar grayish hue. Although the neonate reacts to bright light and to gross objects passed before the eyes, he has little true vision.

The lacrimal glands do not secrete tears until several weeks after birth. At the time secretion first appears the lacrimal ducts may not yet be open, and tearing may be noted. This is not an indication for attempts to open the ducts mechanically, since the condition is usually self-limited.

The frenum of the tongue of the newborn is normally short and tight. This does not mean that the baby is "tongue-tied" and is not an indication for slitting the frenum. The action of the tongue is not important in nursing, and the wise physician will not implicate "tonguetie" as a cause of ineffective feeding.

The chest is nearly circular, and the heart tends to assume a horizontal position, which places the apex beat at about or outside the left nipple line and in the fourth interspace. The lungs may require several days to achieve full expansion, especially at their bases, and basal rales heard during this period are not necessarily cause for concern.

The abdomen is protuberant because of



weak rectus muscles, large internal abdominal organs and sometimes considerable subcutaneous fat. A separation of the sheaths of the rectus muscle along the midline of the abdomen, *diastasis recti*, is not unusual and requires no treatment.

Normally, the umbilical cord mummifies and sloughs off cleanly at the junction of the cord membrane and the skin on the sixth to the tenth day. The blood vessels close functionally at birth, but do not obliterate with fibrous tissue until about the end of the third week. The thrombi which seal them during this period form dangerous potential channels for infection, and the umbilical stump requires special cleanliness for a week or more after the cord has dropped off. Umbilical hernias are common in the newborn, but must not be confused with the occasional umbilical puckering which involves only abdominal skin. These hernias should not be strapped in the neonatal period, because of the danger of infection.

The prepuce is always adherent to the glans and does not separate for several months. The practice of stripping it back at birth is to be condemned. If there is an opening in the prepuce sufficient to permit unobstructed urination, circumcision is not mandatory.

The legs are bowed. With the thighs flexed, the knees can easily be abducted until the legs reach nearly a 90-degree angle with the perpendicular. It is important to attempt this maneuver with all newborn infants and to repeat it in examinations throughout the first two months; failure of easy abduction is indicative of muscle spasm about the hip and is the earliest presumptive sign of a potential dislocation of the hip.

The complex changes in circulation which occur when the cord is cut are described on page 840, but these dramatic anatomic adaptations are not completed immediately. Normal femoral pulsations may not be palpable, and heart murmurs may be discernible for several weeks and may signify merely leakage of blood through fetal channels which have not yet been obliterated. "Cyanotic types" of congenital heart disease may not cause cyanosis in the early weeks of life. Therefore a diagnosis of congenital heart disease in the newborn infant should be made with great caution.

The thymus, which continues to grow rapidly until five years of age, when it has trebled its birth weight, is normally large at

birth and is revealed roentgenographically, especially in the expiratory phase of respiration, as a prominent shadow at the base of the heart. The thymus has never been directly implicated as a cause of respiratory difficulty, and radiation therapy of it, with its possible hazards, has become a rare procedure.

The newborn usually urinates soon after birth, but this event may be delayed for one or two days without causing undue concern. The early voidings contain uric acid crystals which may stain the diaper pink; such staining must not be confused with bleeding.

The infant has his first bowel movement soon after birth; the stools (meconium) are sticky, greenish-black and without odor. When he begins to ingest milk, these meconium stools change gradually to normal stools, usually at the end of the first week.

Within a few days after birth, owing largely to hormones absorbed from the mother, neonates of either sex may exhibit swollen, tense breasts from which milk ("witch's milk") may ooze. This is a physiologic reaction, and no harm comes of it unless attempts are made to squeeze out the milk; such a maneuver may cause formation of a breast abscess.

A few days postnatally there may be a mucoid or mucosanguineous vaginal discharge which is also the result of maternal hormones and is to be considered normal.

The newborn can usually raise his head while lying prone. There is little danger that the healthy infant will smother when allowed to lie on his abdomen, and many supposed instances of smothering have proved on post-mortem examination to be cases of overwhelming infection. Nevertheless it is prudent to use no pillow, to provide a firm mattress and to avoid constricting garments.

The peripheral circulation of the newborn often is not sufficient to keep his extremities as warm as the rest of his body, nor is this necessary. The mother should be reassured on this point, or she will keep her infant overwarm. She should also be told that the skin of the normal newborn usually takes on a mottled, purplish hue when exposed to air.

#### PERIOD OF INFANCY

During the period of infancy, the first two years of life, growth continues at a rapid, though generally decelerating, rate.

Gain in weight during the first three months of life averages approximately 1 ounce per day. However, these large increments



lessen steadily: by the age of five months the infant has usually doubled his birth weight, by the age of one year he has only tripled it, and he will be two and a half years of age before he quadruples it. His mother must be forewarned that the daily gain of 1 ounce which he accomplished in early infancy will not continue and that his appetite will be relatively less as his rate of growth slackens; otherwise she will worry over what she thinks is unsatisfactory progress and urge unwanted food upon him. It is in this way that many feeding problems arise.

Subcutaneous fat increases in amount until the age of about nine months, accounting for the traditionally chubby appearance of infancy, but diminishes thereafter (Fig. 10, p. 16). In the healthy infant this fat feels firm and is a valuable indicator of the state of his nutrition. This chubbiness must not be mistaken as an indication for putting him on a reducing diet. Nor must the normal loss of subcutaneous fat after this age period, when he is being transformed into a lithe, active child, be cause for worry about possible malnutrition.

Growth in length shows a similar progressive slowing up: The infant's birth average of 50.6 cm. (20 inches) is increased by 20 per cent at the age of three months, by only 50 per cent at one year, and by only 75 per cent at two years. He will not double his birth length until he is almost four years of age.

Head circumference increases considerably during the first year of life, owing to extremely rapid growth of the brain. The brain averages 350 gm. at birth and weighs two and a half times as much by one year of age, but less than four times its birth weight at full maturity. The circumference of the head should be recorded at intervals throughout infancy. Such information may provide the clue for early detection of significant intracranial disturbances. When increase in size is too slow, one should suspect failure of adequate brain growth resulting in microcephaly or of premature closure of the sutures (stenocephaly). When increase in size is too rapid, hydrocephalus may be developing, or there may be a space-taking lesion such as a subdural hematoma. The usual head circumference at birth of 35 cm. (13.8 inches) increases by 17 per cent at three months, but only by 25 per cent at six months, and 33 per cent at one year. At the age of six years head circumference has increased only

50 per cent over the birth measurement and has almost achieved adult size.

The circumferences of the head and chest are nearly equal during the first year in the average infant. Striking inequality in these measurements suggests an abnormality, either of the head or of the chest. Stem length corresponds closely in value to these two circumferences during the early months of the first year (Table 6), but thereafter becomes progressively greater.

Small defects in skull ossification which border suture lines are not unusual and are not to be construed as evidence of rickets.

The infant's skull has six fontanels, but only two are found on physical examination. The posterior fontanel has little clinical significance and may not be evident. The anterior, or bregmatic, fontanel, however, merits careful examination during infancy. It is at the junction of the frontal and parietal bones and averages about 2.5 cm. in diameter in the first weeks of life after molding of the skull from birth pressures has disappeared. It may increase in size during the first two or three months, but then normally becomes smaller and is obliterated between eight and fifteen months. A small anterior fontanel is suggestive of microcephaly; delay in closing is suggestive of rickets, cretinism or hydrocephalus.

The rapidity of growth during infancy probably accounts for the relatively large requirements for vitamins A and D and ascorbic

Table 6. Median Values for Circumference of Head and of Thorax and for Stem Length by Age in the First 5 Years of Life

Age		Head Cir- cumference		Chest Cir- cumference		Stem Length	
Yr.	Mo.	In.	Cm.	In.	Cm.	In.	Cm.
	Birth	13.8	35.0	13.0	33.0	—	—
	3	15.9	40.4	15.8	40.2	16.0	40.7
	6	17.1	43.4	17.1	43.4	17.6	44.6
	9	17.8	45.3	18.0	45.7	18.5	47.0
1	— 0	18.3	46.6	18.6	47.3	19.2	48.8
1	— 6	18.9	47.9	19.4	49.2	20.4	51.2
2	— 0	19.3	48.9	19.8	50.4	21.3	54.9
2	— 6	19.5	49.5	20.2	51.4	22.0	56.0
3	— 0	19.6	49.8	20.6	52.2	22.6	57.5
3	— 6	—	—	20.8	52.8	23.2	59.0
4	— 0	19.8	50.4	21.0	53.4	23.9	60.6
5	— 0	20.0	50.8	21.5	54.6	24.8	62.9

From studies at Harvard School of Public Health. For percentile distributions of these measurements by sex, see Tables 11 and 13 (pp. 56, 60).

acid; these must be given early and in adequate amounts if rapidly growing epithelium, mesenchymal tissues and bone are to develop properly. The infant requires large amounts of water daily (about 75 cc. per pound of body weight), since his basal rate of heat production per pound is twice the adult rate because of his relatively larger surface area. As the rate of growth slackens, the need of about 55 to 60 calories per pound of body weight in the early months decreases to about 45 calories at the end of his first year.

The feeding reflexes of the infant are not sufficiently mature to propel a bolus of food from lips to pharynx, where the swallowing reflex takes hold. Hence soft and semisolid foods should be introduced well into his mouth. The infant must be fed with patience in this early period, with the knowledge that he may unwittingly spit out much of what is fed to him.

Deciduous teeth are far advanced in development at birth (p. 25). The first teeth to erupt are usually the mandibular central incisors at about six months of age, but they may be delayed until the end of the first year. There are twenty deciduous teeth, of which all but the four second molars usually erupt between six and eighteen months of age. This is a period during which respiratory and other febrile illnesses are common; teething may occasionally be painful and is frequently accompanied by redness and swelling of the gums, but fever and convulsions can rarely, if ever, be attributed to this process. Most of the permanent teeth begin calcification during infancy; nutritional disturbances and infectious diseases at this time may cause defects which are not recognized until the teeth have erupted.

Vision seems adequate even in the young infant, though absence of cones from the retina during the first few months of life suggests that colors cannot be distinguished. The small eyeballs create a physiologic hyperopia which is slowly corrected in childhood as they grow relatively more in their anteroposterior dimensions. Extraocular movements should begin to coordinate after the first few months of life.

The infantile larynx is small, and minor infections with resultant edema easily impede the airway. After the period of infancy it grows rapidly, and babies who suffer from recurrent croup usually become free of this hazard after the age of two to four years.

The nasal passages in infancy are tiny, and minute amounts of secretion block them; it is fortunate that even the young infant can sneeze vigorously. Mothers must be reassured that sneezing is common and usually is not a sign of respiratory infection. The eustachian tubes remain widely patent and offer infection easy access to the middle ear cavities and the mastoid antrum.

After one month of age the sweat glands become more active. The overclothed infant may then be better able to control his body temperature, but he runs the risk of skin irritation from the resultant perspiration.

The infant differentiates between sweet and sour; oversweet feeding mixtures may create difficulties when unsweetened foods are introduced. His palate is keenly aware of temperature changes, and an artificial feeding mixture must be given at a temperature to which he has become accustomed; its temperature is not important, except that it be not unduly hot. There is no harm in giving an infant cold milk if he will accept it.

The infant's bladder has a powerful detrusor muscle, but sphincter control is weak and not yet under the influence of the cerebral cortex. It is futile to attempt bladder training before conscious inhibition of bladder emptying is anatomically feasible. This does not usually occur before the end of the first year, and the child may be two and a half or three years of age before bladder control is reliable. Bowel control, however, may begin as early as the eighth month.

Several typical reflex responses, resembling those of a decorticate animal, may be elicited. They are of clinical interest because their continued presence in the older child is abnormal. Stimulation of the lateral edge of the infant's foot elicits a *plantar* reflex, which may result in extension of the toes; the normal response of flexion should become established between the first and second years. Persistence of the infantile reaction after this time suggests a pyramidal lesion. Stimulation of the ball of the foot elicits a *grasping* reflex which persists until the age of standing. The *abdominal* reflexes may be elicited in about one third of newborn infants as a diffuse contraction of the abdominal muscles which may also involve the extremities; mature quadrantal responses should develop between six and twelve months. The *sucking* reflex, activated by stimulation of the lips or cheeks, is present at birth; its persistence after the first year may be considered abnormal. The *grasping*



reflex, by which the infant flexes his fingers and hands tightly around objects placed in them, resembles the forced grasping of an older person with a lesion of the frontal lobe; it should disappear between the second and fourth months. The *Moro* reflex, which consists in a symmetrical and consecutive outward, upward and inward grasping motion of the arms, is elicited by startling the infant, as by slapping his mattress sharply. A lack of symmetry of the movements suggests a brachial palsy or a fractured clavicle on the immobile side; the reflex may be absent in the presence of diffuse cerebral birth injury. This reflex should disappear between the third and fifth months. The *tonic neck* reflexes, which result in extension of the arm and occasionally of the leg on the side to which the head is turned and a flexion of the contralateral extremities, should disappear about the middle of the first year. The *otolith* righting reflex may not be present at birth, but should appear by the end of the second month and remain throughout life. It is elicited by covering the infant's eyes, holding him at arms' length in a symmetrical grasp and tilting him forward, backward and laterally; the reflex will cause his head to rotate in a direction which tends to keep it upright.

The sacrococcygeal curve of the spine is present at birth, but the remainder of the spine either forms one long continuation of this curve or is straight. Almost from birth the infant can raise his head from the mattress while lying prone, and the cervical curve develops as he begins to hold his head erect. By the third or fourth month he may be expected to sit with support, and by the seventh to sit alone. By the time the infant is eight or nine months of age he can usually stand with support, and at some time between the tenth and fourteenth months he can stand alone. Standing is first accompanied by a sharp lumbosacral angulation, since the pelvis remains tilted forward in the infantile position for some time. The infant may begin to creep at about nine or ten months, but some infants never manifest this transitory stage of motor development. Shortly after standing with support, the infant will walk if led and will usually walk alone at some time between the tenth and fifteenth months. The true lumbar curve and compensating dorsal curve gradually develop with walking.

By the time he begins to walk the infant has usually lost the bowlegs characteristic of

earlier infancy. Throughout most of his second year he walks clumsily on a wide base, with his legs apart and his feet out-toeing for better balance. His feet are pronated and appear flat, because relaxed ligaments allow the arches to sag, and fat pads fill their concavities. New shoes should be long enough to allow at least  $\frac{1}{2}$  inch beyond the limit of the big toe, because foot growth is rapid in this period. Proper shoes have straight medial borders, flat soles and firm heel structures against which the child may brace his feet in walking. Shoes should be discarded before they become so inadequate in length as to retard foot growth.

It was noted earlier that growth is relatively easy to measure, but that development, involving an increase in complexity of structure and function, is more difficult to evaluate. Table 7 presents certain norms for use in the general appraisal of infant development. Definite deviations from the progress indicated by this table call for study of the infant by a trained examiner. The accomplishments given for the different ages represent average ones; the actual range of normal achievement is broad.

#### PRESCHOOL PERIOD

The preschool years, ages two to six, encompass a period of relatively slow growth. With an average yearly gain in weight of less than 5 pounds, the child who tripled his birth weight in the first year of life manages only to double this one-year weight by his sixth birthday. He does little better than double his birth length during his first six years, but, growing relatively more in height than in weight, he appears to be tall and thin. By the end of this preschool period his head circumference has almost attained adult size.

The rapid changes of fetal and infant life have largely been completed, and the child is learning to coordinate motor mechanisms and functions which have been developing up to this time. He has learned to walk and to talk. He is incurably interested in the world about him and explores it with physical activity and questions which may tax the patience of his elders. This is his way of learning and developing, and it must be tolerated wisely.

Dental care is extremely important in this age group. The deciduous teeth number twelve less than the permanent teeth, but they fill the entire jaws until these structures begin to enlarge at about four years, in anticipation



**Table 7. Principal Motor, Social, Play and Speech Manifestations  
by Months of Age during First 2 Years\***

*One Month*

Generalized reaction to stimulation; mass activity; can hold chin up when prone; focuses eyes on object and watches person; cries from discomfort.

*Two Months*

Can raise chest when prone; eyes follow moving object; averts head from light; smiles at person and listens to voice; coos.

*Three Months*

Supports head steadily; reaches and misses; waves at toy; makes defense movements or selective reflex withdrawal reactions; listens to music; prefers mother; says "aah, ngah."

*Four Months*

Pushes with feet when held erect; sits with support; reaches for rattle; touches adult's hand; puts hand to mouth; plays with own hand; laughs aloud.

*Six Months*

Sits propped; squirms when prone; grasps and holds moving toy; puts toy in mouth; knows stranger; enjoys mirror; babbles to person.

*Eight Months*

Rolls over; sits alone; stands with help; pats toy; transfers it from one hand to other and puts it in mouth; discovers that toy falls down; plays with toes; stretches arms to come; calls for attention; pulls hair; practices consonants.

*Ten Months*

Stands if held; creeps; hitches; picks up pellet; points index finger; exploits adults; plays "peek-a-boo" and waves "bye-bye"; scolds; expresses joy; uses a word meaningfully; knows names frequently heard as own, siblings' or pets'; lifts on to hands and toes.

*Twelve Months*

Walks if led; pulls to stand and "cruises" by holding to furniture; exploits toys; notices babies; repeats words; recognizes sound and obeys "no, no"; plays "pat-a-cake"; draws adults into play.

*Fifteen Months*

Stands and walks alone; climbs stair steps; opens boxes; pokes fingers into holes; marks with pencil; names objects and familiar pictures; responds to familiar phrases.

*Eighteen Months*

Runs; puts block in hole; explores drawers and furniture; seeks help when in trouble; uses adjective-noun phrases.

*Twenty-one Months*

Climbs on furniture; jumps; explores further; obeys simple commands; uses verbs and pronouns.

\* Adapted from Mary Shirley, Harvard School of Public Health.

The sequence of appearance of these behavior manifestations is characteristic, but the age of accomplishment of each differs considerably within normal limits among individual infants. The reactions listed at each age are those customarily becoming manifest during the preceding interval. In using the table one must avoid the conclusion or even the implication that a child whose development is behind the schedule is necessarily retarded.

*Table 8. Illustrations of Average Development of Neuromotor and Mental Abilities from 2 to 9 Years\**

*Two Years*

Names familiar animals and objects such as dogs, cats, key, penny, watch; tells experiences; plays catch and toss with a ball; can run; can walk upstairs by holding onto railing; uses simple sentences and phrases; builds a tower of 3 or more blocks; can be taught to put away toys in proper place; folds paper once, imitatively; listens to stories illustrated with pictures; asks for things at table by name; helps to undress himself; can open doors; uses toilet during waking hours.

*Three Years*

Can tell whether a little boy or a little girl; repeats 3 numbers; enumerates objects in a picture; knows his own family name; repeats a sentence of 6 syllables, e.g., "It is cold and snowing"; may try to sing; jumps, tries to dance; can walk backwards; can go downstairs alone; can ride tricycle; attempts to draw pictures and to string beads; can copy a circle; plays simple games; can help dress himself; can unbutton clothes; can wash hands, and perhaps brush teeth; does not wet bed.

*Four Years*

Names 3 familiar objects in succession, e. g., key, knife, penny; repeats 4 numbers; uses scissors in cutting out pictures; points out longer of 2 lines; climbs well; plays games with several children; can count 4 pennies; can copy a square.

*Five Years*

Tells which is the heavier of 2 weights; repeats a sentence of 10 syllables, e.g., "His name is John, he is a very good boy"; reconstructs oblong card which has been cut diagonally into 2 pieces; names 4 colors, e.g., red, blue, green, yellow.

*Six Years*

Counts 13 pennies; knows whether it is morning or afternoon; defines common objects, e.g., fork, chair, table, in terms of what they are used for; obeys triple commands in succession, e.g., puts key on chair, brings box, shuts door; shows right hand and left ear; says which is pretty and which is ugly of a series of drawings of faces; describes the objects in a picture, not simply enumerates them.

*Seven Years*

Notices that certain parts are missing from drawings of incomplete figures; can copy a diamond; repeats 5 numbers in succession, e.g., "4, 7, 3, 9, 5"; can repeat 3 such numbers backwards.

*Eight Years*

Gives similarities and differences between 2 things from memory, such as fly and butterfly, wood and glass, paper and cloth; counts backwards from 20 to 1; repeats the days of the week.

*Nine Years*

Describes common objects in detail, not merely their use; knows the date; repeats the months in order; tells time; makes change out of a quarter, arranges 5 weights in order of heaviness; can repeat 4 numbers backward.

\* Adapted from data by A. L. Gesell, by J. S. Plant.

of the more numerous permanent teeth. Caries of the deciduous teeth nearly always begins during the preschool years and may spread rapidly. The deciduous teeth act as guides for the positions of the permanent teeth, the deciduous second molars being especially important in this respect. The permanent six-year molars, which erupt behind them, tend to drift anteriorly under normal circumstances. This drift is exaggerated when a deciduous second molar is lost prematurely; as a result, the permanent canine teeth, which erupt late, may be crowded out of line.

The preschool child should gradually overcome his infantile lordosis, learn to walk with a narrow base, and lose the waddle of infancy. Foot pronation should correct itself, and foot arches should begin to develop. The child may be expected to make great progress from an infantile toward an adult posture and gait. This is a period of relative thinness, loose ligaments and limited musculature, and constant physical activity during waking hours; hence chronic fatigue and functionally poor posture are common.

Table 8 presents illustrations of the average neuromotor development and mental abilities from two through nine years of age.

The lively interest of the preschool child in exploring his environment and many other matters causes him to have much less interest than formerly in eating. This must be dealt with by other means than attempts to force him to take unwanted food. Diet regulation, immunizing procedures, gastrointestinal and dermatologic difficulties are not the important items they were in infancy. Respiratory infections are common, but seldom serious, yet collectively they provide a considerable block of the medical problems of this age. The non-preventable contagious diseases are relatively frequent, but serious complications have been greatly reduced.

Accidents are the leading cause of death in childhood, killing more than 17,000 children each year in the United States. About half of the deaths occur in those under five years. During this time the physician can help parents teach their children the importance of accident prevention (p. 143).

Most frequently the preschool child and his mother need the physician's help and guidance in smoothing over the problems which arise when an easily controlled infant begins to exhibit a more mature personality and a stronger ego not yet controlled or socialized. His needs for independent, yet super-

vised, opportunities to explore his environment as well as for love and protection are greatly increased, and his attempts to fulfill these needs mean constant impacts against the family and home environment. The mother must be shown how to cope with these activities and needs in a common-sense, practical way so that the child is not completely frustrated, but explores his environment with safety to himself and a minimum of chaos to the family. Routine visits to the physician's office may often consist principally in interpretative and reassuring talks with the mother.

#### SCHOOL PERIOD

The so-called school period, six to ten years in girls, and six to twelve years in boys, is characterized by increasingly slow growth in height and increasingly rapid gain in weight, so that the child tends to lose the thin, wiry appearance of his preschool days. Growth in general is slow and will not deviate from this pattern until the onset of puberty, which is marked by an accelerated gain in height and a still more accelerated gain in weight.

In the school period the child is frequently exposed to the common communicable diseases. It is wise to follow his growth carefully during this time, since it may be affected adversely by malnutrition resulting from repeated infections or faulty habits of diet. The child may have insufficient time for breakfast, he may have a scanty lunch, and may show a general lack of interest in his diet, which is often poorly supervised. Some children, however, become progressively more obese during these years. This trend should be recognized promptly and its emotional as well as dietary causes sought.

Vision must be tested at least annually; refractive changes commonly result from growth in the anteroposterior diameter of the eyeball, and myopia may develop rapidly. As a result of middle ear infections or blockage of the eustachian tubes by lymphatic tissue, deafness is not uncommon. Hearing acuity should be tested at least every two years, or whenever progress in school becomes unsatisfactory.

Lymphatic tissue reaches the height of its development in this age period, and large adenoids and tonsils are physiologic. Size alone is not an indication for their surgical removal unless they are foci of infection or cause serious mechanical obstruction.

The vertebral bones and ligaments are still



relatively malleable. Long hours in an ill-fitting chair before an inappropriately sized desk and other undesirable postural habits result in functional, and ultimately may lead to permanent, structural curvatures of the spine. The child of this age should have overcome his earlier lordosis, but if he has not done so or if functionally abnormal curvatures have developed, an effort should be made to develop better muscles and postural reflexes. Persistently poor posture is suggestive of chronic fatigue and malnutrition.

The bones of the face grow rapidly after late infancy. The frontal sinuses are fairly well developed by about six years of age, and all the sinuses become more likely foci of infection. The jaws begin to grow more rapidly about four years of age, as is evident in lengthening of the face, in spacing of the deciduous teeth and in extension forward of the previously receding mandible. This growth is so extensive that there is room for the first and second permanent molars to erupt behind the deciduous teeth. The six-year molar is the first permanent tooth to erupt and is the keystone for the permanent dental arch. Unfortunately, this important tooth is most susceptible to early and rapid decay. Because it often erupts before any deciduous teeth have been exfoliated and is difficult to see, many mothers mistake it for a baby tooth and neglect it until it has deteriorated beyond saving.

Orthodontic problems require consideration, but must be viewed with an appreciation of the correction which maturity may provide for the crowding, malalignment and malocclusion commonly present during the early period of the permanent dentition.

Pubescent changes characteristic of the beginning of adolescence begin to appear toward the end of this period. The physician must be alert to recognize them if he is to understand the basis for many of the complaints and problems and give appropriate counsel. Normal children may begin to manifest these changes as much as two years before or two years later than average expectancy. Clearly, children of the same age, but in such widely different stages of development, require different care and counsel.

#### ADOLESCENT PERIOD (see also p. 147)

This is the period in which the child "grows up" from childhood to manhood or womanhood. It is a period of profound changes in physical, physiologic, mental and emotional development. Endocrine and reproductive

organ developments result in sexual maturity, and other phases of growth and development are completed. It is difficult to define accurately the beginning of adolescence in the individual. Gains in weight increase in magnitude yearly from about five years of age, and the added spurt of adolescence may not be easy to demarcate except in retrospect. The rate of growth in height, however, which has been diminishing yearly from the time of birth, starts to increase again, and may be used as one of the indications of the onset of adolescence.

Figure 8 (p. 14) shows that gain in weight is relatively greater than gain in height during this time, and the adolescent tends normally to a stocky appearance, as he did in mid-infancy. The adolescent obesity which may result is important from both a physical and a psychologic standpoint. The effect on participation in sports and other activities, and hence on muscular development and body mechanics, may be profound; its effect on social adjustments and emotional life may be no less significant.

The gain in height is abrupt at the onset of adolescence and continues at a rapid rate for a year or two, and then decelerates with equal rapidity. Gain in weight persists for a longer time than that in height.

At all ages of childhood there are individual differences in the rates of growth, but these are far more important and confusing during adolescence than at any other period. Owing to the lack of conformity between developmental age and chronologic age, most children will deviate from their customary percentile positions temporarily at the time of their maximum adolescent growth. Each child, however, tends to follow a predictable pattern once the adolescent changes have been initiated.

Early-maturing subjects tend to exhibit greater spurts in growth than do those maturing late, but they terminate growth earlier. Hence the ultimate heights may not be very different from those of children maturing at a later age. In fact, early-maturing children who are very tall during prepubescence may be relatively short at maturity.

Food requirements and other needs will differ for those who mature at different ages: When late-maturing children are growing at their slowest pace, "average" children are in their period of maximum growth, and the most advanced have essentially completed it. Within each group, however, there will be

some who are naturally small and others who are naturally large, each of whom has a different growth potential. Furthermore, some adolescents are more advanced in one aspect of development than another; these asymmetries should be noted, since they may add to the stresses and misunderstandings of the period.

The tendency for girls to have more subcutaneous tissue than boys is exaggerated at this time, and obesity tends to be particularly disturbing to them. Boys, however, tend to develop much larger muscles. After growth in height has ceased and sex characters suggest that the boy is fully grown and mature he does not yet have the muscular development or, therefore, the strength of the adult. It is imperative that the adolescent receive adequate nutrition and have appropriate physical activity. The heart muscle may not develop so rapidly as the skeletal musculature, and the strapping, muscular adolescent boy may not have a heart as proportionately well developed.

In conformity with the law of cephalocaudal progression of growth, leg length increases rapidly during early adolescence, but slows down and ceases before growth of the trunk is terminated. Thus the adult loses the long-legged, gangling appearance of the adolescent. Girls become relatively broad-hipped from about the age of twelve, whereas boys grow rapidly in shoulder breadth from about the age of thirteen.

Skeletal size increases markedly in adolescence, especially in boys. Certain stages of osseous development parallel so closely secondary sex development that they can serve as an index of the degree of maturation: For instance, menarche usually occurs within six months after beginning fusion of the epiphysis and diaphysis in the distal phalanx of the second finger. In general, at the time of adolescence, girls are two years in advance of boys in osseous development and in other aspects of the maturing process.

The development of primary and secondary sex characters follows a natural sequence with great consistency, but there are differences in the chronologic ages at which different milestones are passed. Hence there is a wide range in the size or general appearance of the sex characters and the functional state of the sex organs of boys or girls of the same chronologic age, especially between ten and eighteen years of age. The nutritional, psychologic and social needs vary with the stage of adolescence. The development of sex characters is

a helpful guide by which to judge these needs at a time when chronologic age is an uncertain and often misleading index of expected growth and development.

The male primary sex organs are the testes, the epididymes, the seminal vesicles, the prostate and the penis. They are rudimentary structures in infancy and largely remain so until the onset of the adolescent period, when there is rapid growth until the sixteenth to the twentieth year. Prostatic secretion appears fairly soon after that gland has begun to enlarge, but mature spermatozoa are not usually found until fifteen or sixteen years of age. The capacity to reproduce is probably not present until general growth has become slow, after most of the epiphyses of the long bones have fused with their diaphyses, and when all the secondary sex characters are well advanced—sometime after the sixteenth year.

The development of the principal male secondary sex character, adult body hair, is a useful index of the development of less easily recognized but more important sexual attributes. The character and distribution of hair should be noted in four locations in the routine examination of adolescent boys. It appears first in the pubic region, about the time of the adolescent growth spurt, as fine, vellus hair, which changes slowly to a coarse, dense, pigmented type which finally curls or kinks. About the time when growth begins to decelerate, the pubic hair has spread laterally to the inguinal creases and upward to the pubic crest, forming the inverted triangle characteristic of adult female distribution. Toward the end of adolescence and appearing as a convenient index of approaching sexual maturation, pubic hair extends upward toward the umbilicus and outward to the femoral areas of the thighs to form the diamond-shaped distribution characteristic of the adult male. Some months after the appearance of pubic hair, axillary hair makes its appearance, and subsequently facial hair begins to grow. About this time, but often considerably later, the hairline of the forehead may begin to recede on either side, producing the laterally indented configuration of the masculine type. The extensive development of mature hair on the chest and extremities comes last of all and may continue well into adult life.

About the time of the appearance of axillary hair, some development of the breasts in boys may occur, with elevation of the nipples and occasionally a mass of firm tissue under-



lying a slightly full areola which disappears after a number of months. Change of voice does not begin until these sexual changes are fairly well advanced, and the voice does not usually acquire the deeper tone characteristic of the mature male until the fifteenth year. The entire pattern of secondary sex character maturation rarely takes less than three years for its development and may take longer. Boys who begin to mature early tend to pass through this period rapidly.

The female primary sex organs, the uterus, the ovaries and the vagina, begin rapid growth about the age of eight or ten years, but do not reach adult size until the age of eighteen or twenty. Secondary sex characters are useful indices of this development. Throughout adolescence the hips round out, owing to broadening of the bony pelvis and an increased deposition of subcutaneous fat. Usually the earliest signs of beginning sexual maturation are evident in the breasts: Between the tenth and twelfth years the areolas enlarge and tend to embed the papilla. The enlargement is occasionally irregular and may simulate a small tumor; parents should be assured that this is a normal phenomenon. Eventually the breast itself enlarges, incorporating the formerly elevated areola, but leaving the nipple elevated. Usually the breasts are moderately well developed at menarche. About a year before the first menstrual period, and when the breasts have shown their first areolar changes, the vaginal tissues become hypertrophic and grayish; the reaction changes from alkaline to acid, and the epithelial cells become cornified. Hair appears first in the pubic region above or about the labia and spreads medially and upward to the crest of the pubis and laterally to the inguinal region. Lack of body hair above the pubis accounts for the characteristically triangular pattern of adult female pubic hair. Axillary hair appears about six months after pubic hair, and each progresses from a downy to a coarse, curly type.

Menarche occurs about the time of the appearance of axillary hair, between eleven and fifteen years of age, most commonly about thirteen years. During the first year of menstruation, periods are often irregular or entirely missed; some girls may even require a longer time to develop regularity. These early irregularities rarely are significant. Dysmenorrhea and irregularity seem to occur more frequently in girls of a "masculine" build. Conception seems to be unlikely until a year

after periods have begun. Indeed, from studies of promiscuous girls, it appears that conception is uncommon before the age of sixteen and not probable until four or five years after menarche. Thus the end of adolescence in girls may be placed at about eighteen years.

#### FACTORS AFFECTING GROWTH AND DEVELOPMENT, AND CAUSES OF INDIVIDUAL DIFFERENCES

An attempt is often made to distinguish individual differences or aberrations of growth due to heredity from those due to environment or disease. Such a distinction can be made for only a few constitutional characteristics and developmental defects. In following the progress of a child one must recognize, so far as knowledge permits, those attributes which are primarily expressions of his intrinsic make-up: that is, his appropriate physical habitus and characteristic pattern of growth. One must also distinguish these from physical manifestations which denote interference with optimal status and progress. In making such distinctions one should never overlook the possible interrelations between these influences or the opportunities for improvement of the constitutionally inferior or handicapped person by correcting defects or improving environment.

*Heredo-constitutional factors* (see also p. 234) are primarily responsible for the wide variability in the manifestations of normal attributes, such as stature and physique, and for individual characteristics of growth patterns. Abnormal genes are responsible for certain specific anomalies, familial diseases and certain types of dwarfism. Congenital defects, however, are not solely due to these factors. Many occur more frequently in some families than in others, yet not necessarily in accord with the mendelian laws. It would appear that genes differ in expressivity; a genetic factor may predispose to a specific defect, but environmental circumstances surrounding the embryo determine to some extent whether the defect becomes manifest and the degree to which the abnormality develops.

Environmental factors undoubtedly affect growth of the ovum and of the spermatozoon before conception, and development of the fertilized egg from the moment of conception to the delivery of the infant.

The order of birth appears to affect the infant's size at birth, the average firstborn being lighter in weight than the second, and



birth weight tends to increase with increasing birth order. The linear dimensions of the firstborn are also somewhat smaller than those of the later born. Measurements of infants born in different socio-economic groups indicate that on the average the newborn of the poor are smaller in length and weight than those of the well-to-do. There is accumulating evidence that the nutritional state of the mother and her long-time dietary habits are in some way related to the rate of linear and ponderal growth during the fetal period and to the progress of maturation as evidenced by the stage of osseous development at birth.

*Environmental forces* play a much more important part in determining the course of growth and development after birth, especially during infancy. There are real differences in the average sizes of infants and children and in their average rates of growth in relation to the socio-economic status of the families to which they belong and to the general local environmental conditions. For example, white boys in the United States of professional and managerial class families tend to be taller and heavier for their age than those of unskilled and semiskilled class families. Since adequate diet depends in part upon family income, these associations are not surprising.

**Sex.** At some ages boys are so different from girls in size, rate of growth, physical proportions and stage of maturation that entirely different base lines of normality must be adopted. However, all distributions of data for the two sexes overlap, and individual subjects tend to show certain characteristics of the opposite sex. For example, broad shoulders, narrow hips, thin panniculus, angular contours and tall stature are primarily masculine characters, but are seen in varying degrees in many girls. So, also, boys may have narrow shoulders, broad hips, thick panniculus, rounded contours and short stature, which are characteristically feminine traits.

**Race or National Origin.** Anthropologists have described many physical differences between national groups; a familiar example is the tallness of the Scot in contrast with the shortness of the Italian. Racial and national characteristics undoubtedly have developed in the main from segregation within geographic areas and the consequent transmission of genetic traits through common ancestry. It seems probable, however, that common environment and customs have influenced many national traits to an important degree. When

such customs are changed, many supposedly racial characteristics begin to be modified. For example, short stature is characteristic of the Japanese people, but each successive generation of Japanese children living in the United States becomes more like American children in stature.

**Inborn Metabolic Errors.** Recognized inborn metabolic errors are relatively rare, but when they occur, they often retard growth by interference with various metabolic functions; they include such conditions as cystinosis, "renal rickets," oxaluria, hepatic glycogen storage disease and galactosemia.

**Endocrine Factors.** Endocrine factors undoubtedly play an important part in establishing many "normal" variations as well as many of the gross deviations of growth and development. The activities of the glands of internal secretion are determined in part by heredo-constitutional factors, but many disturbances of them may be acquired. Nutrition, disease and other environmental circumstances affect hormonal activities. The glands of internal secretion, especially the thyroid and the pituitary, are the principal mechanisms through which heredo-constitutional and environmental forces are mediated to bring about individual differences and major deviations in growth and development.

**Prematurity.** Premature infants, as a group, have an increased incidence of birth injuries, including cerebral damage, congenital malformations, anemia, rickets, feeding problems, and infections. All these can affect growth adversely and add considerably to the difficulties of an infant who is small at birth and who would probably require two years to catch up with his full-term colleague without these complications.

**Congenital Defects.** Congenital defects may be due to abnormal environment during the embryonic period, as well as to heredo-constitutional factors. A classic example is the multiple defects often found in the newborn whose mother had rubella during the first trimester of pregnancy. Furthermore, congenital defects not only are caused by prenatal environmental influences, but may also themselves interfere with fetal or postnatal growth in a variety of ways. If the defect is incompatible with prenatal existence, the fetus will be stillborn; if it is incompatible with extra-uterine existence, death will occur at or shortly after birth. Some defects are compatible with life, but severely limit physiologic activities and adjustments, so that death

will probably take place during infancy or early childhood, when illness or other circumstance imposes special strain. Thus the unfit are in large part disposed of by natural processes in early life. Many defects, however, interfere not with essential processes, but rather with the development of special parts or organs and hence with certain functions. Mental deficiencies, central nervous system defects, including blindness and deafness, skeletal anomalies and defects of the heart and blood vessels and of the gastrointestinal tract and the genitourinary system may all produce characteristic handicaps of varying severity. They provide a unique set of problems to physicians who care for children. For permanently handicapped children the period of growth and development is one of special hazards, but is often also one of great opportunities.

Although congenital defects usually manifest themselves by specific signs or effects, they may do so only by interfering with general growth and may be discovered only through intensive studies. Defects in the central nervous, cardiovascular, urinary or gastrointestinal systems may be discovered only in the search for a cause for failure to grow normally, especially during the first few years of life.

**Climate.** Geographic or climatic conditions and seasonal circumstances appear to account for slight differences in size, maturation and rates of growth of children of given ages. Children tend to grow more rapidly in height during the spring than in the fall, and to gain weight much more rapidly in the fall than in the spring. Changes in physical activities associated with the length of daylight hours and the conduciveness of weather conditions for outdoor activities possibly have much to do with the slowing of gain in weight during the spring and the increase during the fall.

**Malnutrition.** Nutritional factors, both in health and in illness, undoubtedly account for a large proportion of retardations of growth and development. Lack of food, unwillingness to take suitable foods when provided, improper utilization of foods because of physical defects and illness, all contribute to interference with growth. Specific deficiencies as of vitamins C and D result in characteristic deviations from normal growth, but general malnutrition, principally owing to lack of adequate amounts of calories and suitable proteins, is usually manifest simply by less than optimal growth. Thus an effective means of

dealing with the under-par, malnourished child, in whom a careful search reveals no specific defects, is to study and correct dietary habits. This is usually a difficult and time-consuming undertaking, because social, psychologic and habit factors are almost always involved. The mechanism by which emotional disturbances influence growth is not always clear: it may be by simple anorexia or may be through a more complex psychosomatic device.

**Illness.** Infections, such as repeated attacks of acute tonsillitis or a chronic disease such as tuberculosis, create malnutrition by decreasing the child's appetite, interfering with the proper digestion and absorption of food-stuffs, and by increasing the metabolic need for nutrients. They may depress the bone marrow, and the resulting anemia can deprive the tissues of adequate oxygen. Chronic or repeated infections are probably the most frequent cause of malnutrition in American children. Illness may also cause permanent damage to particular parts or organs. When the nerve supply or circulation of a part is interfered with, as in a limb paralyzed by poliomyelitis, that part will not grow normally. The outcome will, of course, depend upon the age at which the injury occurred, but will be far more deforming and crippling than if injury took place after growth had been completed. Some diseases cause distortion of growth processes which creates deformities, as, for example, rickets.

Since most diseases are short-lived and there appears to be an adaptive mechanism through which growth rates may be accelerated during convalescence, the transitory effects of many illnesses are usually not recognizable. Chronically ill children may be retarded in one or many ways, the degree being greatest when there is interference with important life processes. For example, dwarfism is more likely with chronic anemias, cardiac defects which cause chronic cyanosis, renal diseases which interfere profoundly with function, and so on. Any chronically ill child, however, is likely to be less well developed than had he enjoyed good health.

**Activity.** Normal growth and development depend to a considerable extent upon adequate physical activity. Although a bedridden child will grow, his progress will be affected by the imposed interference with activity. The effects will be noted especially in the muscular system, but others also occur. Children's motor development is greatly affected



by their habits of activity, particularly during the adolescent period, when muscles are normally growing rapidly. Malnutrition, fatigue and inactivity are closely related, and a suitable balance between rest and activity, appropriate for age and circumstances, is a basic requirement for satisfactory development.

**Trauma.** Injuries may retard growth and development, but the factors and mechanisms involved are not clearly understood. They appear to be multiple and may be emotional as well as physical; tissue repair may constitute a nutritional drain; appetite failure may result from fear and pain; love and affection may be deficient.

#### **EVALUATION OF PHYSICAL STATUS AND OF THE PROGRESS OF GROWTH AND DEVELOPMENT**

Evaluations of physical status and the progress of growth and development should be integral parts of the child's routine pediatric care. The health history should provide a picture of the child's physical state at successive periods and the characteristics of his progress. This history is usually difficult to elicit satisfactorily except for the recent past and therefore is most serviceable when obtained periodically. The physical examination should include observations and appropriate measurements, calculated to bring attention to any undesirable features of growth and development. The physician whose training and interest limit his examination to the search for evident pathologic changes will miss much of importance. When unusual findings are discovered, special studies may be indicated, such as roentgenograms, more detailed measurements and laboratory determinations, but subsequent physical examinations will usually be necessary to determine the significance of such findings.

The physician must often evaluate the significance of unusual features of physical status, such as short stature, extreme linearity of build, apparent obesity, small or flabby muscles, peculiarities of posture. He must also consider the significance of slow growth or retarded progress in various aspects of development. His first problem is to determine the accuracy of the complaints. If they appear to be justified, they must be considered in respect to their causes and their significance for health and well-being. The significance of possible unusual growth or development should be viewed not only from the stand-

point of the moment, but also from that of the child's future growth and physical well-being. The parent requires and should receive considered advice on these matters, but appropriate advice depends upon correct evaluation and proper understanding of unusual findings. Attention will be focused here upon means of evaluating physical attributes in relation to standards based upon normal occurrences.

The physician can readily recognize unusual degrees of variation and can describe a child after inspection as short or tall, fat or thin, and in respect to many other attributes. It is difficult by inspection alone, however, to be sure that a boy is tall for his age. Sometimes thinness makes him appear tall when in reality he is shorter than the average for his age. More importantly, a physician cannot judge the extent of growth between two examinations on the basis of clinical descriptions. For example, if he rates a boy short at six years and then considers him so again at seven years, the question remains unanswered whether the boy has grown an expected amount during the year or has failed to make good progress. Rate of growth is usually more important than actual size; progress cannot be evaluated without precise data obtained through serial measurements. Furthermore, these data must be evaluated in relation to appropriate standards derived from large groups of normal subjects of the same age and sex, which permit consideration of variability as well as average occurrences.

In Figure 13 (p. 18) two sets of figures are given below the normal distribution curve, indicating particular positions within the range of the distribution. The first figures are percentiles and indicate the expected positions of the third, tenth, twenty-fifth, and so on, of any hundred in order of magnitude. In this theoretic "normal" curve the fiftieth percentile represents an average and is at the peak or central point in the curve. The twenty-fifth and seventy-fifth percentiles are equidistant from the average and include between them half of the total series. Similarly, the tenth and ninetieth percentiles are equidistant from the average and include 80 per cent of the total, excluding on the left hand side the smallest ten and on the right side the largest ten in the series.

The second set of figures gives the average as the mean and expresses any given position under the curve in terms of the standard deviation from the mean. Standard deviations



below the mean are negative, and those above, positive. By this method the mean plus or minus 1 standard deviation encompasses approximately 68, and plus or minus 2 standard deviations about 95, of the hundred. These are the common methods for expressing the position of a measurement in relation to the variations normally encountered.\*

The percentile method of expressing position within a distribution is usually preferable in clinical practice to using the mean and standard deviation for two reasons: (1) The concept of percentile position is more readily understood and its location more easily found by one unfamiliar with mathematical concepts. (2) Some distributions normally show skewness to one or the other side of the mean (Figs. 15, 16), and percentiles are more accurate when applied under these circumstances.

The idea of percentile position is readily conveyed by the following hypothetical situation. One hundred boys of the same age are lined up in order of height, the shortest boy being at the left end of the line and the tallest one at the right. The short and the tall boys will readily be arranged in line because they will stand out from the group and differ appreciably one from the other. The middle or most nearly average boy will be hard to select because there will be many quite like him. Thus there will be a greater difference in height between the shortest and the twenty-fifth boy or the tallest and the seventy-fifth boy, than between the twenty-fifth and the fiftieth or the seventy-fifth and the fiftieth.

Tables giving selected percentiles for the principal measurements at each age and sex are given at the end of this chapter. When measurements for successive ages are plotted, the graphs (Figs. 19, 20) permit consideration of consistency in position at different ages as well as position at the moment, thus permitting evaluation of growth progress as well as growth status.

\* The term "normal" is used in this connection as a statistical concept to denote the range of values for a given measurement or determination usually encountered among like children under ordinary or given circumstances. It does not imply that all children falling within the total distribution or in prescribed positions of it are well or healthy or that those outside these limits are necessarily abnormal in any health sense. Unusual position within the range as well as outside it may be related to health, however, and values far removed from those of the "normal" range may be accepted as abnormal from the medical point of view.

Various factors must be considered before arriving at an opinion as to the significance of an unusual position of a particular child. The consistency of the positions held for a given measurement at successive age periods is important. One would be less concerned if a child held the same low percentile position in height at all previous ages than if he had held a higher position regularly up to a given time and then lost his relative position rapidly—an indication of failure to grow normally. The consistency between measurements must also be considered: Being uniformly small in all measurements is less likely to have health implication than being small in only one or several. For example, a child who holds a position close to the tenth percentile in weight, height and pelvic breadth is far less likely to be undernourished than one at the tenth percentile in weight, but above the fiftieth in the other two. Differences in position in various measurements, however, may be due to characteristics of body build and may be appropriate for the individual. A boy may be high in the range for height and low in that for weight because of a strong constitutional linearity in build, but he may also be so because of chronic malnutrition, faulty muscular development or other causes.

Sheldon developed a photographic method for describing and classifying individuals in respect to body build. He attempted to make the evaluation of build more objective by using measurements taken from these photographs in relation to three components, which he terms "endomorph," "mesomorph" and "ectomorph" (Fig. 18). All persons combine some degree of all three components of build, and most people are not strikingly dominant in any one. Although body type is primarily a constitutional attribute, it is not often clearly manifest in early life and appears to become fully established only in adolescence. When there is definite dominance, the pattern can often be recognized in early childhood.

The correlations between relative height and dominance of each component of body build are not close, each type showing a wide range from short to tall individuals. The chief relations between somatotype dominance and growth and development appear to be in speed of maturation. Endomorphs tend to mature early, whereas ectomorphs do so late. This results in the former appearing to be tall and the latter short in late childhood. The early

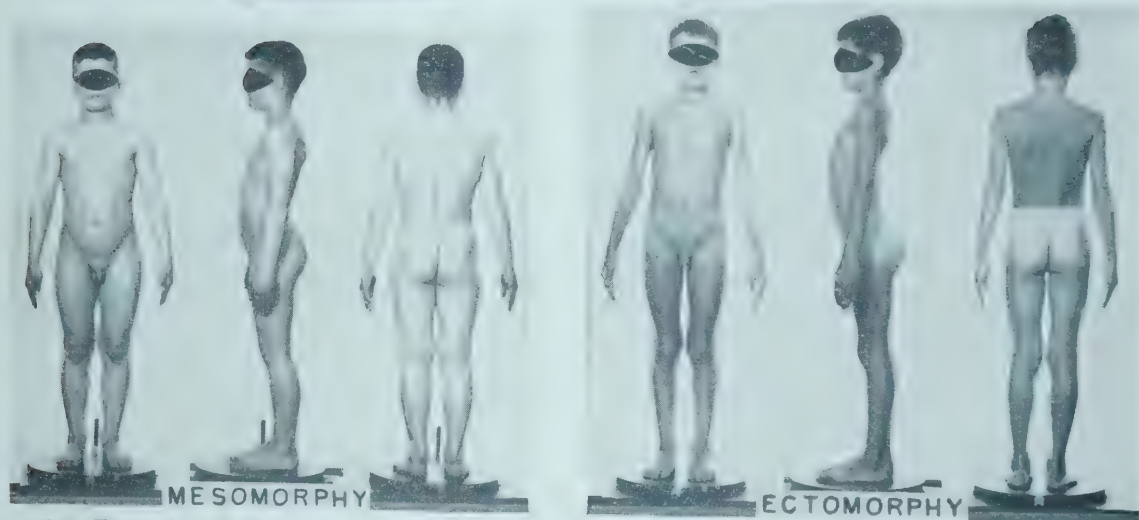


FIG. 18. Examples of dominance of the 3 types of body build according to somatotype classification of Sheldon.\* (Photos provided by E. E. Hunt, Forsyth Dental Infirmary, Boston.)

The principal characteristics of each of the 3 components of bodily constitution, some of which may be recognized in these photographs, are:

*Endomorphy*—relative preponderance of soft roundness throughout the body, with large digestive viscera and accumulations of fat, usually large trunk and thighs and tapering extremities.

*Mesomorphy*—relative preponderance of muscle, bone and connective tissue, with heavy, hard physique of rectangular outline.

*Ectomorphy*—relative preponderance of linearity and fragility, with large surface area and thin muscles and subcutaneous tissue.

\* Sheldon: *The Varieties of Human Physique*. New York, Harper & Brothers.



THE CHILDREN'S MEDICAL CENTER, BOSTON - ANTHROPOMETRIC CHART

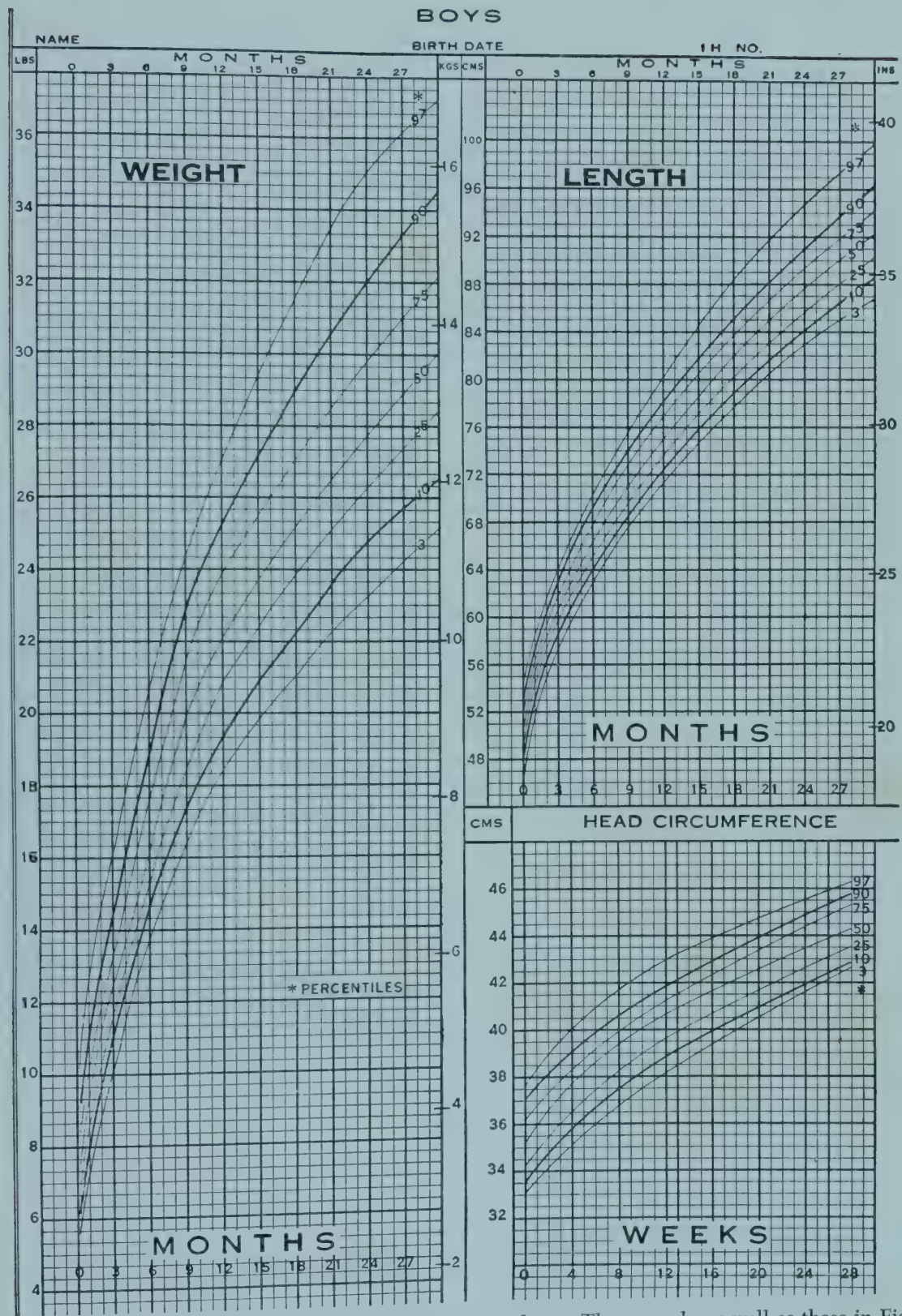


FIG. 19. Graphs for plotting selected measurements in infancy. These graphs as well as those in Figure 20 are based on studies conducted by the Harvard School of Public Health of white children in Boston of predominantly north European stock. Separate charts are used for girls, since norms for the 2 sexes differ appreciably.

These graphs serve for plotting weight and height measurements up to 30 months and head circumference up to 30 weeks. The percentile values on which they are based are given in Tables 7 and 9.



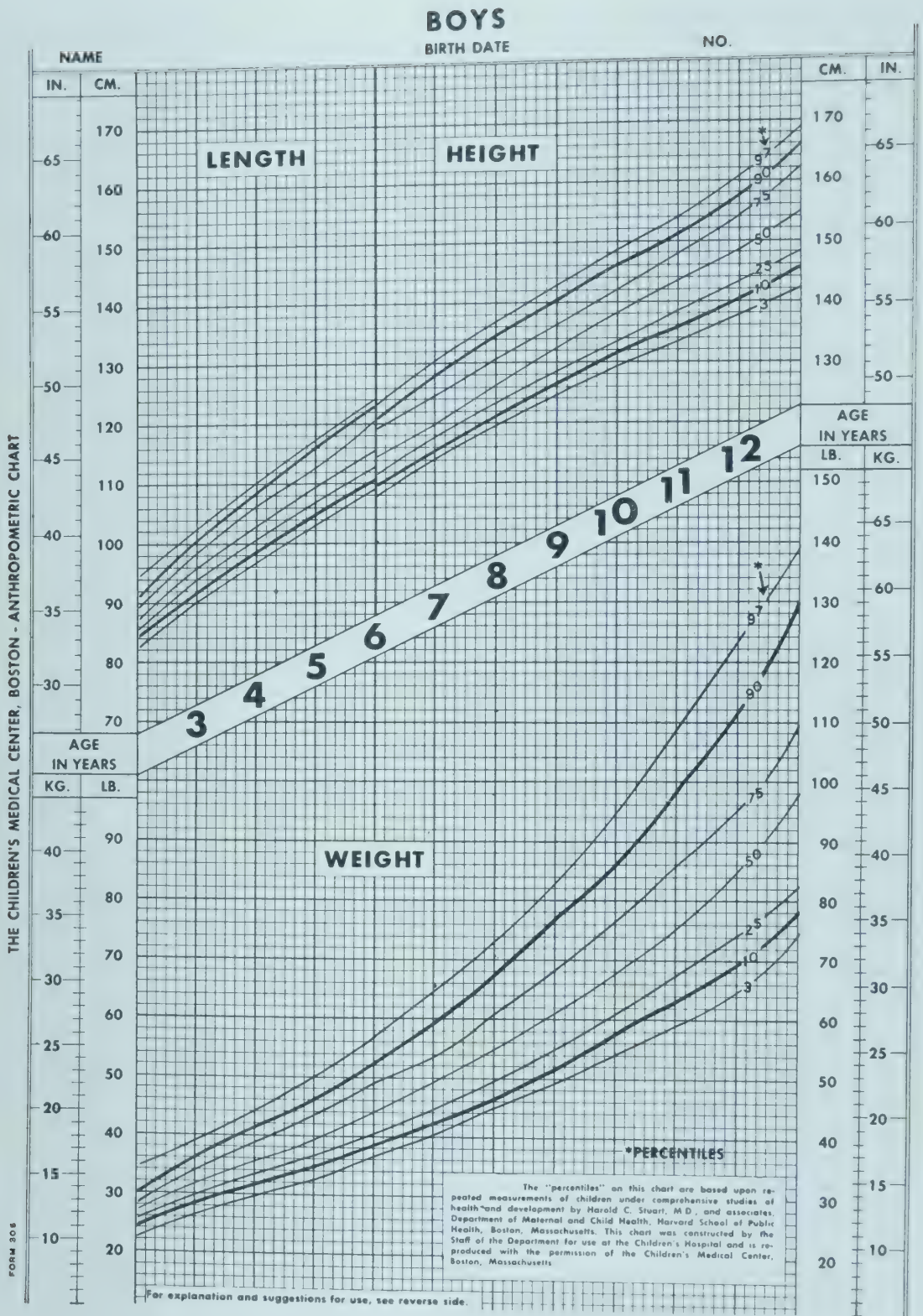


FIG. 20. Graphs for plotting weight and height in childhood. This graph serves to plot weight and height from 2 to 13 years of age (height is measured in recumbent position to 6 years of age).

Percentile graphs for plotting measurements against chronologic age are not as satisfactory for use after 13 years, owing to the wide age variability in the timing of maximum growth during adolescence. For graphs which extend to 18 years based on the percentile values given in Tables 8 and 10, see Stuart and Meredith: *Am. J. Pub. Health*, Vol. 36. Other percentile graphs covering various age periods are available from the Iowa Child Welfare Research Station, University of Iowa.

In evaluation of the measurements of the 13 year-old child it is usually possible to recognize by the appearance of secondary sex characters those children who deviate from expected percentile positions because of early or late pubescence.

termination of growth in the former and the long continuance of it in the latter tend to lessen this difference and sometimes to reverse it in the adult.

The particular pattern of growth for a given child, as demonstrated graphically on charts such as those illustrated in Figures 19 and 20, may differ markedly from what might be considered "normal" in the sense of "usual" and yet be appropriate for him. Children manifesting unusual trends in growth should be followed closely, but not necessarily with concern. Such trends may have serious significance, but they may also reflect intrinsic differences in individual growth patterns or merely transitory responses to diet or other circumstance. Infants on permissive feeding regimens, for example, frequently rise far above their customary channels for weight, or weight and length, only to return after a few months to their former channels. Some children, particularly during the preschool or early school years, gradually drift in one or more measurements from a low to a high position or the reverse. Most children, as noted previously, digress sharply but temporarily from their previous channels on these charts at the time of rapid adolescent growth.

Many methods devised for the use and interpretation of body measurements differ in various ways from the percentile one described here. Some are basically the same, as, for example, the charts prepared by Jackson and Kelly. Some are different in principle and may be used to advantage in conjunction with the percentile graph method in order to reveal a different aspect of measurement relationships or the same aspect in a different way. For many years the most widely used height and weight measurements were the tables prepared by Woodbury for infants and pre-

school children and those by Baldwin and Wood for school age children. These give the average weight for each sex by age and height. Faber later prepared a similar type of table giving a range of weights rather than the average weight for each age and height, a preferable procedure if height-weight relationships are to be considered in this way. Pryor carried the concept of an appropriate weight somewhat further by preparing separate tables for each sex and age which give expected weight for each height under several different categories of pelvic (bicristal) breadths.

Wetzel constructed two charts (grids) for evaluating growth and development, one for infants, the other for children. The latter has been used principally with children of school age. One graph on the left of the chart provides for plotting weight against height on double logarithmic paper. Straight channels, representing different types of physique or body build, traverse the graph from lower left to upper right. These are crossed at regular intervals by parallel lines representing development levels. These lines extend to a second graph on the right which contains percentile developmental curves (auxodromes).

No single method of using measurements affords a short and, by itself, a reliable means of evaluating growth. The physician must understand the basis and limits of the method or methods he uses and must apply his knowledge of the general progress of growth and normal variability to the interpretations drawn from any method. The student, therefore, is urged to practice the application of at least one method which he has studied thoroughly and to continue its use as an essential part of evaluation of his pediatric patients.

## TABLES OF NORMS FOR USE AS REFERENCE STANDARDS IN THE EVALUATION OF BODY MEASUREMENTS

Table 9 gives percentile values by sex and age for weights and lengths from birth to five years of age. Table 10 gives the same from five to eighteen years. All weight values are expressed in pounds and kilograms, and length or height values in inches and centimeters. In order to simplify presentation, pounds and inches are given to the first decimal place. As noted on page 43, the number of percentile indicates the position which a measurement of the given value would hold in any

typical series of 100 children. Tables 11 and 12 present in a similar manner values for other measurements, selected on the basis of clinical usefulness. In these tables measurements are given only in centimeters.

The norms for all measurements from birth to five years of age (Tables 9, 11) are based upon repeated measurements at the ages given of a group of white children of north European descent living in or near Boston. These children were considered to be free



from important defects or chronic diseases. Although they belonged for the most part to families in the lower economic brackets, they had the advantage of regular health supervision. The norms for all measurements from five to eighteen years (Tables 10, 12) are based upon similar studies in Iowa City. The children in this group were almost entirely of northwest European descent and predominantly from the professional and managerial classes. Although this places them in a somewhat higher economic classification than the Boston children, comparison of the distributions for measurements of the two groups at the same ages shows them to have been similar in physical dimensions.

The norms given under specified ages are not composite groupings of measurements of children at intervening ages, but are based upon children at or near the age in question. Norms are given at three-month intervals from birth to eighteen months and at six-month intervals thereafter. In referring a given measurement of a child to the appropriate table the child may be considered at an age given in the table if close to it; otherwise halfway between two given ages.

Norms for sitting height are useful in the study of children with disproportions or abnormalities of growth; they are presented in Table 13.

## TECHNIQUES FOR TAKING MEASUREMENTS

The first consideration in using these tables is to be certain that the measurements to be referred to them have been taken according to the techniques used in obtaining the data they present. A slight variation in technique may cause a considerable difference in the percentile rank in which the measurement will fall. In hospital practice certain variations from the techniques described are occasionally required by the condition of the patient, but these should be noted and allowance made for them in interpretation.

Certain differences in procedure are necessary or desirable in infancy. These do not alter the percentile position of the measurement if the physician is careful to use the correct procedure for age. For example, norms for recumbent length are given up to five years because of the difficulty of securing reliable measurements of standing height under this age. Standing height is generally a more convenient measurement after five years of age, so that norms for it are given from this

age. If recumbent length must be used after six years of age, the value obtained should be reduced by 1 cm. before placement in the range for standing height.

Measurements should be taken without clothing, though after six years of age shorts or some other undergarment is permitted.

**Length.** Body length, measured in the recumbent position, should be used to five or six years of age, depending on the standard of reference used. The child lies on a firm table with a measuring stick at least 125 cm. or 50 inches long inserted along one edge. The soles of the feet are held firmly against a fixed upright placed at the zero mark. A movable upright crosses the table above the head and is brought firmly against the vertex.

**Height.** Stature, or standing height, should be used at five years and thereafter. The child stands erect against a firm upright containing a 2-meter or 2-yard stick or other accurate measuring device. A wooden headpiece having two faces at right angles is placed firmly on the head against the measuring scale. The child's heels should be closely placed, and heels, buttocks, upper part of back and occiput should be against the vertical upright, the arms hanging at the sides in a natural position. The external orifice of the ear and the lower border of the bony orbit should lie in a plane parallel with the floor.

**Pelvic Breadth.** Pelvic, bi-iliac or bicristal breadth is the distance between the lateralmost points of the iliac crests of the pelvis, including the overlying soft tissues. It is conveniently measured on the infant and young child by spreading or obstetrical calipers with the infant recumbent. The norms up to five years are based upon this procedure. After five years, to conform with the norms in Table 10, the pelvis should be measured with a broad sliding caliper applied over the crests of the iliums, the child standing and facing the measurer.

The points of spreading calipers should not be pressed deeply into the soft tissue; whereas, with sliding calipers, the maximum pressure without causing pain should be applied. If these precautions are followed, measurements taken by the two instruments will not differ appreciably; otherwise, measurements by spreading calipers will be somewhat smaller than those by sliding calipers in obese children.

Measurements of circumferences may be taken with either a steel or linen tape marked in millimeters. The latter is more convenient with infants, but is subject to shrinking and



stretching and should be checked frequently against a meter stick.

**Head Circumference.** This measurement is particularly valuable under one year of age and need not be taken after three years. The tape is applied firmly over the glabella and supraorbital ridges anteriorly and that part of the occiput posteriorly which gives the maximum circumference.

**Chest Circumference.** Up to five years of age the norms for this measurement are taken with the child recumbent. The girth of the thorax is measured with the tape at the level of the xiphoid cartilage or substernal notch, and in a plane at a right angle to the vertebral column. The reading is made in midrespiration. At five years and thereafter, for reference to Table 10, chest circumference should be taken with the child standing in a natural manner, facing forward, and the arms slightly away from the sides of the body. One must be sure that the child is not holding his breath with lungs inflated.

**Abdominal Circumference.** This measurement is taken to three years only and is of value principally in recognizing chronic intestinal disturbances. The tape is applied with light pressure in the plane of the umbilicus with the infant recumbent.

**Leg Circumference.** This is the maximum circumference of the calf and is taken after five years only. The child stands with his feet

several inches apart and his weight equally distributed through both lower limbs. The tape is passed around the calf and adjusted until the maximum girth is obtained.

HAROLD C. STUART  
STUART S. STEVENSON

#### REFERENCES

- Ellis, R. W. B., and others: *Child Health and Development*. 2nd ed. New York, Grune & Stratton, Inc., 1956.
- Gesell, A., and others: *The First Five Years of Life*. New York, Harper & Brothers, 1940.
- Greulich, W. W., and Pyle, S. I. (After Todd, T. W.): *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford, California, Stanford University Press, 1950.
- Rand, W., Sweeney, M. E., Vincent, E. L., Breckenridge, M. E., and Murphy, M. N.: *Growth and Development of the Young Child*. 5th ed. Philadelphia, W. B. Saunders Company, 1953.
- Stevenson, S. S.: Growth Failure. *Pediat. Clin. North America*, May, 1954, p. 433.
- Stuart, H. C.: Normal Growth and Development during Adolescence. *New England J. Med.*, 234: 666, 693, 732, 1946.
- Washburn, A. H.: The Appraisal of Health during Growth from Birth to Adolescence; in Brenne-  
mann: *Practice of Pediatrics*. Hagerstown, Maryland, W. F. Prior Co., Inc., 1954, Vol. 1, Chap. 8.
- Watson, E. H., and Lowrey, G. H.: *Growth and Development of Children*. 2nd ed. Chicago, Year Book Publishers, Inc., 1954.

Table 9. Percentiles for Weight and Length—Birth to 5 Years

PERCENTILES (BOYS)							PERCENTILES (GIRLS)						
3	10	25	50	75	90	97	3	10	25	50	75	90	97
Birth													
5.8	6.3	6.9	7.5	8.3	9.1	10.1	5.8	6.2	6.9	7.4	8.1	8.6	9.4
2.63	2.86	3.13	3.4	3.76	4.13	4.58	2.63	2.81	3.13	3.36	3.67	3.9	4.26
18.2	18.9	19.4	19.9	20.5	21.0	21.5	18.5	18.8	19.3	19.8	20.1	20.4	21.1
46.3	48.1	49.3	50.6	52.0	53.3	54.6	47.1	47.8	49.0	50.2	51.0	51.9	53.6
3 Months													
10.6	11.1	11.8	12.6	13.6	14.5	16.4	9.8	10.7	11.4	12.4	13.2	14.0	14.9
4.81	5.03	5.35	5.72	6.17	6.58	7.44	4.45	4.85	5.17	5.62	5.99	6.35	6.76
22.4	22.8	23.3	23.8	24.3	24.7	25.1	22.0	22.4	22.8	23.4	23.9	24.3	24.8
56.8	57.8	59.3	60.4	61.8	62.8	63.7	55.8	56.9	57.9	59.5	60.7	61.7	63.1
6 Months													
14.0	14.8	15.6	16.7	18.0	19.2	20.8	12.7	14.1	15.0	16.0	17.5	18.6	20.0
6.35	6.71	7.08	7.58	8.16	8.71	9.43	5.76	6.4	6.8	7.26	7.94	8.44	9.07
24.8	25.2	25.7	26.1	26.7	27.3	27.7	24.0	24.6	25.1	25.7	26.2	26.7	27.1
63.0	63.9	65.2	66.4	67.8	69.3	70.4	61.1	62.5	63.7	65.2	66.6	67.8	68.8
9 Months													
16.6	17.8	18.7	20.0	21.5	22.9	24.4	15.1	16.6	17.8	19.2	20.8	22.4	24.2
7.53	8.07	8.48	9.07	9.75	10.39	11.07	6.85	7.53	8.03	8.71	9.43	10.16	10.98
26.6	27.0	27.5	28.0	28.7	29.2	29.9	25.7	26.4	26.9	27.6	28.2	28.7	29.2
67.7	68.6	69.8	71.2	72.9	74.2	75.9	65.4	67.0	68.4	70.1	71.7	72.9	74.1
12 Months													
18.5	19.6	20.9	22.2	23.8	25.4	27.3	16.8	18.4	19.8	21.5	23.0	24.8	27.1
8.39	8.89	9.48	10.07	10.8	11.52	12.38	7.62	8.35	8.98	9.75	10.43	11.25	12.29
28.1	28.5	29.0	29.6	30.3	30.7	31.6	27.1	27.8	28.5	29.2	29.9	30.3	31.0
71.3	72.4	73.7	75.2	76.9	78.1	80.3	68.9	70.6	72.3	74.2	75.9	77.1	78.8
15 Months													
19.8	21.0	22.4	23.7	25.4	27.2	29.4	18.1	19.8	21.3	23.0	24.6	26.6	29.0
8.98	9.53	10.16	10.75	11.52	12.34	13.33	8.21	8.98	9.66	10.43	11.16	12.07	13.15
29.3	29.8	30.3	30.9	31.6	32.1	33.1	28.3	29.0	29.8	30.5	31.3	31.8	32.6
74.4	75.6	77.0	78.5	80.3	81.5	84.2	71.9	73.7	75.6	77.6	79.4	80.8	82.8
18 Months													
21.1	22.3	23.8	25.2	26.9	29.0	31.5	19.4	21.2	22.7	24.5	26.2	28.3	30.9
9.57	10.12	10.8	11.43	12.2	13.15	14.29	8.8	9.62	10.3	11.11	11.88	12.84	14.02



# PHYSICAL GROWTH AND DEVELOPMENT

51

77.5	78.8	80.3	81.8	83.7	85.0	86.2	Length in Cm.	74.3	76.8	79.0	80.9	82.3	83.0	83.7	84.4
23.3	24.7	26.3	27.7	29.7	31.9	34.9	2 Years	21.6	23.5	25.3	27.1	29.2	31.7	34.4	34.4
10.57	11.2	11.93	12.56	13.47	14.47	15.83	Weight in Kg.	9.8	10.66	11.48	12.29	13.25	14.38	15.6	15.6
32.6	33.1	33.8	34.4	35.2	35.9	37.2	Length in Inches	31.5	32.3	33.3	34.1	35.0	35.8	36.7	36.7
82.7	84.2	85.8	87.5	89.4	91.1	94.6	Length in Cm.	80.1	82.0	84.7	86.6	88.9	91.0	93.3	93.3
25.2	26.6	28.4	30.0	32.2	34.5	37.0	2½ Years	23.6	25.5	27.4	29.6	31.9	34.6	38.2	38.2
11.43	12.07	12.88	13.61	14.61	15.65	16.78	Weight in Kg.	10.7	11.57	12.43	13.43	14.47	15.69	17.33	17.33
34.2	34.8	35.5	36.3	37.0	37.9	39.2	Length in Inches	33.3	34.0	35.2	36.0	36.9	37.9	38.9	38.9
86.9	88.5	90.2	92.1	94.1	96.2	99.5	Length in Cm.	84.5	86.3	89.3	91.4	93.8	96.4	98.7	98.7
27.0	28.7	30.3	32.2	34.5	36.8	39.2	3 Years	25.6	27.6	29.6	31.8	34.6	37.4	41.8	41.8
12.25	13.02	13.74	14.61	15.65	16.69	17.78	Weight in Kg.	11.61	12.52	13.43	14.42	15.69	16.96	18.96	18.96
35.7	36.3	37.0	37.9	38.8	39.6	40.5	Length in Inches	34.8	35.6	36.8	37.7	38.6	39.8	40.7	40.7
90.6	92.3	93.9	96.2	98.5	100.5	102.8	Length in Cm.	88.4	90.5	93.4	95.7	98.1	101.1	103.5	103.5
28.5	30.4	32.3	34.3	36.7	39.1	41.5	3½ Years	27.5	29.5	31.5	33.9	37.0	40.4	45.3	45.3
12.93	13.79	14.65	15.56	16.65	17.74	18.82	Weight in Kg.	12.47	13.38	14.29	15.38	16.78	18.33	20.55	20.55
37.1	37.8	38.4	39.3	40.3	41.1	41.9	Length in Inches	36.2	37.1	38.1	39.2	40.2	41.5	42.5	42.5
94.3	96.0	97.5	99.8	102.5	104.5	106.5	Length in Cm.	92.0	94.2	96.9	99.5	102.0	105.4	108.0	108.0
30.1	32.1	34.0	36.4	39.0	41.4	44.3	4 Years	29.2	31.2	33.5	36.2	39.6	43.5	48.2	48.2
13.65	14.56	15.42	16.51	17.69	18.78	20.09	Weight in Kg.	13.25	14.15	15.2	16.42	17.96	19.73	21.86	21.86
38.4	39.1	39.7	40.7	41.9	42.7	43.5	Length in Inches	37.5	38.4	39.5	40.6	41.6	43.1	44.2	44.2
97.5	99.3	100.8	103.4	106.5	108.5	110.4	Length in Cm.	95.2	97.6	100.3	103.2	105.8	109.6	112.3	112.3
31.6	33.8	35.7	38.4	41.4	43.9	47.4	4½ Years	30.7	32.9	35.3	38.5	42.1	46.7	50.9	50.9
14.33	15.33	16.19	17.42	18.78	19.91	21.5	Weight in Kg.	13.93	14.92	16.01	17.46	19.1	21.18	23.09	23.09
39.6	40.3	40.9	42.0	43.3	44.2	45.0	Length in Inches	38.6	39.7	40.8	42.0	43.0	44.7	45.7	45.7
100.6	102.4	104.0	106.7	109.9	112.3	114.3	Length in Cm.	98.1	100.9	103.6	106.8	109.3	113.5	116.2	116.2
33.6	35.5	37.5	40.5	44.1	46.7	50.4	5 Years	32.1	34.8	37.4	40.5	44.8	49.2	52.8	52.8
15.24	16.1	17.01	18.37	20.0	21.18	22.86	Weight in Kg.	14.56	15.79	16.96	18.37	20.32	22.32	23.95	23.95
40.2	40.8	41.7	42.8	44.2	45.2	46.1	Length in Inches	39.4	40.5	41.6	42.9	44.0	45.4	46.8	46.8
102.0	103.7	105.9	108.7	112.3	114.7	117.1	Length in Cm.	100.0	103.0	105.7	109.1	111.7	115.4	118.8	118.8

From Studies of Child Health and Development, Department of Maternal and Child Health, Harvard School of Public Health.  
The figures for the several percentiles of each measurement at 5 years differ slightly from those given in Table 10 for this age because they were obtained from a different population of children.

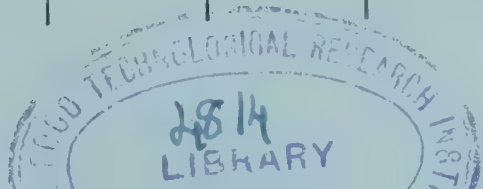


Table 10. Percentiles for Weight and Height—5 to 18 Years

PERCENTILES (BOYS)							PERCENTILES (GIRLS)						
3	10	25	50	75	90	97	3	10	25	50	75	90	97
5 Years													
Weight in Pounds							Weight in Pounds						
34.5	36.6	39.6	42.8	46.5	49.7	53.2	33.7	36.1	38.6	41.4	44.2	48.2	51.8
15.65	16.6	17.96	19.41	21.09	22.54	24.13	15.29	16.37	17.51	18.78	20.05	21.86	23.5
Height in Inches							Height in Inches						
40.2	41.5	42.6	43.8	45.0	45.9	47.0	40.4	41.3	42.2	43.2	44.4	45.4	46.5
102.1	105.3	108.3	111.3	114.2	116.7	119.5	102.6	105.0	107.2	109.7	112.9	115.4	118.0
5½ Years													
Weight in Pounds							Weight in Pounds						
	38.8	42.0	45.6	49.3	53.1			38.0	40.8	44.0	47.2	51.2	
	17.6	19.05	20.68	22.36	24.09			17.24	18.51	19.96	21.41	23.22	
Height in Inches							Height in Inches						
	42.6	43.8	45.0	46.3	47.3			42.4	43.4	44.4	45.7	46.8	
	108.3	111.2	114.4	117.5	120.1			107.8	110.2	112.8	116.1	118.9	
6 Years													
Weight in Pounds							Weight in Pounds						
38.5	40.9	44.4	48.3	52.1	56.4	61.1	37.2	39.6	42.9	46.5	50.2	54.2	58.7
17.46	18.55	20.14	21.91	23.63	25.58	27.71	16.87	17.96	19.46	21.09	22.77	24.58	26.63
Height in Inches							Height in Inches						
42.7	43.8	44.9	46.3	47.6	48.6	49.7	42.5	43.5	44.6	45.6	47.0	48.1	49.4
108.5	111.2	114.1	117.5	120.8	123.5	126.2	108.0	110.6	113.2	115.9	119.3	122.3	125.4
6½ Years													
Weight in Pounds							Weight in Pounds						
	43.4	47.1	51.2	55.4	60.4			42.2	45.5	49.4	53.3	57.7	
	19.69	21.36	23.22	25.13	27.4			19.14	20.64	22.41	24.18	26.17	
Height in Inches							Height in Inches						
	44.9	46.1	47.6	48.9	50.0			44.8	45.7	46.9	48.3	49.4	
	114.1	117.2	120.8	124.2	127.0			113.7	116.2	119.1	122.6	125.6	
7 Years													
Weight in Pounds							Weight in Pounds						
43.0	45.8	49.7	54.1	58.7	64.4	69.9	41.3	44.5	48.1	52.2	56.3	61.2	67.3
19.5	20.77	22.54	24.54	26.63	29.21	31.71	18.73	20.19	21.82	23.68	25.54	27.76	30.53
Height in Inches							Height in Inches						
44.9	46.0	47.4	48.9	50.2	51.4	52.5	44.9	46.0	46.9	48.1	49.6	50.7	51.9
114.0	116.9	120.3	124.1	127.6	130.5	133.4	114.0	116.8	119.2	122.3	125.9	128.9	131.7
7½ Years													
Weight in Pounds							Weight in Pounds						
	48.5	52.6	57.1	62.1	68.7			46.6	50.6	55.2	59.8	65.6	
	22.0	23.86	25.9	28.17	31.16			21.14	22.95	25.04	27.13	29.76	
Height in Inches							Height in Inches						
	47.2	48.6	50.0	51.5	52.7			47.0	48.0	49.3	50.7	51.9	
	120.0	123.5	127.1	130.9	133.9			119.5	122.0	125.2	128.8	131.8	

The figures for the several percentiles of each measurement at 5 years differ slightly from those in Table 9 for this age because they were obtained from a different population of children.



48.0	51.2	55.5	60.1	65.5	73.0	79.4	Weight in Pounds	45.3	48.6	53.1	58.1	63.3	69.9	76.9
21.77	23.22	25.17	27.26	29.71	33.11	36.02	Weight in Kg.	20.55	22.04	24.09	26.35	28.71	31.71	35.79
47.1	48.5	49.8	51.2	52.8	54.0	55.2	Height in Inches	46.9	48.1	49.1	50.4	51.8	53.0	54.1
119.6	123.1	126.6	130.0	134.2	137.3	140.2	Height in Cm.	119.1	122.1	124.8	128.0	131.6	134.6	137.4
8½ Years														
	53.8	58.3	63.1	68.9	77.0		Weight in Pounds		50.6	55.5	61.0	66.9	74.5	
	24.4	26.44	28.62	31.25	34.93		Weight in Kg.		22.95	25.17	27.67	30.35	33.79	
	49.5	50.8	52.3	53.9	55.1		Height in Inches		49.0	50.1	51.4	52.9	54.1	
	125.7	129.1	132.8	137.0	140.0		Height in Cm.		124.6	127.3	130.5	134.4	137.5	
9 Years														
52.5	56.3	61.1	66.0	72.3	81.0	89.8	Weight in Pounds	49.1	52.6	57.9	63.8	70.5	79.1	89.9
23.81	25.54	27.71	29.94	32.8	36.74	40.73	Weight in Kg.	22.27	23.86	26.26	28.94	31.98	35.88	40.78
48.9	50.5	51.8	53.3	55.0	56.1	57.2	Height in Inches	48.7	50.0	51.1	52.3	54.0	55.3	56.5
124.2	128.3	131.6	135.5	139.8	142.6	145.3	Height in Cm.	123.6	127.0	129.7	132.9	137.1	140.4	143.4
9½ Years														
	58.7	63.7	69.0	76.0	85.5		Weight in Pounds		54.9	60.4	67.1	74.8	84.4	
	26.63	28.89	31.3	34.47	38.78		Weight in Kg.		24.9	27.4	30.44	33.93	38.28	
	51.4	52.7	54.3	55.9	57.1		Height in Inches		50.9	52.0	53.5	55.1	56.4	
	130.6	134.0	137.9	142.1	145.1		Height in Cm.		129.4	132.2	135.8	139.9	143.2	
10 Years														
56.8	61.1	66.3	71.9	79.6	89.9	100.0	Weight in Pounds	53.2	57.1	62.8	70.3	79.1	89.7	101.9
25.76	27.71	30.07	32.61	36.11	40.78	45.36	Weight in Kg.	24.13	25.9	28.49	31.89	35.88	40.69	46.22
50.7	52.3	53.7	55.2	56.8	58.1	59.2	Height in Inches	50.3	51.8	53.0	54.6	56.1	57.5	58.8
128.7	132.8	136.3	140.3	144.4	147.5	150.3	Height in Cm.	127.7	131.7	134.6	138.6	142.6	146.0	149.3
10½ Years														
	63.7	69.0	74.8	83.4	94.6		Weight in Pounds		59.9	66.4	74.6	84.1	95.1	
	28.89	31.3	33.93	37.83	42.91		Weight in Kg.		27.17	30.12	33.79	38.15	43.14	
	53.2	54.5	56.0	57.8	58.9		Height in Inches		52.9	54.1	55.8	57.4	58.9	
	135.1	138.4	142.3	146.8	149.7		Height in Cm.		134.4	137.5	141.7	145.9	149.7	
11 Years														
61.8	66.3	71.6	77.6	87.2	99.3	111.7	Weight in Pounds	57.9	62.6	69.9	78.8	89.1	100.4	112.9
28.03	30.07	32.48	35.2	39.55	45.04	50.67	Weight in Kg.	26.26	28.4	31.71	35.74	40.42	45.54	51.21
52.5	54.0	55.3	56.8	58.7	59.8	60.8	Height in Inches	52.1	53.9	55.2	57.0	58.7	60.4	62.0
133.4	137.3	140.5	144.2	149.2	151.8	154.4	Height in Cm.	132.3	137.0	140.3	144.7	149.2	153.4	157.4
11½ Years														
	69.2	74.6	81.0	91.6	104.5		Weight in Pounds		66.1	74.0	83.2	94.0	106.0	
	31.39	33.84	36.74	41.55	47.4		Weight in Kg.		29.98	33.57	37.74	42.64	48.08	
	55.0	56.3	57.8	59.6	60.9		Height in Inches		55.0	56.3	58.3	60.2	61.8	
	139.8	142.9	146.9	151.4	154.8		Height in Cm.		139.8	143.1	148.1	152.9	157.0	





91.3 41.41 59.7 151.7	99.4 45.09 62.1 157.8	108.2 49.08 63.9 162.3	120.1 54.48 66.1 167.8	135.0 61.23 68.1 173.0	147.8 67.04 69.6 176.7	161.6 73.3 71.6 181.8	15 Years Weight in Pounds Weight in Kg. Height in Inches Height in Cm.	89.0 40.37 59.1 150.2	97.4 44.18 61.1 155.2	105.1 47.67 62.1 157.7	113.5 51.48 63.4 161.1	123.9 56.2 64.9 164.9	138.1 62.64 66.2 168.1	155.2 70.4 67.6 171.6
103.4 46.9 61.6 156.5	105.2 47.7% 63.1 160.3	113.5 51.48 64.8 164.7	124.9 56.65 66.8 169.7	139.7 63.37 68.8 174.8	152.6 69.22 70.2 178.2	161.6 73.3 71.6 181.8	15½ Years Weight in Pounds Weight in Kg. Height in Inches Height in Cm.	99.2 45.0 61.3 155.7	106.8 48.44 62.3 158.2	115.3 52.3 63.7 161.7	125.6 56.97 65.1 165.3	139.6 63.32 66.4 168.6	157.7 71.53 67.7 172.0	157.7 71.53 67.7 172.0
110.5 50.12 62.6 159.0	114.3 51.85 64.6 164.2	121.6 55.16 66.3 168.4	133.0 60.33 68.0 172.7	147.9 67.09 69.8 177.4	161.0 73.03 71.1 180.7	175.6 79.65 73.5 186.6	16½ Years Weight in Pounds Weight in Kg. Height in Inches Height in Cm.	101.9 46.22 61.5 156.2	109.4 49.62 62.5 158.8	118.1 53.57 63.9 162.4	128.4 58.24 65.3 165.9	142.2 64.5 66.6 169.2	159.5 72.35 67.8 172.2	159.5 72.35 67.8 172.2
113.0 51.96 62.8 159.6	118.8 53.89 65.3 165.9	125.8 57.06 67.0 170.1	137.6 62.41 68.5 174.1	153.6 69.67 70.3 178.5	166.8 75.66 71.6 182.0	179.0 81.19 73.9 187.6	17½ Years Weight in Pounds Weight in Kg. Height in Inches Height in Cm.	103.2 46.81 61.5 156.3	110.8 50.26 62.6 159.0	119.5 54.2 64.0 162.5	130.2 59.06 65.4 166.1	143.9 65.27 66.7 169.4	160.7 72.89 67.8 172.2	160.7 72.89 67.8 172.2
113.0 51.96 62.8 159.6	120.0 54.43 65.5 166.3	127.1 57.65 67.0 170.5	139.0 63.05 68.7 174.5	155.7 70.62 70.4 178.9	169.0 76.66 71.8 182.4	179.0 81.19 73.9 187.6	18 Years Weight in Pounds Weight in Kg. Height in Inches Height in Cm.	103.5 46.95 61.5 156.3	111.2 50.44 62.6 159.0	119.9 54.39 64.0 162.5	130.8 59.33 65.4 166.1	144.5 65.54 66.7 169.4	160.7 72.89 67.8 172.2	160.7 72.89 67.8 172.2

The measurements in this table are from studies by and are reproduced by courtesy of Howard V. Meredith, Iowa Child Welfare Research Station, The State University of Iowa.

Table 11. Percentiles for Selected Measurements—Birth to 5 Years—in Centimeters

PERCENTILES (BOYS)							PERCENTILES (GIRLS)							
3	10	25	50	75	90	97		3	10	25	50	75	90	97
7.1 33.0 29.8	7.4 33.5 30.6	7.7 34.4 31.8	8.1 35.3 33.2	8.4 36.2 34.4	8.7 37.0 35.7	9.0 37.5 36.8	Birth Pelvic Breadth Head Circ. Chest Circ.	7.0 32.5 30.0	7.2 33.4 30.8	7.4 33.9 31.8	7.7 34.7 32.9	8.2 35.4 34.0	8.5 36.0 35.0	8.9 36.6 36.0
9.8 38.7 37.6 33.6	10.0 39.2 38.3 35.5	10.2 40.0 39.3 36.8	10.6 40.9 40.6 38.5	11.2 41.5 41.6 39.8	11.5 42.1 42.9 41.4	12.1 43.2 44.1 43.5	3 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	9.4 37.9 36.5 32.3	9.6 38.5 37.6 34.4	9.9 39.2 38.8 36.8	10.4 40.0 39.8 38.4	10.9 40.8 40.9 40.4	11.4 41.7 42.0 41.7	12.2 42.3 43.0 42.7
10.5 42.1 40.1 36.4	10.8 42.7 41.6 38.4	11.2 43.3 42.5 39.8	11.6 43.9 43.7 41.4	12.0 44.8 45.0 43.2	12.4 45.4 46.3 45.0	13.1 45.9 47.2 46.0	6 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	10.3 40.9 39.4 36.2	10.5 41.4 40.6 37.9	10.8 42.0 41.8 39.5	11.3 42.8 43.0 41.4	11.8 43.6 44.2 43.5	12.4 44.5 45.4 45.0	13.2 45.4 46.6 46.2
11.0 43.8 42.0 38.1	11.5 44.5 43.7 40.1	11.9 45.1 44.8 41.7	12.3 46.0 46.0 43.4	12.7 46.5 47.5 45.6	13.1 47.1 48.9 47.6	13.7 47.8 49.9 48.4	9 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	11.0 42.6 41.7 38.0	11.3 43.2 42.7 39.9	11.5 43.8 44.0 41.3	12.0 44.6 45.4 43.4	12.5 45.4 46.6 45.7	13.1 46.3 47.9 47.7	13.8 47.2 49.2 49.2
11.4 44.9 43.5 39.3	11.9 45.5 45.1 41.1	12.4 46.5 46.3 42.9	12.8 47.3 47.6 44.6	13.2 47.8 49.3 47.0	13.7 48.4 50.7 48.9	14.2 48.9 51.9 50.0	12 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	11.4 43.6 43.1 38.7	11.7 44.3 44.2 40.9	12.0 45.0 45.6 42.4	12.4 45.8 47.0 44.5	13.0 46.7 48.2 46.9	13.6 47.7 49.5 49.2	14.4 48.4 50.9 51.1
11.8 45.6 44.7 40.0	12.4 46.3 46.1 41.7	12.8 47.1 47.3 43.5	13.3 48.0 48.6 45.1	13.7 48.5 50.1 47.4	14.2 49.2 51.7 49.3	14.7 49.8 52.8 50.5	15 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	11.6 44.3 44.1 39.3	12.1 44.9 45.1 41.5	12.4 45.6 46.5 43.0	12.9 46.5 47.9 45.0	13.5 47.4 49.2 47.3	14.1 48.4 50.5 49.8	14.8 49.1 51.9 51.8



12.1	12.8	13.2	13.7	14.2	14.7	15.2	18 Months Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	11.8	12.4	12.8	13.3	13.9	14.5	15.2
46.2	47.0	47.7	48.7	49.2	49.9	50.6		44.9	45.5	46.2	47.1	48.0	49.0	49.8
45.9	47.0	48.2	49.5	50.9	52.6	53.7		45.0	46.0	47.3	48.8	50.2	51.4	52.9
40.6	42.2	44.0	45.5	47.8	49.6	50.9		39.8	42.1	43.6	45.5	47.6	50.3	52.5
12.8	13.5	13.9	14.4	15.0	15.5	16.1	2 Years Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	12.5	13.1	13.5	14.1	14.7	15.3	16.1
47.0	48.0	48.2	49.7	50.2	51.0	51.7		45.8	46.4	47.2	48.1	49.1	50.1	50.9
47.4	48.4	49.5	50.8	52.2	53.9	54.9		46.3	47.4	48.6	50.1	51.8	53.0	54.2
41.6	43.4	44.8	46.2	48.4	50.2	51.5		40.7	42.8	44.4	46.3	48.5	51.4	53.5
13.6	14.2	14.6	15.1	15.7	16.2	16.7	2½ Years Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	13.2	13.7	14.2	14.8	15.4	16.1	16.9
47.5	48.5	49.2	50.2	50.9	51.6	52.3		46.3	47.0	47.8	48.8	49.8	50.8	51.5
48.2	49.3	50.3	51.7	53.2	54.9	55.8		47.3	48.4	49.7	51.2	52.8	54.3	55.5
42.0	44.0	45.5	46.7	49.1	50.7	52.0		41.7	43.6	45.2	47.0	49.4	52.6	54.7
14.2	14.8	15.2	15.8	16.4	16.9	17.4	3 Years Pelvic Breadth Head Circ. Chest Circ. Abd. Circ.	13.8	14.3	14.8	15.4	16.1	16.8	17.7
47.9	48.9	49.6	50.4	51.3	51.9	52.7		46.8	47.5	48.4	49.3	50.3	51.1	52.0
48.9	49.9	51.0	52.4	54.1	55.8	57.0		47.9	49.3	50.5	51.9	53.5	55.1	56.7
42.1	44.6	46.0	47.2	49.6	51.1	52.7		42.7	44.5	46.0	47.7	50.2	53.6	55.8
14.7	15.3	15.7	16.3	16.9	17.4	17.9	3½ Years Pelvic Breadth Chest Circ.	14.4	14.9	15.4	16.0	16.7	17.4	18.3
49.6	50.5	51.6	53.1	54.9	56.6	58.0		48.5	50.1	51.2	52.5	54.1	55.8	58.1
15.2	15.8	16.2	16.9	17.5	18.0	18.5	4 Years Pelvic Breadth Chest Circ.	15.0	15.4	15.9	16.5	17.2	17.9	18.9
50.1	51.1	52.2	53.7	55.5	57.2	58.9		49.2	50.7	51.7	53.1	54.7	56.5	59.0
15.7	16.2	16.6	17.3	18.0	18.5	19.1	4½ Years Pelvic Breadth Chest Circ.	15.5	15.9	16.4	17.0	17.7	18.5	19.4
50.7	51.7	52.9	54.4	56.3	58.0	59.3		49.8	51.3	52.3	53.7	55.4	57.3	59.6
16.1	16.7	17.1	17.8	18.5	19.0	19.7	5 Years Pelvic Breadth Chest Circ.	16.0	16.3	16.8	17.5	18.2	18.9	19.8
51.2	52.3	53.5	55.0	57.0	58.8	60.5		50.4	51.7	52.8	54.2	56.0	57.9	60.2

From Studies of Child Health and Development, Department of Maternal and Child Health, Harvard School of Public Health.

The figures for the several percentiles of each measurement at 5 years differ slightly from those given in Table 12 for this age because they were obtained from a different population of children.

Table 12. Percentiles for Selected Measurements—5 to 18 Years—in Centimeters

PERCENTILES (BOYS)						PERCENTILES (GIRLS)				
10	25	50	75	90		10	25	50	75	90
17.0	17.6	18.3	18.9	19.6	5 Years Pelvic Breadth	17.0	17.4	18.0	18.7	19.4
51.6	52.8	54.5	56.2	57.5	Chest Circ.	50.2	51.4	52.9	54.6	56.5
21.0	21.7	22.6	23.6	24.6	Leg Circ.	21.1	21.8	22.8	23.8	24.7
17.4	18.0	18.7	19.4	20.1	5½ Years Pelvic Breadth	17.4	17.8	18.4	19.1	20.0
52.4	53.6	55.3	57.1	58.5	Chest Circ.	50.9	52.2	53.7	55.5	57.4
21.4	22.2	23.1	24.1	25.2	Leg Circ.	21.5	22.3	23.3	24.3	25.3
17.7	18.4	19.1	19.8	20.5	6 Years Pelvic Breadth	17.7	18.2	18.8	19.5	20.5
53.2	54.4	56.1	57.9	59.5	Chest Circ.	51.5	52.9	54.5	56.3	58.2
21.8	22.6	23.6	24.6	25.7	Leg Circ.	21.9	22.7	23.8	24.8	25.8
18.1	18.8	19.5	20.2	21.0	6½ Years Pelvic Breadth	18.1	18.6	19.2	20.0	21.1
54.1	55.3	57.0	58.9	60.6	Chest Circ.	52.2	53.7	55.3	57.2	59.2
22.2	23.1	24.1	25.2	26.3	Leg Circ.	22.3	23.2	24.3	25.4	26.4
18.5	19.2	19.9	20.6	21.4	7 Years Pelvic Breadth	18.4	18.9	19.6	20.4	21.6
54.9	56.1	57.8	59.8	61.6	Chest Circ.	52.8	54.4	56.1	58.0	60.1
22.6	23.5	24.6	25.7	26.9	Leg Circ.	22.7	23.7	24.8	25.9	27.0
18.9	19.6	20.3	21.0	21.9	7½ Years Pelvic Breadth	18.8	19.3	20.1	20.9	22.1
55.8	57.1	58.8	61.0	62.9	Chest Circ.	53.5	55.1	57.0	59.0	61.2
23.1	24.1	25.2	26.3	27.6	Leg Circ.	23.1	24.2	25.3	26.4	27.7
19.2	19.9	20.7	21.4	22.3	8 Years Pelvic Breadth	19.1	19.7	20.5	21.3	22.6
56.7	58.0	59.8	62.1	64.1	Chest Circ.	54.2	55.8	57.8	59.9	62.3
23.6	24.6	25.7	26.8	28.2	Leg Circ.	23.5	24.6	25.8	26.9	28.3
19.6	20.3	21.1	21.8	22.7	8½ Years Pelvic Breadth	19.4	20.1	20.9	21.8	23.1
57.6	59.0	60.8	63.3	65.4	Chest Circ.	54.9	56.5	58.7	60.9	63.5
24.1	25.1	26.3	27.4	28.9	Leg Circ.	23.9	25.0	26.3	27.5	28.9
19.9	20.6	21.4	22.2	23.0	9 Years Pelvic Breadth	19.7	20.5	21.3	22.2	23.5
58.4	59.9	61.8	64.4	66.7	Chest Circ.	55.5	57.2	59.6	61.9	64.7
24.5	25.6	26.8	28.0	29.5	Leg Circ.	24.2	25.4	26.8	28.1	29.5
20.2	21.0	21.7	22.6	23.5	9½ Years Pelvic Breadth	20.1	20.9	21.8	22.8	24.1
59.3	60.9	62.9	65.5	68.1	Chest Circ.	56.2	58.0	60.5	63.2	66.1
24.9	26.0	27.3	28.5	30.1	Leg Circ.	24.7	25.9	27.3	28.6	30.2
20.4	21.3	22.0	22.9	23.9	10 Years Pelvic Breadth	20.5	21.2	22.2	23.3	24.6
60.1	61.8	63.9	66.6	69.4	Chest Circ.	56.9	58.7	61.4	64.4	67.4
25.3	26.4	27.7	29.0	30.7	Leg Circ.	25.1	26.3	27.7	29.1	30.9
20.8	21.6	22.3	23.2	24.4	10½ Years Pelvic Breadth	21.0	21.7	22.9	24.0	25.3
60.9	62.8	64.9	67.7	70.7	Chest Circ.	57.8	59.9	62.8	65.8	69.0
25.7	26.8	28.1	29.5	31.4	Leg Circ.	25.6	26.8	28.3	29.9	31.8
21.1	21.8	22.6	23.5	24.8	11 Years Pelvic Breadth	21.4	22.2	23.5	24.6	26.0
61.7	63.7	65.9	68.8	71.9	Chest Circ.	58.6	61.1	64.2	67.2	70.5
26.0	27.1	28.5	30.0	32.0	Leg Circ.	26.0	27.3	28.9	30.6	32.6

The figures for the several percentiles of each measurement at 5 years differs lightly from those in Table 11 for this age because they were obtained from a different population of children.

The measurements in this table are from studies by and are reproduced by courtesy of Howard V. Meredith, the Iowa Child Welfare Research Station, The State University of Iowa.



Table 12 (Continued)

PERCENTILES (BOYS)						PERCENTILES (GIRLS)				
10	25	50	75	90		10	25	50	75	90
21.5	22.2	23.1	24.0	25.3	11½ Years					
62.5	64.6	66.9	69.9	73.1	Pelvic Breadth	21.9	22.8	24.2	25.4	26.8
26.4	27.6	29.0	30.6	32.8	Chest Circ.	59.6	62.5	65.5	68.5	72.2
					Leg Circ.	26.6	27.9	29.5	31.2	33.2
					12 Years					
21.9	22.6	23.5	24.5	25.8	Pelvic Breadth	22.4	23.4	24.9	26.2	27.6
63.3	65.5	67.8	70.9	74.2	Chest Circ.	60.6	63.8	66.7	69.7	73.8
26.8	28.0	29.5	31.2	33.5	Leg Circ.	27.1	28.5	30.1	31.8	33.8
					12½ Years					
22.3	23.1	24.1	25.1	26.5	Pelvic Breadth	23.0	24.0	25.5	26.8	28.3
64.2	66.5	69.1	72.4	75.8	Chest Circ.	61.8	64.9	67.7	70.9	75.3
27.3	28.6	30.1	32.0	34.2	Leg Circ.	27.7	29.1	30.7	32.4	34.3
					13 Years					
22.7	23.6	24.6	25.6	27.2	Pelvic Breadth	23.6	24.6	26.0	27.4	29.0
65.0	67.4	70.3	73.8	77.4	Chest Circ.	62.9	65.9	68.6	72.0	76.7
27.8	29.2	30.8	32.7	34.8	Leg Circ.	28.2	29.7	31.2	32.9	34.8
					13½ Years					
23.2	24.1	25.2	26.4	27.8	Pelvic Breadth	24.2	25.2	26.5	27.8	29.5
66.3	68.8	72.4	75.8	79.4	Chest Circ.	63.8	66.6	69.3	72.9	77.7
28.5	29.9	31.6	33.4	35.3	Leg Circ.	28.7	30.2	31.6	33.4	35.1
					14 Years					
23.6	24.6	25.8	27.1	28.3	Pelvic Breadth	24.8	25.8	26.9	28.1	29.9
67.6	70.2	74.5	77.8	81.4	Chest Circ.	64.6	67.2	69.9	73.7	78.6
29.1	30.6	32.3	34.1	35.8	Leg Circ.	29.2	30.6	32.0	33.8	35.4
					14½ Years					
24.1	25.1	26.3	27.5	28.7	Pelvic Breadth	25.2	26.2	27.2	28.4	30.3
69.4	72.3	76.3	79.6	83.1	Chest Circ.	65.1	67.7	70.4	74.2	79.2
29.8	31.3	32.9	34.6	36.2	Leg Circ.	29.6	30.9	32.3	34.1	35.7
					15 Years					
24.6	25.6	26.7	27.9	29.1	Pelvic Breadth	25.6	26.5	27.5	28.7	30.6
71.1	74.4	78.0	81.3	84.8	Chest Circ.	65.5	68.1	70.9	74.7	79.8
30.4	31.9	33.4	35.1	36.6	Leg Circ.	29.9	31.1	32.6	34.3	35.9
					15½ Years					
25.1	26.0	27.1	28.2	29.4	Pelvic Breadth	25.9	26.7	27.8	29.0	30.8
72.8	75.8	79.4	82.9	86.3	Chest Circ.	65.8	68.4	71.3	75.1	80.2
30.9	32.3	33.8	35.5	37.0	Leg Circ.	30.1	31.4	32.9	34.5	36.1
					16 Years					
25.6	26.4	27.4	28.4	29.6	Pelvic Breadth	26.1	26.9	28.0	29.2	31.0
74.4	77.2	80.7	84.5	87.8	Chest Circ.	66.1	68.7	71.6	75.4	80.5
31.3	32.7	34.2	35.8	37.3	Leg Circ.	30.3	31.6	33.1	34.6	36.3
					16½ Years					
25.9	26.7	27.6	28.6	29.8	Pelvic Breadth	26.2	27.0	28.2	29.3	31.1
75.4	78.1	81.6	85.4	88.8	Chest Circ.	66.3	69.0	71.9	75.7	80.7
31.5	32.9	34.4	36.1	37.6	Leg Circ.	30.5	31.8	33.3	34.8	36.5
					17 Years					
26.1	26.9	27.8	28.7	29.9	Pelvic Breadth	26.3	27.1	28.3	29.4	31.2
76.4	78.9	82.5	86.2	89.7	Chest Circ.	66.4	69.2	72.1	75.9	80.9
31.7	33.1	34.6	36.3	37.8	Leg Circ.	30.6	31.9	33.4	34.9	36.6
					17½ Years					
26.3	27.0	27.9	28.8	30.0	Pelvic Breadth	26.4	27.2	28.4	29.5	31.3
77.0	79.4	83.0	86.7	90.2	Chest Circ.	66.5	69.3	72.2	76.0	81.0
31.8	33.3	34.8	36.5	38.0	Leg Circ.	30.7	32.0	33.5	35.0	36.7
					18 Years					
26.5	27.1	28.0	28.9	30.1	Pelvic Breadth	26.4	27.2	28.4	29.5	31.3
77.5	79.8	83.4	87.1	90.7	Chest Circ.	66.6	69.4	72.3	76.1	81.1
31.9	33.4	34.9	36.6	38.1	Leg Circ.	30.8	32.1	33.6	35.1	36.8

Table 13. Sitting Height (Stem Length) in Centimeters

PERCENTILES (BOYS)							AGE (YRS.)	PERCENTILES (GIRLS)						
3	10	25	50	75	90	97		3	10	25	50	75	90	97
41.4	42.3	43.4	44.8	46.2	47.4	48.4	0.5	40.0	41.0	42.1	43.3	44.5	45.6	46.8
45.1	46.1	47.4	48.7	50.1	51.2	52.4	1.0	44.2	45.2	46.3	47.5	48.7	49.8	50.9
48.3	49.2	50.3	51.6	52.9	54.1	55.4	1.5	47.1	48.1	49.2	50.4	51.6	52.7	53.9
50.6	51.4	52.5	53.8	55.1	56.3	57.6	2.0	49.2	50.2	51.4	52.7	54.0	55.2	56.4
52.2	53.1	54.2	55.6	56.9	58.1	59.5	2.5	50.9	51.9	53.1	54.4	55.7	57.0	58.3
53.5	54.5	55.6	57.1	58.5	59.7	61.1	3.0	52.2	53.4	54.6	56.0	57.4	58.7	60.0
54.8	55.8	57.0	58.6	60.0	61.2	62.6	3.5	53.6	54.8	56.1	57.5	59.0	60.3	61.6
56.0	57.1	58.3	60.0	61.4	62.6	64.0	4.0	54.9	56.1	57.4	58.9	60.4	61.7	62.1
57.1	58.3	59.6	61.3	62.8	64.0	65.4	4.5	56.1	57.4	58.7	60.2	61.7	63.1	64.5
58.2	59.5	60.9	62.6	64.2	65.4	66.8	5.0	57.3	58.6	59.9	61.4	63.0	64.4	65.9
59.3	60.7	62.1	63.9	65.6	66.8	68.2	5.5	58.6	59.9	61.2	62.7	64.3	65.8	67.3
60.4	61.8	63.3	65.2	66.9	68.2	69.6	6.0	59.9	61.2	62.5	64.1	65.6	67.1	68.7
61.5	62.9	64.5	66.4	68.2	69.6	71.0	6.5	61.2	62.5	63.8	65.4	66.9	68.4	70.0
62.6	64.1	65.8	67.6	69.4	71.0	72.4	7.0	62.5	63.7	65.0	66.6	68.2	69.7	71.3
63.7	65.4	67.0	68.8	70.7	72.3	73.8	7.5	63.6	64.9	66.2	67.8	69.4	70.9	72.6
64.9	66.6	68.2	70.0	72.0	73.6	75.1	8.0	64.6	65.9	67.3	68.9	70.5	72.1	73.8
66.0	67.7	69.3	71.2	73.2	74.8	76.4	8.5	65.5	66.8	68.2	69.8	71.4	73.1	74.9
67.0	68.6	70.3	72.2	74.2	76.0	77.6	9.0	66.3	67.7	69.1	70.7	72.4	74.1	76.0



67.9	69.5	71.2	73.1	75.2	77.1	78.8	9.5	67.1	68.5	70.0	71.7	73.4	75.2	77.1
68.8	70.3	72.0	73.9	76.1	78.1	79.9	10.0	67.8	69.4	71.1	72.8	74.5	76.3	78.3
69.6	71.0	72.7	74.6	76.9	78.9	80.8	10.5	68.6	70.4	72.2	73.9	75.7	77.6	79.6
70.2	71.7	73.4	75.3	77.6	79.8	81.7	11.0	69.6	71.5	73.4	75.3	77.2	79.2	81.2
70.9	72.5	74.2	76.2	78.5	80.7	82.8	11.5	70.7	72.8	74.8	76.8	78.9	81.0	83.2
71.6	73.3	75.0	77.2	79.6	81.9	84.2	12.0	72.0	74.2	76.4	78.7	80.8	82.9	85.1
72.4	74.1	76.0	78.3	81.0	83.4	86.0	12.5	73.7	76.0	78.2	80.3	82.4	84.6	86.8
73.3	75.0	77.0	79.6	82.5	85.4	88.1	13.0	75.2	77.5	79.7	81.8	83.8	86.0	88.2
74.3	76.1	78.4	81.2	84.3	87.4	89.9	13.5	76.6	78.9	81.0	83.1	85.0	87.0	89.1
75.6	77.4	80.0	82.9	86.1	89.3	91.4	14.0	77.9	80.0	81.9	84.0	85.9	87.8	89.8
77.0	78.9	81.7	84.7	87.7	90.7	92.7	14.5	79.1	80.9	82.7	84.7	86.6	88.4	90.2
78.5	80.6	83.4	86.3	89.2	91.9	93.7	15.0	80.0	81.7	83.4	85.2	87.0	88.7	90.4
80.3	82.5	85.0	87.7	90.4	92.8	94.6	15.5	80.7	82.3	83.9	85.6	87.4	89.0	90.5
82.0	84.1	86.4	88.9	91.4	93.6	95.3	16.0	81.2	82.7	84.2	85.9	87.6	89.1	90.6
83.2	85.2	87.5	89.8	92.1	94.2	95.9	16.5	81.4	82.9	84.4	86.1	87.7	89.2	90.7
83.9	86.0	88.4	90.4	92.7	94.6	96.4	17.0	81.6	83.1	84.6	86.2	87.8	89.3	90.8
84.4	86.5	88.8	90.7	93.1	94.9	96.7	17.5	81.7	83.2	84.7	86.3	87.9	89.4	90.8
84.7	86.8	89.0	90.9	93.4	95.0	96.8	18.0	81.7	83.2	84.7	86.3	87.9	89.4	90.8

The data were collected 1930-46 on Iowa City boys of northwest European ancestry in attendance at the University of Iowa experimental schools.

Technique for measuring sitting height: The child sits on a horizontal bench about 30 cm. high at the base of a vertical measuring rod. The knees are flexed and spread apart and the ankles crossed, and the sacral, upper thoracic and occipital regions are in contact with the scale. The measurement is taken as in height. This measurement is of value when the question of disproportionate growth is being considered: disproportions will be evident when the percentile positions for standing height and sitting height differ appreciably.

The measurements in this table are from studies by and are reproduced by courtesy of Howard V. Meredith, the Iowa Child Welfare Research Station, the State University of Iowa.

# MENTAL AND EMOTIONAL DEVELOPMENT

Many children present problems purely of personality or faulty social adjustment; emotional reactions often complicate or are complications of physical disorders. Actually, the child grows as a whole with an intricate interplay of physical, mental and social factors. The following summary of intellectual and emotional development will rarely be found in such pure culture in the individual child.

Mental and emotional development is always in a state of flux. The physician must form the habit of noting mental and emotional symptoms even more than physical ones as part of the child's progressive development. The newborn infant lives a vegetative existence which depends largely on functioning of the spinal cord and the lower levels of the midbrain. Soon, however, he begins to use certain facilitated pathways in the nervous system which link the actions of various muscle groups. The more deeply patterned of these pathways are termed "prepotent reflexes," a term which has superseded its predecessor, "instincts." The higher cerebral levels soon begin to function, and environmental influences then rapidly increase in importance in modifying behavior. Many people, however, fail to recognize that through the "psychomotor tensions" the various factors of environment have made definite impressions from the day of birth. This is the term for the way we talk, walk, hold the baby and cuddle him, the nuances that accompany all human interrelationships. Nothing is more important than for the physician to realize that the tension of each voice in the home, the furrowed or serene brow in the office or at the bedside—all mean more to the child than whole volumes of words.

## HEREDITY AND ENVIRONMENT

**Heredity.** The relative importance of heredity and environment in determining behavior is not known. The understanding of human heredity is so incomplete that the physician should assume every behavior problem to be of some environmental origin. On such a basis prevention and treatment may be considered possible. Of course physical characteristics and many physical defects cannot be changed. This is also largely true of intellectual defects. There are, however, means for improving the lot of many children. The care of the handicapped child and of those chronically ill has

become one of the great responsibilities of pediatrics.

**Environment. Family experiences.** The child's environment begins to crystallize long before he is born. His parents, in their teens, began dreaming about what their children should have or should be. No two children of any family have the same relationship to parents; with each new child the family pattern undergoes a change.

The family experiences of the child, owing to his susceptibility, are the most determining of his entire life. The physician must know what the parents are like, the siblings, and what each child means to the family. Is each child accepted for himself, an individual loved because he is what he is? Or are the parents overcome with resentment because a girl is not a boy? How is the newborn accepted by various members of the family? These and many other factors are important in the development of the child's emotional pattern.

**Ancillary factors.** The physician, nurse and school teacher have significant roles. Each is considered more or less a magical person and is listened to by parents, who accept his guidance with little question because he is an expert. This being so, the physician, as well as other advisors, must be aware of the implications for good or bad every time he gives advice. A fair share of behavior problems are iatrogenic, brought on by well-meaning physicians who do not always understand human behavior and who make suggestions which turn normal developmental patterns into abnormal ones. For example, messy eating habits, normal in the preschool child, may be bottled up by rigorous attempts at cleanliness, with the result that the child becomes not only a finical eater, but also compulsively clean and even constipated. Or a misinterpretation of deliberate withholding of feces, if treated by mechanical manipulation of the anus, can result in obstipation.

**Neighborhood.** When the child is about two years of age, the neighborhood becomes an integral part of his environment and a powerful force in molding his personality. He needs opportunities to meet other children with whom he may play in a small group under supervision of a responsible adult. As he grows older, the group can be larger and the supervision less individual. The child



graduates from playing in his or a neighbor's backyard with a companion or two to larger group activities which require larger play areas and some degree of organization.

**Nursery school.** The nursery school can assist the preschool child to grow up. Unfortunately there are many misconceptions about its usefulness and purpose. The good nursery school provides the preschool child with socialization opportunities which help him to become independent of his parents in a healthy way; it also provides opportunities to play in ways which many homes cannot tolerate because of his messiness and destructiveness. A good school helps parents as well as children by individual guidance about behavior. Early signs of maladjustment may be detected and steps taken to prevent further development of behavior problems. Parents can see that their children have many characteristics common to others of the same age and thus are reassured that development is proceeding as it should. *Not every preschool child needs nursery school experience.* It is particularly helpful to the only child and his parents, or when living quarters are cramped and inadequate. The physician should not advise concerning a particular nursery school until he has visited it and found out its general philosophy.

**Grammar school.** The child from six or seven years of age onwards is required by law to attend school unless there are physical or mental handicaps which excuse him. School has so many advantages that every attempt should be made for even the severely handicapped to have this opportunity. The school-age child is a "natural" to learn, because of his curiosity about everything. He learns best when he is with people who understand and love him and are skilled in bringing out his natural abilities. School also offers relationships with adults with whom to identify as the child fashions his own image of an adult. Where parents served first, teachers now take over. Like the physician and the nurse, the teacher needs to know that he is used by growing children as a model. In his own age group the child finds protection as well as stimulation. He wants to be like others, and fashions himself after his schoolmates; joining the gang or group multiplies his strength and permits him to do things he could not do alone. Here he can be both a follower and a leader. Behavior problems may arise anywhere in the chain of school experiences. Inability to learn, anxiety of competition, fear and

resentment against a teacher who does not understand, withdrawal from the group owing to feelings of difference or fear—all are examples of behavior difficulties brought to a physician. Every school should have on its staff a physician and a nurse, and probably a social worker, who, with the teacher, can detect a child who is in trouble and introduce measures to help him. A school physician thus becomes more than one whose role is making periodic physical examinations or checking skin and nose and throat at morning roll call. This physician needs a close working relationship with all members of the school staff, as well as with the child's family physician. When problems appear in a child, he should also have an understanding of the home life, and the child should be thoroughly studied physically, mentally and socially.

**Recreation.** Although school curriculums should provide time for supervised play during school sessions, each child needs additional time to play. School yards and buildings should be community resources for providing recreation to all members of families.

**Religion.** Religious education and worship are important forces in the development of children. The child of four or five is eager to go to church school, because most children attend by that age. He may be repelled if his religious experiences are too fear-inspiring. The school-age child has a strict conscience, based on fear of disappointing parents and other people. He may become so guilt-ridden by pressures in religion that his behavior indicates emotional disturbance such as compulsive acts (penance) and protective rituals, or extreme goodness and feelings of unworthiness.

## REFLEX ACTIONS AND LEARNING,

The reflexes are important because the time of their appearance is an indication of the child's development and because the manner of their use indicates the intactness of the nervous system. Reflexes tend to develop in an orderly fashion. This development is not in order of complexity, since, for example, swallowing is present even before birth. Those reflexes most necessary to life develop earliest. Usually the development proceeds in an outward direction; e.g., the reflexes of the hands and feet develop later than those of the arms and legs. A common mistake is that of urging the use of pencils and other objects requiring fine finger coordination before the

child has familiarized himself with the coarser coordination of the arm and forearm. Much clumsiness in writing and the ever present complaint of destructiveness are due to failure to fit toys to the normal progression of development.

In general, failure of a reflex activity to develop at the proper time indicates retardation which will become more evident in the succeeding months when other and more important reflexes should appear. Weakness or absence of a reflex suggests a lesion in the peripheral reflex arc; exaggeration and jerkiness, a lesion in the central nervous system.

**Progression of Motor Development.** (See Table 7, p. 34.) Behavior which began as a reflex progresses to a more complicated pattern through repetition, learning (from stimuli within the self) and teaching (stimuli from outside). An example is that of grasping—a reflex present at birth which becomes integrated so that by three months it is purposeful and voluntary, and by six months a bottle or rattle will be grasped. By about eight months simple objects can be manipulated, and simple movements imitated and the infant will “pat-a-cake” and play “peek-a-boo.”

When lying on his stomach, an infant of a few weeks of age will lift his head momentarily, but he does not have this ability when lying on his back until about three months; by five months he will roll over. Muscular power and coordination increase, and he will sit erect without support by six or seven months, creep by seven months, stand by eight or ten months, and walk soon after. He will usually be able to run at two years and will walk backwards or go downstairs alone by thirty months.

This progress depends on the functioning of well patterned reflex pathways and training; the pleasure obtained from these activities is a reward which fosters their continuation. It is, however, necessary to recognize the orderly progression of reflexes and the child's readiness for certain behavior which is individual with him, so that the child is *allowed* rather than forced to develop.

**Learning.** Children learn if they have the proper physical equipment such as intact sensory systems, and if they have the opportunity and the proper teaching. There are many theories of learning, but all agree that each child has to do his own learning.

Many repetitions of an act determine pathways in the nervous system, so that a pattern of response occurs when the appropriate stim-

ulus is given. These acts have the appearance of reflexes, but are termed “habits”; they differ from reflexes chiefly in the fact that they are more easily modified or are voluntary. These pattern responses are also called “conditioned reflexes,” and are believed by some to embrace a large part of the child's learning. Children may learn the use of the toilet by conditioning. The trouble with this kind of learning is that it can break down when the setting is changed even slightly. A different bathroom from the accustomed one may interfere with defecation.

Learning through teaching whereby the child understands and has feeling for the behavior learned is more useful and longer lasting. That is why children who learn by doing get a feel for their actions and retain what is learned so that they are able to apply it correctly when called upon. This does not mean that learning cannot be hastened by drill and practice.

Four principles or factors apply to learning by the child. These are (1) emotional and physical ability; (2) desire to learn; (3) previous experiences; and (4) active participation. For example, he will learn to read when he is ready (not all children are ready at six years), when he has the interest, and when he gets pleasure from the act so that he wants to repeat it and one day do it by himself. In a general way, high or low levels of intellectual ability are transmitted to children by parents of corresponding levels, but there are many exceptions. However good a child's native ability is, it can be helped or hindered by environmental factors.

## SENSORY DEVELOPMENT

The protopathic sensations are well developed at birth, although poorly localized. They include those of pain, temperature, touch and equilibrium, the kinesthetic sense of muscles and joints and the various sensations of discomfort or satisfaction in the functioning of the gastrointestinal and urinary tracts.

**Special Senses. Smell and taste.** These two senses are present at birth. By two or three months of age, taste is acute, and the infant will notice a change in the amount of sugar in a formula or a change in type of milk mixture and demonstrate pleasure or displeasure. The infant explores his environment in this way and it is normal for him to put everything into his mouth. This exploratory activity with the mouth, along with



much sucking, usually persists through infancy and is a part of normal development, not an activity to be curtailed. Persistence of "mouthing," drooling or excessive sucking of fingers or objects after the age of three years should suggest a study of the child's mental health.

**Sight.** In the first few weeks of life sight is limited to the ability to distinguish light from darkness. Bright light causes contraction of the pupils and closure of the eyelids. By about one month the eyes will follow bright objects; they will turn toward the direction of an unusual sound, and the eyelids will close if objects are brought near the eyes. By three months the infant will recognize his bottle or a similarly familiar object, and the movements of the eyes are usually coordinated, although incoordination may persist for several months longer. By five or six months visual impulses are stored up (memory), so that there is increasing recognition of familiar faces and objects; about this age the emotional response of fear begins to show a stereotyped pattern, with crying at the sight of strange faces and objects. Infants are normally farsighted.

**Hearing.** A few days after birth, hearing is acute, especially for high-pitched noises. Musical notes may be pleasing by four months of age; even earlier, some infants are soothed by a soft voice or a lullaby. Serious defects in hearing are often overlooked because of the custom of accompanying words with appropriate gestures.

## SPEECH

The development of speech is one of the best measures of intellectual progress; though environmental factors play a role in acquiring speech, undue delay in its development is a bad prognostic sign. The important consideration is not the clarity of speech, but whether the child tends to use a distinctive sound or symbol for an object. For example, does he consistently make the same sound to indicate a chair even though the word "chair" is not distinctly enunciated?

The relation of environmental factors to speech is not predictable. Thus a child who is constantly associated with adults is often precocious in speech. Less frequently these same conditions retard speech, since the child need not learn to enunciate distinctly when oversolicitous adults fulfill his needs without his asking. Often twins will show retardation in

speech, since they have learned to understand each other by other means.

## EMOTIONAL DEVELOPMENT

In comparison with the knowledge of physical growth, little is known about emotional development. There is unquestionably an ordered emotional development just as there is an ordered intellectual and physical development. There are, however, no standardized methods of determining the normality of a child's emotional growth, although there do seem to be distinct phases of development. Gesell and co-workers have devised mental tests which assess performance and behavior at different stages of infancy and are helpful in differentiating the intellectually normal from the mentally defective child. Other tests such as the *thematic apperception tests*, the Rorschach being an example, have been devised as short cuts in appraising affective development and emotional disturbances, but the complexities of personality require more detailed investigation.

Although the various concepts of emotional development disagree in some respects, there is agreement that the human personality is the product of a dynamic process which is ever changing and growing as the body develops and matures. This process may be regarded as an interplay of forces in the child with those in his environment. The experiences of early life are important in forming the subsequent personality structure. For this reason the role of the child's physician as a guide is of paramount importance.

Of the influences which determine behavior, probably most important is that of the mother, or her surrogate, who cares for the child from birth on. If the mother is able to respond to him naturally, accepting him as he is with love and permitting dependency without fostering it, she will naturally become aware of his needs.

Feeding of the infant by the mother permits early establishment of a good interpersonal bond when the procedure is satisfactory to both of them. Contrariwise, feeding practices which are forced will foster problems in various areas of behavior. The dependency which the infant shows toward his parents, particularly the mother, is gradually replaced by independence and self-sufficiency. The beginnings of such emancipation are seen around the age of two years. This psychologic weaning is not uniform; it probably begins

with self-feeding and ends after adolescence, but its progress and final resolution vary. Some parents attempt to speed up emotional development and are abetted by professional persons who mistake physiologic dependency for immaturity and interpret cuddling as coddling. A child who is pushed psychologically beyond his depth or faster than his natural rhythm will become tense and anxious. On the other hand, when parents try to slow up progress, the normal child will throw off the yoke of oversolicitude and pampering.

## INTELLECTUAL GROWTH

For practical purposes, intelligence may be defined as associative memory. Mere memory, however, is not intelligence, and the child who recognizes different makes of automobiles or remembers innumerable telephone numbers is not necessarily intelligent.

A distinction must be made between "formal intelligence," which is used in academic learning, and "contentional intelligence," which may be defined as common sense, shrewdness, astuteness or the ability to get along with people. Probably both types of intelligence are somewhat determined congenitally, education and environment playing an important role in altering them. Much confusion has arisen over failure to recognize that the so-called intelligence tests do not measure contentional intelligence. At present there are no standardized tests for this important function, and the physician must use, as in the field of emotional development, subjective judgment of the child's ability in this respect.

**Intelligence Tests.** These tests measure only formal intelligence. Though they do not measure to any significant degree the ability to make social adjustments, they do reflect the capacity for learning.

The intelligence quotient (I.Q.) is obtained by dividing the mental age (M.A.) by the chronologic age (C.A.) and multiplying the result by 100. Thus if a child of eight years of age performs the tests which an average child of ten years is able to perform, his I.Q. is 125; whereas if he only performs the tests which are expected of a six-year-old child, his I.Q. is 75. The most widely used test in this country is the Stanford revision of the Binet-Simon tests. The I.Q. remains practically constant, but in children under six years of age it is only of approximate prognostic value. Emotional disturbances such

as anxiety, fear and worry, and physical factors, such as fatigue and inadequate nourishment, may modify the rating.

Though only approximately correct, an I.Q. over 140 (genius) signifies that there should be amplification of the school curriculum; 120 to 140 (very superior intelligence) represents capability of professional school attainment; 110 to 120 (superior intelligence) indicates good college potentialities; 90 to 110 (normal intelligence), good high school ability; 70 to 90 (dull normal intelligence), good sixth to eighth grade ability; 50 to 70 (moron), that school work will be unsatisfactory, but there is the ability to do simple repetitive types of manual work; 30 to 50 (imbecile), that there should be permanent placement in an institution (most good school systems exclude children with an I.Q. below 50 as uneducable); below 30 (idiot), that there is no capability for self-care. Although tests should be performed only by those familiar with their interpretations, Table 8 (p. 35) can be used to form a rough estimate of intellectual development.

Inequalities between demands or expectations of parents or teachers and the ability of the child are frequent sources of difficulty and lead to such symptoms as nausea, anorexia, stammering and tics and to such behavior difficulties as irritability, rebelliousness, truancy and seclusiveness. Faulty school placement also is the source of such behavior disturbances. The physician need not be an expert in education, but he should know first-hand the child's school and its demands. The child's I.Q. is important in relation to that of the general average of his class or school. Children with I.Q.'s only a little below the average are under much more strain than those whose ability is sufficiently low so that they are not expected to keep up. The physician must look at the "whole child" and recognize that a child of seven years with an I.Q. of 130, but without comparable development in other respects, is different from one of seven years who has the physical, emotional and intellectual development of a child of nine years. The former should be kept in second grade with an enriched curriculum; the latter is better in third or, on occasion, even fourth grade. School promotions are not problems for the physician, but recognition of the related difficulties may serve to explain certain baffling and stubborn behavior disorders.



## MENTAL HYGIENE

The role of the pediatrician in helping parents and children in personality disorders, psychosomatic illness or deviant behavior is not always clear. By training, experience and the limits of his practice the pediatrician seldom is prepared to serve as a psychiatrist. However, he and the general practitioner most often see psychologic problems in their incipency. For this reason he must assume some kind of role. Ideally, he should have a working knowledge of growth and development and of interpersonal relationships and should incorporate psychotherapeutic principles with the diagnostic study and treatment of each patient.

### A WORKING HYPOTHESIS OF BEHAVIOR\*

There are a number of theories of behavior; disagreement among the proponents of the various ones has delayed acceptance of mental hygiene concepts in medicine. The pediatrician who takes time to listen to parents, carries out his examination in an individual, careful and humane manner, and then patiently and objectively attempts to evaluate the results, practices mental hygiene. For guidance and teaching the physician may look to persons who are specially trained in medical psychology and psychiatry. Insight which comes in this manner is preferred to the so-called common-sense approach, which may sound reasonable, yet in practice too often turns out to be highly subjective and often irrational.

It is possible for the physician to have a practical yardstick to measure the behavior of many of his patients. In a number of instances, however, help of a psychiatrist or psychologist will be necessary.

The child comes into the world with certain "raw drives," e.g., the compelling one of the desire for food. Soon society begins to place barriers in front of this desire and to frustrate it—"you can do so and so if . . ." This type of frustration produces emotions, and emotions are the driving force for behavior of any form, be it socially acceptable and useful or socially condemned. There is, on the one hand, the orderly sequence of biologic and instinctual growth and development, and on the other the laws of social order. Periodically they meet in conflict, setting up emotional reactions in the child. There should be no attempt at destruction of

the "raw drive," but, instead, modification in keeping with cultural attitudes so that the resulting emotion will be optimally healthy and will permit the child both to experience his feeling and to get release in a way which is satisfactory to him and to society.

### EMOTIONAL GROWING PAINS

There are many traits of behavior in childhood which are part of healthy growing up, but are unacceptable to adults. They are characteristics which the adults also have, but wish they did not. Adults would like their children to be free of them and become upset when they are manifest.

**Jealousy.** Parents worry because children demonstrate jealousy, failing to realize that it is a normal reaction. In part it represents a self-protective device. For example, the arrival of a new baby is threatening to other children in the family, who become jealous of their status in the family. Rivalry is frequently an accompanying attitude and grows out of a wish to be recognized and to win one's share of attention, admiration and love. These feelings may also exist between playmates and classmates in school. When a child is unusually jealous, his parents should consult a physician, who may do much to reduce the tensions which seem to threaten the child. The meaning of the behavior must be sought, rather than a direct attack made on the behavior itself. Feelings of jealousy and rivalry are sometimes fostered by parents in an attempt to encourage a child to increase his efforts at learning or in improving his behavior in general. When children cannot successfully meet competition, they may be forced into a variety of behavioral characteristics which may include jealousy and a whole constellation of disturbing traits.

**Fear.** Fear is useful if it is transmuted to caution and prudence. Often, however, in conditioning the child to be cautious of fire, hot stoves, traffic hazards, strange dogs and the like, parents become disturbed when the child shows too much caution about things which they think he should not fear. Fears may be taken up almost as if by contagion when parents themselves are frightened. The physician will often be consulted about such problems as fear of sleeping in the dark, fear of other children or fear of going on errands alone. In many instances the parents have made such an issue of certain fears that what was a natural caution is fixed as an overpowering fear. Fortunately, most children

\* See also page 73.

rapidly lose unnecessary fears as they make contacts with other children.

Fears which are irrational and so severe that they interfere with normal activity are more properly termed anxieties. It is normal for anxieties to appear in all children in response to certain experiences. The young infant who in the first half-year of life does not seem to mind when his parents leave him, suddenly at six to eight months of age develops anxiety whenever they leave. At this time he also becomes anxious at the sight of strangers. Knowing that certain anxieties tend to develop at particular ages will be reassuring to parents and will help them to avoid situations which may intensify the anxieties. If a child must be separated from his parents, as in hospitalization, he should be prepared for it and the separation should be as brief as possible. Every effort should be made to maintain family contacts by writing, telephoning and visiting as frequently as possible.

The causes of anxiety are not always easy to ascertain, since they are frequently subconscious and part of defense mechanisms. For example, a child who has done wrong feels guilty and develops feelings of anxiety and fear of punishment. As children grow older and gain mastery over many of their impulses, their sense of reality becomes more mature and their tendency to become anxious is modified. Adequate maturation depends particularly on the relationship with the parents. The child needs to feel that they will go on loving him, despite his misdemeanors. Children frequently feel anxious about new experiences, and at these times particularly need encouragement and support. A sense of security fostered through many years of parental affection and confidence is the best protection against the development of abnormal anxiety.

**Anger.** The emotion of anger usually disturbs parents more in the way it is manifest than in its mere existence; many recognize it as a useful and protective mechanism. In early life the child shows this emotion readily, and temper tantrums are a common response to frustration in the first decade. After that age the child may hesitate to display this emotion because of fear of social reprimand.

Temper tantrums are violent physical responses accompanying anger. Sources of the emotion should be sought. When the child uses the tantrum as a device for gain, the question must be raised why this is the method of choice. An effective method of

managing a temper reaction is that of disregarding it. On occasion, holding the child (a difficult physical feat!) to quiet him, rather than for punitive restraint is recommended. The physician must never forget that anger arises justifiably when a child does not receive something which he actually needs or feels is due him, or when he is told to do something beyond his capacity. When the child at any age consistently feels and expresses anger of an unusual degree, or when he seems too passive, medical and psychologic appraisal is indicated.

**Stealing.** Young children do not naturally know about the rights of private property. They may help themselves to articles which belong to others; this is not stealing. As the young child's own property rights are acknowledged by parents and protected by them against the acquisitive tendencies of other children, the child gradually becomes aware of what is his and what belongs to others. He may occasionally take things from others without their permission, and society labels this as stealing. The causes of such behavior are many; for some children this constitutes a game, as if to see "how much one can get away with." Others steal in order to acquire material things which they seem unable to get by other methods. Stealing which persists, which is more than occasional and becomes more or less habitual, constitutes psychopathic behavior. In such instances psychiatric assistance should be sought.

**Lying.** Many parents have forgotten how they transmuted their earlier experiences into what they now term diplomacy, or white lies, or keeping up a front, or not making trouble by telling everything they know. Parents should distinguish between the make-believe which every child has and lying. The child does not distinguish till the school years. His first lies may be natural defenses when pressured by adults. Most children tell the truth until it is uncomfortable for them to tell it, when they begin to distort. "Make-believe" which the child cannot distinguish from reality, and persistent defensive lying are indications that something is going wrong and that a thorough evaluation of the child and his environment is necessary. Perhaps referral to a child guidance clinic should be considered.

**Summary.** The preceding paragraphs are illustrative of the more common problems involved in transmuting what we have termed "raw drives" into socially useful and acceptable modes of behavior. In general the physi-



cian will find that parents make three mistakes in this field: (1) Many do not understand the naturalness of these raw drives. They are worried over the degeneracy of their children. They bring them to the physician because they steal, because they are jealous and because they are always under foot, without realizing that it is precisely these impulses of acquisitiveness and ambition, and the wish to be in the center of things, that make the world go round. Such parents should be helped to remove the moral implications from the drives, and to understand that, properly directed, these attributes are the children's best assets. (2) Many parents try to convert these impulses too rapidly. Thus they expect children to earn all their spending money, often when they are too young or are incapable. Children who are exhorted to get better grades in school than they are able often resort to cheating, to sulking or to stealing money with which they can buy social favor. (3) Many parents have never progressed much beyond the childish drives. They tell lies (white lies), they steal (successful financing), they bully (feel that others should know their place), they cringe (are careful and conservative), and they are intolerant (have a position in society to hold). Before attempting to deal with a family of this type, the physician must decide what he expects to accomplish. Obviously he can do little for the child unless he changes the attitude of the parents. Patience on his part will be more effective than coercion in helping parents to understand gradually the need to change their views and interpersonal relationships.

#### PROPHYLAXIS

*A child whose psychologic needs are met is well on the road to good mental health and a successful social adjustment.* The physician will do a real service by explaining these needs to the parents. They are as follows:

1. *A sense of belonging* in his family group, a position he has because of who he is rather than of what he does. Parents should show this attitude toward their children by word and by act. Children are quick to sense the implications of voice sounds even before they understand the meanings of words. They also require physical expression of affection throughout childhood. Parental championing is necessary as a sign to the child that he has protection and a safe haven. Parents may bestow praise or blame; nevertheless the child has an assured place that he cannot lose. Such

factors are the psychomotor tensions which mold the child's behavior patterns. The child who does not have the feeling of belonging is termed "the rejected child."

2. *A set of parents with whom to identify* while growing into manhood or womanhood from infancy through adolescence. This means a father and a mother who are around enough so that the child can see what a man and a woman are like, and how they meet life's experiences. Through imitation, but even more by unconscious identification, each child will fashion himself after his parents, one day having full recognition of his own identity as a person.

3. *Experiences in being needed*, in the sense that the family actually depends upon him for some part of its life. These experiences must be real; the child quickly sees through artificially created chores or responsibilities which a parent will take over when he fails. For example, most so-called student government plans do not fool children when they become aware that an adult will see that nothing serious will happen.

4. *Opportunities for finding satisfaction in the world about him*, rather than in his day-dreams.

5. *A chance for adjustment with a group* which will help him to be both a follower and a leader. He needs to feel the advantages of being an individual, yet a person who also is able to fit into a group.

6. *Experiences in self-sufficiency and independency.* In the first two years of life the child is naturally dependent for much of his care. However, even by the sixth month he begins to strike out for himself in self-feeding, and from that time on has a drive to take care of himself. In becoming independent he regresses, on occasion, as if to get strength before moving ahead. Parents expect independence to proceed regularly, and even rapidly. Such parents tend to force and urge independence, which may lead to greater clinging. Others try to hold back, which leads to a clash of wills as the child fights for the chance to be on his own. The physician can serve as an interpreter of the laws of behavior and as arbiter in the struggle between children and their parents.

7. *The security of stable circumstances*, particularly of dependable human relations. Children are confused and emotionally upset when parents are in disagreement. The discipline which every child craves should be consistent and understanding.

### PROBLEMS OF TRAINING

Parents and the physician must try to find out what the child is attempting to do. The child's methods need not always be approved, but certainly he is not to be laughed at or scorned. There must be honest explanation and direction; there should be praise for correct actions and as little emphasis upon wrong ones as possible. Demands must not exceed the child's ability; and the natural consequences of his acts should be pointed out, rather than an attempt made to control them too stringently.

**Obedience and Discipline.** Problems related to obedience and discipline will come to the attention of the physician. The most frequent are (1) *insistence upon obedience for its own sake*, all sorts of unreasonable acts being demanded of the child. Such important matters as musical education or the drinking of milk are frequently confused with the highly engaging but totally irrelevant question of "Who's going to win?" Problems related to authority should be anticipated; i.e., the child should clearly understand what penalties will be imposed for certain acts, and these penalties should be invoked if the acts are committed. (2) *Too much authority and punishment.* A child becomes negativistic and rebellious when parents insist upon too many rules and regulations. (3) *Irregular discipline.* When discipline is neglected, the child does as he pleases in disregard of threats of punishment, only to have the whole storm break suddenly, often over some trivial matter. (4) *Failure to realize that a child must be taught obedience.* When he is allowed to do what he pleases under the guise of unhampered development, he must learn bitter lessons later in life. When the physician advises some degree of control of a child in such a family, he probably will be looked upon as an ignorant barbarian. (5) *Divided authority.* When one parent is strict and the other lenient, each in emphasizing his or her attitude tends to counteract the other. A situation between the father and the child should be their affair, and bringing the mother into it is a sign of weakness. If she disagrees with the father, both parents are in a most embarrassing situation which the child will not forget. If she agrees with the father, the child is crushed. It is inexcusable to humiliate a child before adults or other children.

**Punishment.** Punishment should be kept to a minimum. It should be short and meaningful, and should be related in time as closely

as possible to the wrongdoing. In some instances spanking may be the only appropriate punishment, in others deprivation may be more effective, and many children are adequately disciplined merely by words. So far as possible children should know what act will incur a penalty, and the penalty which has been explained should invariably be insisted upon. Corporal punishment has fallen into disrepute because many parents use it to vent their own exasperation; but, properly administered, a spanking is much to be preferred to long and vague verbal attempts to clear the situation.

**Cruelty.** The physician will often be consulted about cruelty of the child. In most instances this is nothing more than the child's ignorance of the effects of his curiosity or overweening affection. Persistent and willful cruelty, like jealousy, is a strong indication that the child needs psychologic help.

**"Dawdling Play."** Play, often of an aimless sort, is a constant necessity in youth; but many parents who think of life only as a serious affair worry over any play that is not educational. A child appears normally to waste much time; perhaps these are the periods when he solidifies the gains made at such lightning speed at other moments.

**Negativism.** Doing the opposite of what is asked may be a defense reaction against too frequent correction. It is difficult to treat, because most parents insist on advice as to how to make the child obey, when the problem is that he has already had an overdose of precisely that. All normal children show periods of negativism as they try to adjust to growing pressures from the world around them, and the physician may well worry over the emotional retardation of the child who is uniformly compliant and polite. A "negative" child often demonstrates a physical withdrawal, a stiffening or shrinking which is the opposite of cuddling. In a group he always manages to be a little apart from other children instead of merging with them.

**Carelessness.** Parents frequently complain of carelessness and lack of cleanliness. Within limits these faults must be considered part of the average child's behavior. They are often inadequately dealt with until interest in the opposite sex occurs at adolescence, when a rapid improvement may be expected in the care of clothes and in personal appearance. In the earlier years carelessness can sometimes be overcome by removing toys or other possessions from the child who does not treat them properly. The penalty must be made



clear ahead of time; then it must invariably be carried out if the occasion arises.

## PLAY

All children like to play. Unobtrusive supervision is necessary, but play should not be interfered with. Perhaps more can be learned about a child through his play life than through any form of study; it is the time when he builds his own culture. His real venturings or timidities, his ideas as to what is fair, his sociability, and so forth, are not trammelled in play by what he thinks his parents want. The physician should know in general the ages at which the child plays peek-a-boo, tag, hop-scotch, marbles, and the like; he will then have a quick and reliable index of the child's emotional age or contention intelligence. Play with other children should be encouraged because of the great educational values of imitation, competition and the requirement for emotional control.

The most important criterion to be met by play materials is that of safety. Toys should not have sharp corners, cutting edges, exposed mechanisms in which fingers can be cut or pinched, or small detachable parts which could be swallowed or aspirated. If the eyes of dolls and animals are not fastened securely, they should be removed, and embroidered or painted eyes substituted. Toys should be colored with lead-free paint or vegetable dyes. They should be sufficiently durable to withstand banging, dropping and general abuse. Washable toys are preferable, particularly for young children. The child's toys and games should be appropriate to his stage of development. Children two to four years of age prefer simple and realistic toys rather than too many or too elaborate ones. Older children should be supplied toys or play materials with more detail, which allow individual effort and skill to be exercised. Large but lightweight blocks which demand arm movement should precede the smaller ones with which the fingers must be used; these small blocks in turn must precede large crayons or chalk, and these again must be used before small crayons and pencils. Each child is his own competent guide as to when certain reflex arcs are ready for use; he will invariably use the finer adjustments of the muscles at the ends of his arms and legs when the mechanisms for them are ready. Hastening of writing and of using intricate toys should not be permitted.

## SEX EDUCATION

Curiosity about the anatomic and physiologic differences between the sexes always arises in the child's mind, and information must be furnished from some source. This curiosity is at first only part of the child's general inquisitiveness. A child who does not ask his parents questions about sex either is being instructed elsewhere, often incorrectly and viciously, or has been repulsed. When the physician is consulted about the child's persistent interest in sex, he will find that this interest comes mainly from the parents' own disturbance over such questions. Obscene pictures and notes, which bother teachers so much, almost never originate from children properly placed in school and happy in their work. The child uses discussion of sex to gain certain important ends. If the physician cannot spare the time to find out what the child is trying to do with his so-called sexual interest, he had better let the matter alone. Treating the problem as a sexual one only assures the child that his methods are efficient. There are infrequent exceptions to this rule; some of these originate in abnormalities or irritative conditions of the genitals, others from maladjusted playmates.

The natural educators in matters of sex are the child's parents, who have the opportunity to answer naturally the normal and simple questions as they arise. Few parents, however, or even physicians are able to answer such questions without embarrassment. The present-day insistence that parents tell the truth has created a difficult problem for most of them. Adults do not even have a good vocabulary for this sort of venture. Parents should tell the truth, if they know it, and can tell it without having the child realize he has asked an upsetting question. If not, they had better resurrect the story of the stork, rather than let the child feel that there is something sinful and dirty about his questions. It is far more important that the child come to adolescence with the right attitude about sex than that he have stray bits of information which he has to learn over again.

In young children discussion of methods of reproduction in plants and lower animals leads naturally to the same questions concerning human beings. The presence of dogs or other animals in the neighborhood helps the child to realize the naturalness of the reproductive cycle. The mother can usually act better as an instructor for older girls and the

father for boys, although with younger children of both sexes the mother more naturally meets the issue. If parents are unable to supply adequate sex education—and many cannot—it is better, for children past eight or nine years of age, that someone such as the physician take the time to do this simply and naturally. Explanation should be given to the boy at the proper age when he must expect certain physiologic changes such as erections and nocturnal emissions; the girls must likewise know the facts of menstruation and their significance.

There is a surprising amount of homosexuality at the age of puberty. This takes the form of "crushes" between girls; and the same phenomenon occurs, although less markedly, in boys. The harmfulness of these usually temporary homosexual tendencies is greatly overestimated. The treatment must be indirect by seeing that there is healthy play life and satisfactory school adjustment, by discussion of budding plans for the future, rather than by direct attack upon the wrongness of

the affair. Masturbation is discussed on page 79.

MILTON J. E. SENN

#### REFERENCES

- Aldrich, C. A., and Aldrich, M. M.: *Babies Are Human Beings*. New York, Macmillan Company, 1938.
- Allen, F. H.: *Psychotherapy with Children*. New York, W. W. Norton & Co., 1942.
- English, O. S., and Pearson, G. H. J.: *Emotional Problems of Living*. New York, W. W. Norton & Co., 1945.
- Erickson, E.: *Childhood and Society*. New York, W. W. Norton & Co., 1950.
- Freud, A.: *The Ego and the Mechanisms of Defense*. New York, International Universities Press, 1946.
- Josselyn, I.: *The Happy Child*. New York, Random House, 1955.
- Kanner, L.: *Child Psychiatry*. 2nd ed. Springfield, Ill., Charles C Thomas, 1948.
- Lerrigo, M. O., and Southard, H.: *A Series of Pamphlets on Sex Education*. Chicago, Am. Med. Assn., 1955.
- Plant, J. S.: *Personality and the Cultural Pattern*. New York, Commonwealth Fund, 1937.
- Senn, M. J. E.: *The Psychotherapeutic Role of the Pediatrician*. *Pediatrics*, 2:147, 1948.



# PSYCHOLOGIC DISORDERS

## GENERAL CONSIDERATIONS

Deviant behavior in infancy and childhood usually results from a clash between the biologic drives within the child and forces outside of him. These outside forces may be parental or other environmental influences which for the most part serve as useful agents in the acculturation of the human organism so that he will one day fit into society; unfortunately, attempts at acculturation are often made prematurely and inappropriately. The pediatrician has a responsibility in protecting infants and children from such trauma. To do this and to promote optimal development and maturation, he must understand the needs of children, patterns of growth and development (physical, psychologic, social and intellectual) and the dynamics of behavior and of interpersonal relationships. This also implies an understanding of the role of parents and of their rights in parenthood. It is an old saying in pediatric practice that "treatment of a child includes treatment of the mother." A child is cared for best when considered in the environment in which he lives and grows.

Many of the behavior problems for which children are brought to the pediatrician, such as "nervousness," temper tantrums, finger-sucking, eating and sleeping disorders, turn out on investigation to be normal responses of infancy and childhood. At times they may be exaggerations of normal traits. They are problems when they cause concern to parents and others in the community, although the behavior itself may not represent abnormality in the child. Presentation of a problem in such instances may be indicative of psychologic disturbance in the parent. The remedy will then be more in helping the parent than in treating the child.

In children over five years of age behavior problems and emotional disturbances usually signify psychopathology within the child, even though the causes may be in his environment. After five years the psychologic mechanisms within the child are activated in a

more complex fashion and produce behavior which tends to be less infantile and to resemble some adult responses to psychologic difficulty. With growth and maturation of the child, behavioral reactions assume patterns in keeping with his developmental status and his cultural milieu. As a result it is common for children over five years of age to present (1) psychosomatic illness (pain, constipation, diarrhea, colitis), (2) neurotic symptoms (tension states, anxiety, fears, compulsions, tics, hysteria) which resemble the neuroses of adults, (3) conduct disorders, (4) sexual aberrations, and even (5) psychoses.

It will be helpful to the pediatrician if he is able to view child development in the following way: The child is a product, first, of his ancestry and, second, of an interaction between himself and various forces. These forces consist of physical, psychologic, cultural, social and economic forces in his environment. For example, the physical factors include pathogenic organisms, thermal and chemical elements; the psychologic forces contain influences of family members, of playmates, of teachers and physicians and nurses who take care of the child. The cultural forces consist of the current community attitudes toward child care and child rearing, including taboos, folklore and misinformation. Behavior and emotional responses which result from the interaction of the individual and the various influences of the community will be considered normal or abnormal by various standards.

The pediatrician may be called on to distinguish the usual from the unusual in behavior patterns, which is not always easy. Some emotional responses such as fear are natural to a child when he faces real danger, but exaggerated fear of a situation not fraught with danger is abnormal and may have its roots in a number of causes. In general, proof of the normality of many behavior reactions is that all children react more or less with such behavior when confronted with similar situations. When a behavior pattern which seems

extreme persists and is demonstrated by the child repeatedly under situations of ordinary stress, and in time is joined by other symptoms of dysfunction, it may be said to be psychopathologic. It is helpful in determining whether an emotional reaction is normal to consider the stage of psychologic development of the child and to appraise the environmental situations in which he is attempting to adjust. From these and from his life history one may estimate the progress he is making toward a healthy adult emotional development.

#### PSYCHOTHERAPY IN PEDIATRIC PRACTICE

The methods of study and treatment of children with psychologic disorders are, in general, the traditional ones of history taking and examination, but with insight learned from modern psychology. Diagnostic study and therapy proceed together; treatment begins with the very first contact between parent, child and physician.

History taking accomplishes two purposes: (1) collection of data, and (2) therapeutics. The medical history should be an anamnestic interview which does more than record the history of disease or somatic development. It should be the historical account of a human being who comes or is brought to the physician for help because someone feels concern. It is natural for the person coming for help to begin with a statement of the chief complaint, presenting symptoms and reasons for seeking assistance. The complaint is frequently on a somatic level and may include a list of behavior characteristics which disturb the parents more than the child. The first complaint uttered may not be the chief reason for coming to the physician, but, instead, may be a disguise assumed consciously or unconsciously to make a favorable and acceptable impression.

In order to understand the origin and development of the complaint in its relation to the current situation, the informant (usually the parent, but sometimes the child) must have ample time to tell the history as he sees fit. The life history may not be given sequentially; it will be reviewed best when the informant feels free to talk spontaneously without feeling the need to follow a rigid pattern. In such a setting the informant is often able within a unit of time set by the physician, or in a series of interviews arranged closely together, to talk frankly about his difficulties.

As the history is told it usually becomes evident, often even to the informant, that the onset of the symptoms or disturbing behavior coincides with periods of particular stress or disturbing contemporary events. The account of the present illness also often makes it clear that contemporary difficulties have their precursors in the earlier life of the patient. The difficulties may even be repetitions of earlier patterns of adjustment and maladjustment. The medical history provides data about the family at the time of the pregnancy and birth, the feelings of the parents toward each other and toward the newborn baby, about birth, early feeding and sleeping and many other details. *However important such data are, there is still greater significance in gaining, through the medical history, understanding of the feelings and attitudes of the parents as they care for the child in everyday matters such as feeding, toilet training, education and discipline, and of the infant's reactive feelings to these measures.*

The pediatrician who conducts the interview in this way soon recognizes that a relationship has been set up between himself and the patient. The informant quite as much as the physician recognizes that something helpful is taking place as he spontaneously presents material about himself and his family in a longitudinal and associative perspective. This interpersonal relationship, which may be called rapport or transference, is essential for therapy of any kind, whether medical, surgical or psychiatric.

The "talking-out" treatment, to be fully effective, must contain two basic elements: (1) the person must feel free to talk to an authoritative person such as a physician, and (2) the physician must be interested and sympathetic, able to listen and not bound to do something hurriedly. When he talks, he should use carefully chosen and properly timed questions and note whether the responses bring relief or upset the informant. He will be guided in how far to go and what topics to discuss by these responses. Under no circumstances is his task that of probing into conscious or unconscious motivations, exacting confessions or judging critically. Instead, he should attempt to develop confidence so that the informant will naturally bring out memories of the past and knowledge of the present which are relevant to the problem.

Such sharing through talking is beneficial and, when accompanied by simple explanations of the mechanisms involved in the etiol-



ogy of symptoms, may lead to a better understanding by parents of themselves and of their children, and of their mutual problems. One such psychologic adjunct is reassurance, and in this the authoritativeness of the physician may be used in a healthy manner. A physical examination done carefully is, in itself, reassuring, not only when no disease is found, but even when dysfunction is revealed. This kind of reassurance is truly therapeutic and quite different from that of the back-slapping and "cheer up" variety. The physician who has confidence in his ability to examine a child and to appraise the results conveys this feeling to the child and his parents.

Should the physician, for the sake of scientific completeness, subject the patient to po-

tentially traumatic examinations unnecessarily, he may cause severe emotional trauma. This point is particularly apt in the treatment of such conditions as enuresis, in which unnecessary instrumentation of the genitourinary tract may accentuate rather than help the basic problem.

The pediatrician as a psychotherapist may need assistance, and the psychiatrist as a consultant may be of help both to the pediatrician and to the patient. Social workers are trained in understanding individual, family and community problems, and their services may also be utilized in the therapeutic regimen. Psychologists constitute another group of skilled workers who can assist in therapy through performing tests of intelligence, aptitude and personality.

## NEUROTIC TRAITS

Psychologic dysfunction is often more readily recognized in adults than in children. Although classification of psychologic disturbances is usually not clear-cut and final, it is customary to consider deviant behavior of adults as neurotic, psychotic or psychopathic. In children it is difficult to distinguish between a neurosis and normal behavior; differentiation of a psychosis from a neurosis may be equally hard; and the term "psychopathic" is rarely used. The child responding to everyday stress in the home, at school and in play normally exhibits behavior which resembles neurotic or psychotic behavior of adults.

### "NERVOUSNESS"

In the strict sense, nervousness should not be considered a diagnostic term. At best it represents a symptom-complex and is here applied to children who are abnormally and persistently *restless*, both physically and mentally, who *fatigue easily* and have a *short span of attention*, and who are *overexcitable or timid* without apparent physical cause. The term is much abused. Many parents speak of children as being nervous as an excuse for any sort of fault in upbringing; many physicians use the term to cover their ignorance of the underlying difficulty, and other physicians use it as a means of getting parents to ease the pressure being exerted on the child. The fact remains that many children are

brought to the physician because of "nervousness," and even after the closest scrutiny some remain in this category. For this group of children some designation is necessary.

Some children are congenitally overactive. They have a heightened sensitivity to all sorts of stimuli. Any sort of trauma will produce essentially the same picture, which will disappear with clearing of the disturbance. Continued heavy loads and stresses may produce nervousness, as may severe acute illnesses.

Children also acquire nervous habits by association. When the family is a tense, keyed-up group, even the most placid child will exhibit classic symptoms. Nervous people can live happy, well-adjusted lives if they will accept themselves as such and are so accepted by others. For those who are not inherently nervous, the cause must be detected and eradicated.

The loads which may result in nervousness include the following: (1) undue adult pressure for accomplishment; (2) too much stimulation in play with older children; (3) competition for school promotion or high grades; (4) physical and social inferiorities, such as belonging to a minority group or having fewer advantages than their neighbors; and (5) anxiety reflected from parental worries and from other causes.

Anxiety is a basic emotion with which the growing child and adult need to contend each day. If the physician is able to protect

children from some of the excessive loads our culture often forces on them, they may be happier and healthier and able to achieve better performance levels in the home, in school and in society.

**Clinical Manifestations.** The nervous system seems unable to withstand the strain put upon it, so that the child is restless. The inhibitory powers are decreased, so that there are exaggerated responses such as "flying off the handle" with mild teasing or with frustration. There is usually a sort of tenseness; the pulse and breathing rate rise as the physician approaches, and the muscular movements are quick and jerky. Further information may often be secured by having the child "draw pictures." The nervous child does not make flowing, easy lines and, in his effort at control, often draws minute, exact, short lines, grasping the pencil with firm grimness. The physician will recognize the tightened voice and the inability of the child to be at ease as he sits in the office. The reaction time is usually speeded up, and the responses are inaccurate, as though there were a hair-trigger mechanism that set off the gun before there had been careful aim.

With these basic symptoms there is likely to be every conceivable sort of superficial disturbance which tends to be manifest in the higher reflexes. Thus stammering, reading and writing difficulties, finical appetite, nausea, and clumsiness in fine hand work may appear. The child does not go to sleep easily and shows tenseness in his sleep. Vegetative disturbances include sudden flushing, irregular heart rhythm, and fluctuation between constipation and diarrheal stools.

**Prognosis.** This depends upon the cause. Some children are "coiled up watch springs" and will always be so, but they can make excellent adjustments if this fact is recognized. They should be kept from long, repetitive tasks. Thus they negotiate the school regimen, provided they are given extra outlets for their pent-up restlessness, such as errands two or three times during the day or more black-board work than the others. They are usually happier in high school where they move at the end of each class period. Parents can help by avoiding pressures at home.

But most nervous children are so because of some intercurrent factor such as illness, or extra loads. In such instances the prognosis depends upon how effectively the exciting factor can be eliminated.

**Treatment.** The management of the nervous child is frequently within the province of

the child's physician, the psychiatrist being needed only in the unusual case. The principles set forth in the discussion of mental hygiene (p. 67) should be followed as prophylactic measures. The frequency of maladjustment to environment must be recognized and the situation dealt with accordingly. Late hours, broken sleep, excitement of the young infant by visitors, and other disturbing causes should be avoided; later, caution must be used against forcing him into precocity by efforts to teach him to talk or walk or to advance in mental and physical development beyond what should be expected for his age. In infancy and after there must be an abundance of mental and bodily rest. Especially in the school years careful supervision and judgment are required. A middle ground must be chosen between too much and too little study. Parents must be careful not to be coaxed into yielding to each whim, preparing special foods and constantly exhibiting anxiety. The physician should not discuss the child's problems in his presence.

Tasks and projects should be of a duration in keeping with the child's physical and psychologic condition; sometimes short-time projects are less productive of tension and hence lead to greater accomplishment. If the parents have wisdom, they can appreciate that they must strike a balance between a strait-jacket routine and no routine at all. The "nervous child" realizes that he needs support and welcomes a reasonably planned routine that relieves him of this responsibility.

If the parents lack the required wisdom, it may be advisable to remove the child from some of the unfavorable influence of home associations. Often nursery schools will afford help in these situations. This brings up the subject of parental, substitute parent and group care. Mothers should understand that the young child, up to three years of age as a rule, derives his greatest security from a sense of belonging intimately to his parents. In general, during the first few years of the child's life, parents (particularly the mother) should be discouraged from relinquishing their roles to other persons except for short periods and for emergencies, and then only if a responsible and understanding adult is chosen. First-rate nursery schools with a sufficient number of well trained teachers may serve the child under three years in this way, but as a rule they function best with children over that age, supplementing the child's life where it is needed most in play, companionship with peers and in relationships with understanding



adults. Summer camps, except those which have too strenuous routines and those which are entirely devoid of organization, may be utilized for the vacation months for the school-age child.

Every effort should be made to improve the general health of the child. The diet should be abundant and contain all the necessary minerals and vitamins. After any acute illness there should be an adequate convalescent period. Encouragement and efforts to increase the child's self-confidence are of the utmost importance. Nothing can be accomplished by compulsion, scolding or ridicule when undue fears are present. The nervous child who has a fear of sleeping in the dark should be allowed a dim light in his room until the fear is overcome. With older children a quiet and sympathetic discussion of their fears and an explanation of the groundlessness of them may be helpful; with infants pleasant sensations may be gradually associated with the cause of fear, if the source cannot be removed. Disciplining of nervous children is, of course, required on occasion, but should be adjusted to the child as well as to the offense, and those forms chosen which will not awaken fright or increase anxiety. These children often are afraid of what they might do, and they welcome discipline as a sign that someone else is "keeping them from going too far." There should be *just enough* of this authoritative control.

Sedatives may be required on occasion, but ideally should be given only if the physician is sure that he has located the cause and is well on the road to its removal. At such times sedatives can act to break a pattern that has become self-perpetuating.

### THUMB-SUCKING

Besides thumb-sucking there may be sucking of the tongue, fingers, toes, lips or such objects as a rubber nipple or "comforter," a blanket or sheet or part of the clothing. Much of this is common in infancy, since by this pathway the child explores his world, and it is a matter of little significance in the early months. The sucking may be accompanied by other acts, such as rubbing at the nose, pulling at the hair. Parents have often read enough literature to have become confused, and the physician will find that the main part of treatment is the difficult task of allaying adult anxiety. Thumb-sucking is more likely to occur when the child is about to go to sleep or when he is hungry, sleepless

or ill. It may become a persistent matter when the child feels put out of place by other arrivals or by some other matter absorbing the parents' interest. In these latter instances the physician obviously cannot treat the sucking habit directly, since it will disappear only as the child feels firm in the family affections. In milder cases when sucking is only occasionally practiced, the child may be easily diverted from it. When thumb-sucking is continuous and intense, temporary or, rarely, permanent malposition of the teeth may result, but seldom if ever of the palate; permanent alterations of the thumb rarely occur. The duration of the habit is indefinite; most infants cease of their own accord, but it may last into childhood.

**Treatment.** In mild cases treatment is unnecessary except for reassurance to the parents, which at times may be difficult. When hunger is the initiating factor, cure results when the diet is made sufficient. There is also evidence to suggest that the length of eating and sucking time should be increased, since the sucking habit often results from the fact that rapid eating satisfies the hunger reflexes before the lip and mouth reflexes have run their course. Mechanical restraints, such as elbow splints, metal mitts or thumb covers, are to be avoided. Their use is liable to aggravate rather than help the situation, especially the emotional aspect of it.

### NAIL-BITING

#### (ONYCHOPHAGY)

Nail-biting is common and in sensitive children is related to tension, excitement and worry. Both the causes and the treatment are much the same as for thumb-sucking. It helps to keep the nails cut short, and the fingers may be protected by gloves, though this is likely to allay the feelings of the parents more than it helps the child. All direct approaches must be in terms of pride in nice nails rather than shame for the habit. If possible, the underlying difficulties should be corrected. In all instances nagging and scolding should be avoided and efforts directed to increase the child's self-confidence and sense of security in the home situation.

### TEETH-GRINDING

Teeth-grinding is observed chiefly during sleep; it may be associated with various acute and chronic disturbances or may be indicative merely of mildly disturbing dreams. It

is common in unconscious states which are dependent upon disease, especially of intracranial origin, and it is a frequent symptom of meningitis. It is not pathognomonic of intestinal parasites. It may occur during the waking hours in low grade feeble-minded children, as may any of the neurotic habits. Treatment of teeth-grinding, if any, must be directed against the cause.

### PICKING, PULLING, AND RUBBING HABITS

Picking, pulling or rubbing some part of the body may develop as a habit. Fatigue and emotional stress are to be looked for, as are also disorders of general nutrition. Actual local irritation may be involved. Children suffering from severe illness of any sort often pick at the lips so continuously that restraint is necessary. Fretful infants frequently pull at the hair (*trichotillomania*), and large areas of the scalp may be almost denuded. Continuous eating of hair leads to the condition of hairball in the stomach. A frequent and annoying habit is that of picking at or boring into the nose, for which there is sometimes a local irritating cause.

**Treatment.** Forcible restraint may be necessary in infancy, but should be used only for severe disturbances; in older children reward for ceasing the habit is better than too much admonition, and restraint is seldom indicated. It is important to improve the general health and to remove any local irritation. Frequently these habits are manifestations of unhappiness, and shaming the child only increases the problem even when it temporarily seems successful.

### RHYTHMIC MOVEMENTS

Rhythmic movements occur frequently in mentally defective children, occasionally in infants and children who are emotionally disturbed and at times even in those who are apparently normal. The movements may be of one or more varieties.

**Head-Banging.** Head-banging is a rhythmic knocking of the head against the bed or mattress. This practice is not uncommon among infants and young children, and may occur in those of normal mentality as well as in mentally deficient ones. The habit is usually practiced shortly after the infant or child has been placed in bed, but may be carried out even during sleep. The child rarely injures himself. The habit is usually terminated between the second and fourth years of life.

No treatment is indicated other than removing sharp objects from the bed.

**Head-Rolling.** Head-rolling is not uncommon under the same conditions as head banging, but is more likely to be seen in undernourished or chronically ill children. The child, lying in bed, rolls his head from side to side, and continues this procedure day after day. As a result, the hair is almost completely worn away from the back of the head.

**Head-Nodding.** Head-nodding is to be distinguished from the gyrospasm and nodding spasm described on page 1102 in that it is much more energetic and apparently intentional. It occurs while the child is sitting, and it may be either a vigorous nodding or a lateral shaking movement.

**Swaying, or Body-Rocking.** This is a common habit. The child in a sitting position rocks rapidly backward and forward and continues this movement for hours, generally without the evidence of excitement usually seen in masturbation. Treatment consists in improving the general health and in combating, if possible, any psychologic difficulty present, but not in forcible restraint (see Sleep Disorders).

### BREATH-HOLDING

Holding the breath cannot strictly be called a bad habit, although it is sometimes seemingly voluntary. It is due to emotions like anger or to excitement. It is seen in irritable and high-strung infants and small children who cannot restrain their emotions. Attacks begin most often in the latter part of the first year of life, and generally disappear by the age of four or five years.

When something displeases or startles him, the child cries and hyperventilates; this causes a sudden cessation of respiration, followed by cyanosis and rigidity. In severe cases there is momentary loss of consciousness (syncope), possibly convulsive twitching (p. 1127), pallor which is sometimes extreme, and finally general relaxation. In a few seconds the attack is over and the patient appears as well as before. There may be recurrences several times a day or at longer intervals. In some instances the attack constitutes the terminal stage of a fit of rage, in which the child throws himself on the floor and screams violently for a few moments, or the attack may be both preceded and followed by crying.

**Treatment.** The child should be ignored during the attack, but measures should be



taken to remove precipitating conditions and to correct any faults of general health or environment. The question of discipline depends upon the individual case; punishment itself may cause an attack. Kindness and understanding are more effective than harshness in combating the neurotic condition.

## MASTURBATION

Masturbation is a common habit, and seldom of serious consequence. Impairment of the general health may predispose to masturbation or cause its renewal. Local irritation is a factor in many instances, such as phimosis, the accumulation of smegma behind the corona, balanoposthitis, irritation from tight underclothing, vulvovaginitis, the itching produced by eczema or by the presence of threadworms in the rectum or vagina, constipation, highly acid urine, preputial adhesions and adhesions of the clitoris. Sometimes irresponsible nurses have habitually rubbed the penis of an infant for the purpose of soothing him. In older children masturbation may be initiated by the sensation created by sliding down a banister rail, climbing trees, horseback riding or tight clothing; but at this age it is often taught by companions. At this period of life it is more frequently practiced by boys, although as puberty is approached or even before this time the habit is frequent in girls as well.

**Clinical Manifestations.** In infancy, masturbation usually consists in thigh friction or associated movements. The infant, sitting on the floor or lying on his back with the lower extremities drawn upward, rubs the thighs vigorously together, thus catching and rubbing the genitals between them. The face meanwhile becomes flushed, and the eyes have a fixed, somewhat staring expression. After a short time something suggesting an orgasm is produced, sweat breaking out on the forehead, the face growing paler, and the infant lying back relaxed from temporary exhaustion. The procedure is repeated possibly many times a day or even during sleep. Infants who practice thigh friction may exhibit other signs of neurotic excitement. Examination will frequently show redness of the genitals and perhaps some local source of irritation. Various modifications or substitutions of typical thigh friction are seen. Some infants, lying on the back or sitting, rub the buttocks from side to side on the bed or floor; others rub the genitals against some object, such as a pillow or the leg of a chair. Some-

times movements of other parts of the body are associated with, or even appear to take the place of, those which directly cause friction of the genitals.

After infancy, masturbation is more clearly associated with an early development of sexual excitability. The hand is generally used, and thigh friction is uncommon. As the result of reproof and consequent consciousness of wrongdoing, the habit soon becomes a secret one. Generally the procedure is only occasionally performed, but in extreme cases, when the child is highly neurotic, he may lie awake at night masturbating, or he may perform the act in the day; sometimes he may lose all sense of shame and power of self-control and masturbate in public as well. The local manifestations are varied. The penis may be unusually turgid or enlarged, with a tendency to ready erection, or it may seem relaxed. However, spontaneous erections are frequent in children who are not masturbators. The prepuce may be swollen and slightly inflamed. In girls the clitoris and labia may be larger than normal, and there may be some degree of vaginitis. These signs, however, may all be absent. Excitability, nervousness, apathy, depression, morbidness, shyness, reticence, pallor, loss of memory, debility, headache and many similar conditions have often been ascribed to masturbation; but they are likely manifestations of a neurotic state responsible for the habit. Likewise feeble-mindedness or some psychic disturbance is the cause of masturbation rather than its sequel. Nevertheless frequent masturbation may have an exhausting effect upon the nervous system; and the consciousness of concealed wrongdoing is emotionally disturbing.

In the analysis of a particular situation the following factors should be considered: (1) For children up to five or six years of age there is a tendency on the part of parents to overemphasize masturbation. At any time when the hands are in the genital area, there is much forbidding and shaming, which results in emotional strengthening of the habit. In such instances masturbation can be controlled only when the family really accepts the physician's reassurance that no harm will eventuate, and then only as he convinces them that the child cannot give up the habit until they cease to make it the center of their interests. (2) From about six years on masturbation—like smoking or wearing long trousers—is often a symbol to the child that he does things older people do. There is

therefore a great deal of experimenting as a perfectly normal phenomenon of growth. Adult admonition serves only to impress the child that he is trespassing on adult premises, so that the act attains even greater symbolic value. There is no evidence that harm results, unless the parents or physician has succeeded in loading the habit with so much guilt that the child develops a sense of inferiority. The ready and intense emotional satisfaction that comes from the production of an orgasm must be recognized as a factor favoring continuance of the habit. Masturbation offers a constant invitation to those who are failing in social or scholastic fields. It is important that the child have satisfying outlets in social activities.

**Prognosis.** Thigh friction or other forms of masturbation in infancy usually cease as early childhood is approached, except when masturbation is frequent and a distinct pathologic psychic condition is present. In early childhood there is a tendency to discontinue the habit; in older children it readily becomes fixed. The prognosis, however, for the general development of the child is good, except when masturbation is excessive. Here it is frequently an evidence of severe neurotic disturbance.

**Treatment.** In patients of any age, search must be made for local causes of irritation, and they should be removed. Vulvovaginitis, if present, demands treatment, as do threadworms, constipation and eczema.

Further treatment in older children is frequently unsatisfactory. As a prophylactic measure, proper instruction should have been given in sex matters (p. 71). The general health may need attention, and nervous excitement should be avoided. Life in the open air with abundance of exercise is important. However, abundant and healthy outdoor activity may increase the sexual appetite rather than drain it off. Erotic literature and movies should be guarded against. Punishment is of little value and only makes the patient more secretive. Emphasizing the practice as a sin may cause only despair and even cessation of efforts at control when good resolutions are broken. The confidence of the child should be obtained and the problem presented as a universal one. There should be frank admission that there are no known bad physical effects, but that it is difficult to escape disturbing feelings of guilt and unworthiness from the practice. The activities of the child should be planned so that there is a minimum of opportunity for the practice, but without

the child's being aware of such control. Surveillance which is too apparent serves only to concentrate the attention of the patient upon his practices and to establish the habit more firmly.

## COMPULSIONS

Compulsive acts are responses to thoughts which come obsessively. As a rule, compulsive behavior does not appear before the age of five or six years, and is so frequent after that time that it may be considered normal until the age of puberty. Although such behavior may on occasion be excessive in children under ten to fourteen years, if prolonged beyond this time it is usually considered symptomatic of psychopathology. A compulsion represents a reaction to the child's conscience, which around five years becomes excessively stern, even though the outside pressures may not be unusually hostile. In this period of development the child's feelings of hostility toward people close to him seem unbearable; the child may feel guilty about this, even though he does not recognize what he feels guilty about. Unconsciously he will repress some of these feelings of hostility and will take on behavior which seems to ease his conscience. Although this behavior may be unpleasant and therefore be resisted in part, the child will continue to act in this manner as if to avoid anxiety. Compulsions represent a kind of penance. Such behavior is incongruously proper, careful and repetitive. For example, the child may feel the need of touching certain objects, of counting or repeating numbers or words whenever a certain occasion presents itself. It is common to find the practice of walking so that cracks in a sidewalk are not touched. At times there may be compulsiveness about cleanliness which seems related to the child's early training in toilet habits. He may avoid defecation, so that severe constipation results. (See Constipation, p. 652.) The child of five years and older is especially prone to consider thoughts of sex and genital function as wicked, and his conscience seems to be especially strict about these matters. When parents are unusually stern, such thoughts of the child are exaggerated.

Ordinarily, mild compulsions disappear as the child works through the stages of prepuberal and puberal development, and no treatment is indicated. At any age, however, when compulsions occupy much time or incapacitate the patient to any degree—for ex-



ample, in excessive hand washing, chronic constipation (psychogenic), precautions against germs, elaborate ceremonies in eating, dressing or going to the bathroom—and especially if they are accompanied by other evidences of tension, worry or social withdrawal, psychiatric treatment should be sought.

## ANXIETY AND FEAR

Fear is a normal human reaction; all children experience fear in some degree from birth. The newborn is alarmed by loud noises and loss of support. Fear serves a useful function in protecting one from physical danger and in developing traits of caution and discretion. When fear is absent, one may question the mental status of the person, inasmuch as he is incapable of protecting himself and probably others in the community. Often fear becomes attached to objects and situations in an excessive way. Many infants about six months of age show fear when approached by strangers. Up to that time they may have accepted every newcomer willingly. As the infant grows he learns to rely more on his mother, and he feels apprehensive when she is not around.

Parents may foster fear by either insisting that the child be separated from them and become independent before he is ready for it or, on the other hand, by assuming an excessively protective attitude, preventing the development of independence. The child between one and a half and three years of age is in a phase of development in which he wants and seeks increased independence, but at the same time there is also an increased dependence. This ambivalent attitude causes many clashes between parent and child. The child demands that he do things himself and without help, yet he also demands help from the mother as well as her presence during each day.

As the child grows older he has many fears which are now verbally expressed. For example, a child at three and four years of age may show a fear of animals out of all proportion to his experiences with them. Nocturnal fears and nightmares are also frequent between three and six years of age. There may be an unconscious mechanism whereby fears which have arisen from daytime experience appear at night in sleep.

It is unfortunate that some people use fear to discipline a child. Parents may thoughtlessly handicap a child by telling him untruths about ghosts, bogey men and doc-

tors, or by subjecting him to frightening experiences. For example, a parent may deliberately burn the fingers of a child to teach him the danger of fire. Even less drastic handling as persistent scolding, disapproval and excessive blame may produce chronic timidity and fear so that the child develops into an inadequate and insecure person. It is remarkable how much psychologic trauma a child can take without serious or permanent injury. However, children should not be needlessly exposed to situations which engender irrational fear.

Whatever the causes of fear, children are able to handle it best when they feel secure in their relationship with their parents. Acceptance of the child as he is at each phase of his development is essential. This entails patient management of such situations as feeding, sleeping and toilet training by the parent without giving vent to feelings of rage or hostility. Many of the fears connected with sex and genital function appear to be related to early experiences in poorly devised toilet training.

Illogical or exaggerated fears are sometimes called *phobias*. Many times the child recognizes these feelings as unwarranted and unreasonable, yet seems helpless to overcome them. Sometimes a person may be so overcome by acute fear or the accumulation of it that he loses control of his behavior. The result may be severe impairment of physical and intellectual functioning. Such reaction is referred to as panic. Although clinically one may not distinguish between fear and anxiety, academically it has become customary to think of anxiety as being more malignant and irrational than fear. Anxiety is thought to result from a conflict which is repressed in the unconscious. Anxiety attacks are often characterized by somatic symptoms (p. 87).

**Prevention and Treatment of Fears.** Children become liable to certain fears at different ages which are by-products of various stages of emotional development. Children should be protected as much as possible from unnecessary and unduly fearful situations, but oversolicitous attitudes may foster fear which goes beyond the protection intended. When undesirable fears develop, they should be considered with sympathy and understanding and not with ridicule. A child should be encouraged to talk out his fears in the daytime; when nightmares occur, he should be awakened from his sleep and permitted to verbalize their content. In play he should always be permitted to act out his feelings. This is especially valuable when the child has

had an unfortunate experience through physical illness or hospitalization. Such children should talk about these events, and in play should be encouraged to set up lifelike situations in which they can act out their emotions. Irrational fears, especially if they are of long standing and assume the form of chronic anxiety, are difficult to modify and require psychiatric treatment.

## HYSTERIA

For reasons unknown, the incidence of hysteria has decreased in recent years. Rare in childhood, most cases occur in the puberal age period, more commonly among girls than among boys. The symptoms are quite varied and represent conversions of repressed ideas, wishes and intolerable emotional states into somatic manifestations or episodic behavior. Often the symptoms simulate organic disease, but are distinct in that they usually conform to the child's concept of the disease rather than to those of the disease itself. The manifestations may come on suddenly and disappear rapidly; they may simulate disease of any part of the body. Commonly there is only a single symptom. Sensory symptoms are varied, and include neuralgic pain with contracture about the joints and widespread or localized anesthesia, hyperesthesia, paresthesia, and the like. Sensory disturbances do not follow the course of nerves as would organic lesions, and are further characterized by their variability from time to time and by the susceptibility to suggestion.

Among *motor* symptoms are spasms, either tonic or clonic, and occasionally hysterical convulsions and catalepsy. The spasm may be choreiform or may be represented by contortions of the face, irregular action of the diaphragm and other muscles of respiration, and contraction of muscles elsewhere. Pseudoparalyses are much less common in children than in adults. Aphonia may occur from pseudoparalysis of the muscles of the larynx. The tendon reflexes are usually active, never absent. Cutaneous reflexes are variable, those of the cornea and pharynx being absent at times. Ankle clonus does not occur. Tremor is uncommon.

*Psychic* symptoms include attacks of laughing or crying without sufficient cause, paroxysms of violent anger, great excitability, night terrors or somnambulism, aphasia, a stupor-like condition, and states which resemble delirium and hallucinations.

Symptoms referable to the *special senses*

include blindness, contraction of the visual field, asthenopia, blepharospasm with closure of both eyes, paralysis of ocular muscles, and deafness.

There may be such *respiratory* symptoms as sighing, rapid respirations, yawning, hysterical cough, attacks of dyspnea, and hiccup from spasmodic action of the diaphragm. Among *circulatory* symptoms are palpitation, tachycardia, pallor, flushing and edema. *Gastrointestinal* symptoms may include hysterical dysphagia, gastralgia, umbilical colic, and vomiting which is often persistent. Anorexia nervosa may be a hysterical disturbance. Among other symptoms connected with the intestinal tract are meteorism, long-continued diarrhea, constipation, incontinence of feces and recurrent anal prolapse. Among *genitourinary* symptoms are frequency of urination, polyuria, ischuria and vesical paralysis.

**Diagnosis.** Although organic disorders may be closely simulated, certain features will aid in distinguishing hysterical manifestations. Primarily there is a lack of proportion between the assigned cause and the symptoms produced, and also a tendency for all symptoms to become worse when much attention is paid to them. In hysteria the patient is "gaining an end," although the purpose is often difficult to fathom, since the psychological mechanisms are often unconscious. The symptoms serve to hold the parental affections or to escape some unpleasant situation such as the greater ability or attraction of a sibling. Furthermore, there is likely to be a grouping of symptoms which it is impossible to attribute to any known lesion or lesions. It should, of course, be recognized that hysteria and organic lesions may occur simultaneously.

**Prognosis.** Active manifestations of hysteria usually improve under proper management. However, in a child of a distinctly neurotic tendency the manifestations are likely to recur. Suddenly developing attacks offer the best prognosis.

**Treatment.** Prophylactic aspects are discussed under Nervousness (p. 75). Psychiatric study and treatment are indicated in every case.

## Tics

### (HABIT SPASMS)

Tics are spasmodic, irregular movements of isolated groups of muscles. There is no direct association with organic disease. Tics occur most often in late childhood, but occur even



in the preschool age. Often a local factor determines the site of the tic, such as chronic infection of the upper respiratory tract, defective vision or irritative clothing. Occasionally imitation is the initiating factor, but more often a tic is associated with emotional disturbance. Tics occur in children of all levels of intelligence, but somewhat more frequently in those below average. Maladjustments at home or at school are common, and it is often found that pressure is being made to stimulate the child to mental or physical activity beyond his capabilities.

Tics are of various types and degrees of severity. The movements are only occasional at first, but soon tend to become frequent. They are performed unconsciously, although the child is able to restrain them for a time by force of will. They are increased in intensity and frequency by excitement. The majority of these movements are limited to the face and consist in twitching or distortion of the mouth, wrinkling of the forehead, elevation of the eyebrows, forcible winking, and the like; or there may be sighing or sniffing or jerking movements of the head. Less often there are jerking movements of the body which may be localized in the hands, arms or shoulders. The duration of the tic is variable; sometimes it lasts but a few months, whereas it may continue for years. Occasionally a tic in one region is replaced by a tic in another area.

**Treatment.** Treatment should be directed toward adjustment of the child's psychologic difficulties rather than at the tic itself. This obviously requires a careful psychologic evaluation even when the child seems to be well adjusted. Attention of the child should not be drawn to the tic or suggestions made that he attempt to control it. Pressures of any sort should be removed if possible. Development of self-confidence is perhaps the most important factor. The pattern of the child's life should be adjusted so that he can experience the satisfaction of self-achievement and success within the limits of his capabilities. Under no circumstances should the child be shamed or punished because of a habit spasm.

*Impulsive tic* (Gilles de la Tourette's disease) is an infrequent condition which most often begins in late childhood or at puberty and occurs usually in neurotic families. It is probably more closely allied to hysteria and psychasthenia than to habit spasm. The symptoms are violent twitching or convulsive movements, usually of the muscles of the face and arms, but sometimes of other parts of the body. With the movements there are associated explosive sounds, such as a loud barking cough or the enunciation of certain words. The course is chronic, and the prognosis is not favorable, although the symptoms occasionally disappear if the psychologic disturbances are corrected.

## SCHOOL DIFFICULTIES

See also Reading Disorders, page 95.

Certain focal points in the life of every child are responsible for changes in behavior. Among such important situations is going to school, which involves many new experiences and extends over important years of child development. School difficulties stem from factors related to the adjustments required at the start of school and subsequently to new teachers and for many children to change of school groups. Separation from parents is another factor.

Every normal and healthy child and his parents will be faced with new problems arising out of going to school. But the child who is emotionally disturbed will be particularly pressed, and his behavior difficulties may now stand out more prominently and be-

come aggravated. Among the most frequent problems of school adjustment are those in the five, six and seven year olds who are coming to school for the first time and naturally are restless and overactive. When such children are asked to sit quietly for long periods of time, their motor activity is increased. Frequently such children are punished because they are inattentive and noisy. A more proper solution would be to arrange the school day so that there would not be unduly long periods of sitting quietly in one place. The first days of school are marked by anxiety on the part of children and parents. Some of this stems from the child's desire to be independent, but at the same time cling to his parent for protection. When teachers permit gradual separation of the child from his parent in the first several days by allow-

ing the parent to stay in the classroom or close by, there is less weeping at school and less fighting to remain at home. Night terrors and enuresis are often precipitated by the beginning of school.

The main problems in the school age child arise from difficulties in learning: some children are slow and have trouble learning to read, write and cipher; others are gifted and speed ahead of their classmates. Children in either group need special attention and handling if they are to benefit from school. If neglected, such children become trouble-makers by clowning or becoming aggressive, or withdrawing into a dreamlike world of their own. Most children have some trouble learning to read because this involves new use of their sensory systems in combination with a translation of symbols into thoughts, and finally into spoken or written words and sentences. The main cause of reading difficulty is trying to teach children who are not ready. Reading readiness cannot be determined solely by chronologic age. Although most children are ready at six to seven years, some may not be until one or two years later. As a rule, girls learn earlier and more readily than boys, and this accounts for a greater number of reading problems among boys. Children with visual or hearing defects will also have difficulty in learning to read. General poor physical health may prevent a child from being attentive and concentrating in the learning process. Teachers who are lacking in understanding of children or are frightening and punitive also block children in any kind of learning. The actual technique of teaching reading must also be individual-

ized. When children have trouble learning to read, they should have thorough physical examinations, particularly of the special senses, psychologic tests, including a measurement of intelligence, and an appraisal of what is going on at home and in the classroom. Children living under stressful home conditions may be poor learners. A slow learner who is placed in a classroom with many children will be denied individual attention from the teacher and may lag behind, appearing stupid when he is not.

*Treatment* of a learning difficulty depends on what may be done to remove the cause, as well as on procedures of therapy. These problems are more readily prevented than treated. Remedial teaching by friendly, understanding teachers frequently puts children at ease so that they are able, with individual guidance, to learn the fundamentals, and with this help frequently catch up with their age mates. Emotionally disturbed children require psychiatric treatment. The gifted child, just as much as the slow learner, needs to have a school program fitted to his abilities and capacities. Such planning should be the combined efforts of parents, teachers and others in the school, such as the psychologist and school physician.

Conduct disorders such as aggressiveness, lying and stealing, chronic running away from school, and delinquency warrant thorough investigation of home life, of activities in the school and during recreation, along with sympathetic and objective appraisal of the child by educators and other professional people, such as child guidance personnel.

## CONDUCT DISORDERS

### (AGGRESSION, DELINQUENCY)

In general this group of conditions comprises a range of conduct from aggression to passivity. Aggression that takes the form of antisocial acts is termed delinquency and is easily recognized as being pathologic. Less recognized is the fact that extreme passivity may be equally abnormal. Very good, ever-obedient, "too quiet," "never angry," overpolite and socially withdrawn behavior characterizes the latter. Between these extremes are mixtures of all kinds which make up the personality of the so-called average child. Most children at one time or another get into

difficulty in this field, and there is a growing and thoroughly healthy tendency for parents to turn to the pediatrician for help. The field is now so specialized, however, and involves so much of the disciplines of sociology and psychology that it can be dealt with here only in its broadest outlines.

*Etiology.* The problem child is invariably trying to solve a problem rather than be one. His methods are crude, and his conception of his problem may be faulty; but until the physician has patiently sought, and in sympathetic fashion found, what the child was



trying to do when he stole or played hooky or sulked at home or bullied the little ones, he is in no position to offer advice. There is little or no relation between conduct disorders and such recognized syndromes of illness as feeble-mindedness, glandular dysfunction, physical or mental asthenia, and the like. It is true that wretched home or neighborhood conditions may lead to delinquency in one child, while his siblings show no such reaction. Delinquency does not always occur in weaker children; it may occur in those strong and healthy enough to rebel in their own way against conditions which their brothers and sisters merely accept. Conduct disorders are not of necessity associated with any particular economic group. Many a child of wealthy parents is sent to a strict military school; had the family been poor, the child might well have been a candidate for a reform school.

The basic emotional needs of children are outlined on page 69. The physician will find that most of the conduct disorders appear in children who sense a lack in one or more of these. In getting at the problem it is most important that the child's confidence be gained. This may necessitate that the child come alone to the office; if so, the physician must be restricted in what he tells the parents to that which he and the child have agreed should be told. All attitudes of blame must be carefully shunned. It is a good policy to refrain from the two words that chiefly hamper work in this field, "admit" and "deny." A good basic principle is to use the technique of "the own story." In securing the story from the patient, one antedates the delinquency so that the conversation comes up to the trouble in the same natural sequence in which it actually occurred. Thus one does not say to the child, "Why do you wet the bed?" One begins, rather, before that period (e.g., before the arrival of the new baby) when there was no enuresis, for a short discussion of family relationships, playmates and satisfactions. The "own story" recapitulates the genesis of the trouble.

**Manifestations.** The child with a conduct disorder may have a wide variety of "symptoms," but in general they tend to fall into groups: (1) They may show themselves in the area of the child's "weak link." Thus, no matter what the initiating circumstance, the emotionally unstable child may show increased restlessness and tension with resultant truancy from school because he cannot sit still for hours. (2) They may manifest themselves in the higher reflexes, since these are

the most unstable mechanisms. So, with any precipitating unhappiness or social pressure, the child may become a bed-wetter, a poor reader or a stutterer. (3) The symptoms may be directed at vulnerable spots in the environment. For instance, dirty stories or sex play are exchanged with other children because the child can retaliate in these fields with more disturbance to his adult world than through almost any other interest. (4) The symptoms may be directed against those areas which the child feels have been unfair to him or are most vulnerable. Thus he wets the bed constantly at Aunt Mary's, but never elsewhere. (5) The symptoms may be specific to the problem. Thus he may steal because he is poor. He may run away because he thinks he is badly treated at home. As a general rule, reactions that are clearly specific to the problem involved are not common. The first three groups of symptoms are far more common than the last two.

Analysis of conduct disorders is further complicated by three other factors which may be related to the initial development of symptoms: (1) The appearance of the abnormal symptoms may be directly related to the exciting factor. For example, the child begins to play truant at eleven years of age, and this coincides with his entrance to the sixth grade, where there is a teacher with whom he does not "click." (2) The appearance of the symptoms may merely indicate that he has at last become old enough to fight back against a problem he has always had. For example, a child whose parents simply must have a successful, brilliant son may be seven or eight before he can begin to fight back against a family that has use for him only as long as he can be a shining support of their community position. These children will start bedeviling their parents with every sort of mischief at eight or nine, but the physician will search in vain for any specific cause at that time. (3) The most difficult situations to understand are those analogous to the supersaturated solution in chemistry. In such instances a slowly growing maladjustment which has been present for years is suddenly "crystallized out" by some purely chance incident. Thus a trip to a nearby city, a low mark in arithmetic or an unimportant accident may be the trigger mechanism for marked and persistent enuresis, stealing, truancy or running away from home. When the situation is unraveled, it will be found that the event which the parents and child thought to be causative was simply a chance precipitating

agent for a series of tensions that had been operating for a long time. Family tensions over stepparents or over such conditions as the child feeling that others are more deeply cared for than he may thus suddenly be precipitated into stubborn cases of conduct disorders.

The problem of conduct disorders becomes further involved, since it is a psychologic one directly related to the child's reaction to his world and because his methods of expression are limited. If, with the deepest humility and with knowledge that many an error will be made, the physician will try to analyze the situation with the child and the parent, he is doing the best that can be done.

**Prognosis.** In general, the outlook is good. In spite of the great amount of adult unhappiness and breakdown, it is amazing how many problem children become satisfactorily adjusted in later life. This is not to advise a policy of letting matters be, but rather to emphasize that there is a basic ortho-tendency that tends to produce adjustment, just as with physical illness persons tend to get well if given the opportunity.

**Treatment.** Treatment is a complex affair which must extend into every phase of the child's life. The pediatrician may undertake it because often it involves a simple and natural extension of his existing ties with the child. It may require collaboration, however, with teacher, pastor, scout leader, nurse or social worker, and an understanding of their approach to the child. An increasing number of psychiatrists are specializing in this field, and they may be utilized. There are two conditions which the physician must fully appreciate: (1) The treatment of behavior disorders will require far more time and, in general, will produce far less tangible and measurable results than the treatment of physical illness. (2) The child, justifiably, is fighting back against precisely those who employ the physician and pay the bill. A middle-of-the-road policy by the physician will not do; the issue requires a clear decision of what his stand will be.

Treatment should be preceded by an effort to divide the stresses into those that are individual and those that are situational. Unusually high intelligence, lameness or being a girl are examples of the former. Unhappiness between the parents, the community's racial attitudes, and rigid academic standards in the school belong to the latter. As the areas of attack are defined it is wise to set apart the elements about which nothing can be done.

It is amazing to see how much effort and false hope are expended on matters that are, *at this time*, beyond therapeutic manipulation. So far as is possible, the child must be a real partner in the formation of plans.

The social worker can be a source of help. In general, her training in problems of emotional tensions, family relationships and school pressures far exceeds that of the physician. When there are conflicting interests and drives in the family, she can be of the greatest assistance in seeing a good deal of the parents while the physician sees much more of the child (or vice versa). This allows each one to feel that he has a "friend in court." The social worker frequently has had a professional training equal to that of the physician and is not to be used just to carry out orders. If the relationship cannot be one of real cooperation, it had better not be entered into at all.

Two sets of problems occur so frequently that consideration must be given to them, even though it must still be on a superficial basis. A great many children have feelings of inferiority concerning a wide variety of problems. The physician must make the clearest distinction between a *feeling of inferiority* and an *inferiority complex*. In the former the child openly recognizes his difficulties, which can and should be as openly and sympathetically discussed with him. In the latter the child is making valiant efforts to hide his real inferiority—he bullies because his own group will not accept him, he blusters or shouts or plays truant so that no one else will see his real source of unhappiness. A complex must *always* be treated *indirectly*. The child has done his best to hide his "Achilles' heel," and the physician should not be a party to snatching off the camouflage. In these cases the physician has to guess at the real source of inferiority and to build the child up in this or some kindred field. Only then can the child afford to dispense with the complex.

The other problem is involved in the child's feeling about his own parents. No matter how kind or loving adopting or foster or stepparents may be, each child has to feel that in some way or other his own parents are really all right and that they really love him. Family tragedies occur, adoptions are necessary, divorce and remarriage are often wise steps. All persons, however, must recognize that not every material advantage will replace the child's overpowering need to feel the integrity of his own parentage. It is indefensible to point out to the child that his own par-



ents are, or have been, "bad." Children should never be removed from their homes with that sort of explanation. Moreover, the physician must be prepared to "spiritually stand by"

the child who with sullen bitterness or an uncontrollable flow of tears unfolds his awareness that his own parents were really bad or did not care for him.

## PSYCHOSOMATIC ILLNESS

Although most of the conditions which have been considered so far have both somatic and psychologic components, the disorders to be discussed in this section are more strictly designated as psychosomatic disorders. This group comprises but a few of the physical disturbances which have psychologic origins. The etiology of these illnesses is not necessarily limited to emotional factors, since often there is a mixture of physical (organic) and psychologic agents. The physician is prone to ascribe causes of ill health to either physical or psychologic elements rather than to *both*. The term "psychosomatic" is unfortunate in that to some physicians it represents a dichotomy of etiology and hence of treatment, which does not exist. The term should represent a two-way relationship, psychologic influences on the one hand being capable of causing physical illness, physical agents in turn being able to produce psychologic disturbances.

Emotional reactions may interfere with bodily function in every person, but the degree of interference and the location of the somatic dysfunction are variable and depend upon the individual. Inasmuch as there is a similarity in the psychodynamics of cause and effect of many of the psychosomatic disorders, and since some of the psychologic mechanisms which produce such symptoms have already been considered, only a few illustrative conditions will be reviewed.

One of the most frequent symptoms following an emotional upset is that of pain. The pain may be in any part of the body. Head pain is a common complaint. The discussion on headache which follows may be applied in general to pain in other parts of the body, and for that reason pain will not be discussed in terms of other organ systems. Other symptoms which appear almost as frequently as pain are those related to dysfunction of the gastrointestinal, cardiorespiratory and genitourinary systems. Nausea, vomiting, constipation and diarrhea are the more frequent gastrointestinal manifestations; breathlessness, asthmatic attacks, palpitation and discomfort

in the chest are prominent representatives of cardiorespiratory involvement; and incontinence and enuresis, as well as inability to void, are common urinary symptoms.

### HEADACHE

See also page 1073.

**Etiology.** Headache, although but a symptom, may depend upon many diverse conditions such as (1) organic diseases of the brain or meninges causing increased intracranial pressure; (2) infectious diseases, in which headache is often a prodromal symptom; (3) toxemia, dependent upon gastrointestinal disorders; poisoning by lead, alcohol, opium, and the like; metabolic disturbances such as hypoglycemia; chronic infections, including rheumatic fever; (4) disturbance of the cerebral circulation, often observed in anemia; and the congestive headache which accompanies pertussis, cardiac disease, difficult or delayed menstruation, sunstroke, and intense mental activity; (5) fatigue; (6) disorders of the special senses, of which eyestrain is the most frequent variety; these may be physical or psychologic in origin; (7) disorders of the upper respiratory tract, such as rhinitis, sinusitis and polyps (otitis may occasion an intense pain in the parietal or temporal region); (8) neurologic disorders; neuralgia, which is produced by many of the causes mentioned and is characteristically limited to the distribution of certain of the cranial nerves; (9) migraine (sick headache, hemicrania); and (10) emotional upsets.

**Diagnosis.** In young infants headache may be suggested by wrinkling of the forehead, rubbing of the head, restlessness and crying. In older children localized persistent pain in the head depends most often upon organic disease of the brain; when the cranial nerves are involved, the pain is likely to be neuralgic. Temporary headache with fever is most frequently caused by gastrointestinal disturbance or the onset of some febrile disease; periodic headache may be due to migraine;

frequently recurring headache may depend upon emotional conditions, anemia or eyestrain. The position of the pain is often a guide to the cause. Frontal headache suggests the presence of such conditions as eyestrain, acute infectious disorders, disease of the nose, anemia or gastrointestinal disturbances. Occipital headache suggests eyestrain or otitis.

**Treatment.** The cause must be sought and appropriate treatment instituted. Direct relief from the headache may be obtained by bodily and mental rest, and by the application to the forehead of cold cloths or an icebag. Acetylsalicylic acid (aspirin) in doses of 0.06 gm. (1 grain) per year of age up to five years may be effective, but its use should not detract from remedial therapy.

### MIGRAINE

Migraine is uncommon in infants and children. It is often inherited, apparently as a mendelian dominant factor. Among assigned causes are psychologic disturbances, toxemia, cerebral anemia, cerebral congestion, faulty metabolism, eyestrain and allergy. Migraine is more common in females.

**Clinical Manifestations.** Slight causes, such as fatigue, emotional upset or dietary indiscretion, may initiate an attack. The attacks occur at intervals of weeks or months, often on days when regular routine is not followed, and usually begin with prodromal symptoms such as vertigo or derangement of vision. Headache is intense and generally unilateral, and may be accompanied by photophobia, tinnitus, paresthesia, vertigo or temporary difficulty in speech. Ophthalmoscopic examination often shows blanching of the retina on the affected side. Zigzag, multicolored and scintillating scotomas, with hemianopsia persisting as long as five to thirty minutes at a time, frequently precede the onset of attacks of headache. After a few hours the pain is followed by nausea and vomiting, and then by deep sleep from which the patient awakens free from pain. In young children the headache may be a minor feature, but nausea and vomiting may be marked symptoms. Migraine may later replace attacks of recurrent vomiting.

**Treatment.** The treatment of migraine is far from satisfactory. Attacks can frequently be modified by such procedures as going to bed promptly at the onset and administration of ergotamine tartrate, phenobarbital or bromides. Ergotamine tartrate appears to be the most effective drug. It is best administered intramuscularly or, in severe cases, intra-

venously. The adult dose is 0.25 to 0.5 mg. The side effects of nausea, vomiting and numbness of the extremities may be distressing, and in overdosage it may cause thrombophlebitis, gangrene and anginoid attacks. Thiamine chloride in large doses, niacin (to produce vasodilatation) and repeated injections of histamine have been used, but their role is not well established. If allergy is demonstrated, efforts should be directed toward desensitization. Estrogenic and androgenic substances appear to have little or no place in the therapy of migraine in children. Prompt relief by inhalation of pure oxygen has been reported. Psychotherapy may be necessary.

### EATING DISORDERS

See also pages 112, 133, 647.

#### PICA

Pica, or perverted appetite, occurs most often in the first three years of life. It consists in the ingestion of a large variety of unsuitable substances, such as sand, earth, grass or other plants, wool from blankets, broken glass, animal droppings, paint from furniture, coal, ashes, or plaster from the wall. The crawling infant and the toddler particularly enjoy putting foreign matter to their mouths, partly for exploration of the outside world and partly to satisfy a craving for "mouthing" experience and sucking. This behavior in infants and preschool children (eighteen months to five years) often accompanies messy play activity and interest in dirt (fecal and other varieties). At times there is an underlying nutritional disturbance. In many instances the mental and general health is good; in others there is anemia and malnutrition, and it would appear there may be an unconscious attempt to obtain minerals or vitamins which are absent from the diet. The habit may occur in neurotic children and is common in mentally defective ones. There is a tendency for pica developing in infancy to cease spontaneously by the age of three or four years. The general health may be seriously affected by the harmful action of the objects swallowed; among the possibilities, lead poisoning may result.

**Treatment.** Treatment consists in preventing ingestion of the unnatural articles and in combating any abnormal conditions such as anemia and other specific and general nutritional disorders by appropriate dietary and therapeutic methods, as well as in permitting



infants to have extensive sucking, biting, chewing and other mouth, lip and tongue pleasure when they desire it developmentally.

### ANOREXIA NERVOSA

Usually this is a serious condition, characterized by a remorseless drive toward self-starvation. It may begin as early as eight or ten years of age, but is more commonly seen in its overt form during adolescence, usually in girls, when attempts at adjustments seem particularly stressful. The anorexia is often preceded by a conscious and deliberate refusal of food, even when there is good appetite. The child may also secretly begin taking medications in an attempt to lose weight. A chance remark by a teacher or relative about the child's being "fat" may initiate attempts at self-starvation. Careful history taking may elicit from the child, without much difficulty, her attitude about her body size and shape, and as the confidence of the physician is obtained there may be acknowledgment not only of secret practices related to diet and self-medication, but also of feelings toward parents, particularly the mother, and fantasies about sexual matters. Frequently there is evidence of open conflict between the patient and the family, especially the mother-daughter relationship. Misconceptions about conception and pregnancy are at the core of the sexual fantasies. There may be the belief (fear) that impregnation follows kissing and occurs through the mouth. Sooner or later, as the starvation is extended, a loss of appetite appears, along with amenorrhea and constipation. Vomiting which is self-induced is also occasionally seen. Family pressure in attempts to solve the problems tends to add fuel to the parent-child dissension. Occasionally the child acknowledges gains in the way of more attention and sympathy from the family because of her illness, but the unconscious motives are not revealed unless psychotherapy is utilized.

Occasionally episodes of refusal of food are replaced by periods of overeating and rapid regain of weight, to the point of real obesity. The over-all trend, however, seems to be one of obsessional preoccupation with diets, food values and weight gain, and attempts to reduce the body weight by food refusal, induced vomiting, spitting, and coughing up of huge amounts of sputum which are collected by the patient in a compulsive manner.

This condition must be distinguished from physical disease which causes malnutrition. This usually is not difficult, however, owing

to the prominence of the psychologic manifestations. Occasionally it is confused with Simmonds' cachexia.

*Treatment* consists first in correction of any electrolyte imbalance, and then beginning, slowly, increases in the diet. The child often requires hospitalization. Psychiatric consultation should be sought as early as possible not only to verify the diagnosis, but also to see that the medical management is as psychologically oriented as possible. Removal of the child from a stressful home may result in a favorable change, but recurrence of the abnormal pattern is common upon the return. Intense psychotherapy is always indicated. Unfortunately, even when this is expertly administered, the illness tends to be chronic and the prognosis grave.

## DISORDERS OF SLEEP

### INSOMNIA AND DISTURBED SLEEP

Although, in general, infants and young children require more sleep than those older, there is no fixed inverse relationship between age and hours of sleep (see p. 136). For example, a child of two or three years of age may for a while sleep fewer hours in a twenty-four hour span than he will when he is five to six years of age. This lessened sleep probably is related to events in the waking hours. It is well known that in this preschool age the child goes through a developmental phase when many things seem awry.

The physician will also need to explain to parents that irregular and restless sleep is natural during infancy; similarly, that the peculiar postures which the sleeping child assumes are physiologic, as is much of the pre-sleep behavior which annoys parents who are tired and would welcome earlier sleep hours for their children. Many parents regard the motor restlessness (crib cruising), head shaking, requests for food or water or for holding and rocking as deliberate demands for attention and carefully planned devices for teasing adult members of the household. This may be true in some instances, but this sort of behavior seems developmentally related to some of the emotional episodes of the growth process. For example, fear is engendered when the child passes through phases of rapid growth (e.g., in the prepuberal period); some of this fear may be expressed consciously, and some will appear in forms such as dreams. Consciously the child may beg his parents not to leave him as he falls asleep, or he may awaken at night to see whether his parents

are still there. Among other causes of disturbed sleep in infancy are hunger, pain, itching, local irritation, fever, unusual noises, undue excitement before the sleeping hours, and extreme fatigue. Some so-called nervous infants may be wakeful, either crying during the night or sometimes lying awake. Other possible causes are too much light, poor ventilation, too low or too high a temperature and insufficient or too heavy bedcovering or an uncomfortable bed.

Necessary and normal as sleep is, it is a complicated mechanism which is easily disturbed by any one of a variety of causes. If one is not sufficiently tired or is too tired, sleeplessness may result. In attempting to find the cause of disorders of sleep, two basic facts are worth remembering: (1) A child cannot be made to go to sleep, but reassurance and calmness are of prime importance. (2) Most families fail to come for help until everyone has become unduly concerned. The physician must make it clear that he can do nothing until the patient as well as his family has completely discarded the issue of "who's going to win."

In addition to the causes mentioned, certain others operative in older children are mental overwork, mental stimulation from the radio, moving-pictures or television; emotional excitement of any sort, even pleasurable, shortly before going to bed; and insistence upon sleep when there is no desire for it.

**Treatment.** Sometimes a light evening meal is helpful, but when hunger is the cause, the amount of food taken should be increased or the feeding schedule changed. A warm drink, as of milk, before retiring may have a good effect. A warm bath in the evening may have good results. The room should be darkened or a dim light allowed, according to the need. Everything should be avoided which centers the child's mind on the existence of sleeplessness. Soporifics may be used; they are occasionally helpful in breaking acquired inhibitions to sleep. Their use should not be a substitute for finding the cause and eradicating it, and they should be prescribed in gradually decreasing doses until they are discontinued completely. At times other members of the family may need hypnotics more than the infant, who, in spite of a restless night, enters upon the next day in good condition. Rocking infants in the arms of a parent or in an old-fashioned cradle may be all that is needed.

### EXCESSIVE SLEEPINESS

In feeble newborn infants there may be a disposition to constant sleep even without organic disease of the brain. Later, excessive sleepiness may be seen with exhaustion, at the onset or during the course of febrile diseases, in uremia, in hypothyroidism, in organic cerebral diseases accompanied by increased intracranial pressure, after epileptic convulsions, and as the result of drugs. Narcolepsy is discussed on page 1127.

### DREAMING AND SOMNAMBULISM

Infants may dream, as shown by the sudden startled screaming or evidently purposeful movements of the hands during sleep. Dreaming occurs particularly in children who are emotionally upset, in the restless and disturbed sleep of even mild illnesses, and after excitement. Often dreams are repeated night after night. Psychoanalysts believe that, even in childhood, dreams have psychologic importance. In somnambulism the patient, most often an older child, performs various systematic acts during sleep, actual walking not being a necessary feature. Talking during sleep may or may not be combined with somnambulistic acts.

The *treatment* of these conditions consists in searching for and removing any exciting cause. The temporary administration of sedatives may be helpful.

### TERRIFYING DREAMS

Certain influences may be operative such as are seen in ordinary dreaming, but in many instances the terrors occur repeatedly without such factors being discoverable. Two classes of cases have been described which have been arbitrarily termed "nightmares" and "night terrors." In the *nightmare* the child awakens from sleep in terror and perhaps confused, but ultimately he is cognizant of the dream which disturbed him. The dreams are not those resembling any actual experience, but are associated with fear. There is no recurrence on the same night. The attack comes on most often soon after going to sleep. In *night terrors* the attack usually occurs an hour or two after going to bed when sleep is deepest. Without previous warning the child suddenly sits upright in bed, bathed in perspiration, screaming and trembling; or he may get out of bed and be found sitting on the floor. Sometimes he repeats words or he may point with his finger, indicating the imaginary object which has frightened him.



Although he clutches at his mother or nurse, he does not recognize her, nor does he know where he is, and considerable time is required before he becomes quiet. Sometimes he sleeps again without returning to consciousness; in other instances he becomes partly conscious, cries, and then quickly falls asleep. The child may have no remembrance of the attack. The frequency of attacks varies; they may occur nightly or only at intervals of weeks or months. Epilepsy may at times closely resemble night terrors.

**Treatment.** Treatment of night terrors should be based on an appraisal of the child and his environment. Treatment of the dreams themselves should consist in awakening by the parents or by someone with whom the child feels secure. The child should be reassured verbally and encouraged then, or later, to recount the dream. It may be important to leave a dim light burning in the room or near it for the remainder of that night. A light evening meal and avoidance of bedtime excitement may be helpful. As a rule, late hours should be avoided. It may be necessary to change the milieu in which the

child is being reared or educated or in which he seeks recreation. An attempt should be made to improve his relationships with his parents, siblings and playmates. The pediatrician or general practitioner may initiate these studies, but often he will find it desirable to use psychiatrists or social workers who by training are especially prepared to provide more extensive study and treatment. Night terrors should be considered symptoms and viewed in the light of the total child.

#### DAY TERRORS

Attacks corresponding to night terrors may rarely occur in the daytime during the nap or even when the child is awake. He may be subject to night terrors also. The prognosis of day terrors must be guarded because of a more probable relationship with hysteria, epilepsy, mental or nervous diseases. In young children day terrors may be manifested by fits of violent screaming without discoverable cause. The element of anger must be excluded in making the diagnosis.

MILTON J. E. SENN

## DISORDERS IN LANGUAGE FUNCTION

Man's language function is highly complex. Its efficiency is dependent upon the individual's intelligence, personality and the functional adequacy of the central nervous system and of the peripheral organs of speech. It is a developed facility, not preordained to success, and never static.

Etiologic factors may be endogenous or exogenous, congenital or acquired, physical or psychotic. Etiologic generalizations are unwise, since causative factors are rarely limited to one category. The problem is not: Do certain factors produce language disorders in children?, but, What factors produce a particular disorder in an individual child?

Differential diagnosis is essential for the solution and treatment of any language disorder. Rarely are such problems "pure"; they are usually complex syndromes. Knowledge of the child's genetic, social, emotional and educational backgrounds, of his neurologic integrity, intelligence, achievements, and the dynamics of his personality organization is prerequisite to adequate evaluation. Superficial diagnosis usually means superficial

treatment. Diagnosis and treatment of the *whole* child are essential.

#### SPEECH DISORDERS

It is estimated that there are more than a million children in the United States between the ages of five and eighteen years' who are so defective in speech that remedial treatment and training are indicated. The incidence of each type of defect is greatest between the ages of four and eleven, and boys are affected more frequently than girls.

Speech disorders appear in three general categories. First in order of frequency are functional inefficiencies, such as stuttering, which have mixed or multiple causes. Second are defects originating in anatomic malformations such as cleft palate, malocclusion and harelip. Thirdly are dysfunctions produced by cerebral or cerebellar lesions, such as spastic disturbances, aphasia and central deafness.

**Speech Development.** The child's first vocal sounds, cooing, crowing and crying, do

not constitute speech; they are merely reflective of his general feelings. When he begins to develop an ego, a sense of himself, he will progress from the initial matrix of speech, babbling, to the production of sounds which have meaning and purpose. In the normal infant these primitive speech efforts appear at six to eight months of age. With continued development he will begin to imitate or echo and to associate objects, persons and experiences with the words he hears and is able to produce. By two years of age he should be able to make two- and three-word sentences. Prior to this he will have developed a competent sensitivity to emotional connotations in others' speech. From three to six years of age there is increasingly complex development; the child's psychology shifts from the autistic feelings of omnipotence to an acceptance of the reality of worldly forces. As this transition occurs the contents of his speech transform from initial questing to description, and finally to the understanding and use of abstract words and the expression of intellectual concepts. This progression is most variable and is dependent on intelligence, personality, and the social stimulation of his environment.

Failure to develop speech by twenty to thirty months of age demands evaluation. Nondevelopment may signify that previously noted prenatal or postnatal conditions are more serious than were initially considered. Speech failure is often a concomitant of mental deficiency, but at early ages this is a dangerous presumption. Neuromotor dysfunction, auditory disorders and a variety of psychologic disturbances, including childhood schizophrenia, may contribute to speech failure.

The *feble-minded child* who does not develop speech will exhibit behavior patterns characteristic of his mental level. His play will have little purpose. He will demonstrate only rudimentary understanding of speech, and will make little effort to communicate his needs by gesture. He will not necessarily be withdrawn or autistic, but will not relate well to others around him. The primary problem is determination of his basic intelligence. Speech therapy is slow and unrewarding in such children.

The *deaf child* of normal intelligence who does not speak will be purposeful in play, be obviously alert and attentive, and investigative in demeanor. He will pay little attention to speech or environmental sounds. His attempts to communicate will be principally

pantomimic. He is likely to be apprehensive, tense, easily irritable and overresponsive to tactile stimulation. His vocal sounds will have a metallic monotone of variable but emotionally dissociated pitch. When deafness is suspected, the child should be referred to an otologist and an audiologist. If the child is completely and permanently deafened, a special school, even though residential, is usually indicated. Without early training in lip reading and in the use of his speech musculature the child is unlikely to escape the eventual need for a complicated sign language.

*Aphasia*, due to cortical lesions, may be the cause of nondevelopment of speech. In receptive aphasia the child's auditory acuities may be normal, he may respond to environmental sounds, but he cannot interpret speech. In expressive aphasia the child has normal hearing and understanding of speech, but cannot formulate words despite normal motor function of the speech musculature. In central aphasia inner symbol function is so disturbed that neither receptive nor expressive functions develop. Early diagnosis is imperative.

Some children of normal intellectual and physiologic development may not acquire speech for psychologic reasons. An early illness, or other special circumstances, may centralize the attention of the parents and create situations wherein the child's needs are anticipated. Thus he may not need speech to fulfill his wants. In a few instances children may perversely use their muteness as a means of asserting power over the adults in their world. Some children may regress emotionally upon the arrival of a new baby and thus fail to develop speech at the expected time. There are also children who do not mature personality-wise: the autistic or schizophrenic child whose inner world is primary to him will not acquire speech, owing to his inattention to the world of reality.

Differential diagnosis should lead to a clear understanding of the child's mutism. In cases of organic etiology special techniques used by a qualified therapist can be helpful in accelerating speech. If the problem is psychologic, psychiatric management of the child and his parents is indicated. In some instances the problem may be merely a matter of familial slowness in speech development. Appropriate understanding by the parents of the nature of a child's speech failure is essential in any case. Efforts to evoke speech must *not* touch on the vital aspects of the child's life. Such efforts may be concerned with the



red wagon or the favorite doll, but not with such essentials as food, behavior training or other basic physical and emotional needs. Every attempt to have the child mimic a word should include first the child's visual attention on the speaker's mouth.

**Defective Speech.** Speech requires the synchronous activity of all the cortical areas which subserve the language function. The pertinent sensory regions record kinesthetic, auditory and visual stimuli. Normal speech depends first on the accurate recall and association of these engrams and kinesthetic patterns and then on their innervation into the proper sequential impulses which result in word production.

Defective speech may be secondary to an anatomic anomaly; malformations of the palate and of the larynx are readily discernible. Some of these lesions can be corrected surgically, but when it is desirable to delay repair, as it may be in the case of cleft palate, speech training should be undertaken at an early age.

There are many speech defects whose etiology is not primarily anatomic or neurogenic. These are the functional disorders wherein faulty articulation of consonants is the leading deficiency. The most common errors are made on s, z, th, l, r and w. Substitutions of w for r and r for l are not infrequent. Lipping, when not obviously due to malformation, is the result of faulty tongue action. Infantile speech may result from promiscuous use of baby talk at home. Speech therapy is not always indicated in these functional anomalies. Many children through good social contacts with their peers, and with consistently good speech models in their environment, will achieve spontaneous recovery.

Indistinct speech, nasal delivery, breathiness, hoarseness or weakened volume demands examination of the nasopharyngeal passages and larynx. Enlarged tonsils and adenoids may produce this type of speech defect. Cerebral or cerebellar disease may also be responsible for such dysfunction.

Deficiencies in articulation are also caused by central nervous system lesions. Slurred, mushy, slovenly articulation, or slow, hesitant, syllable-by-syllable or explosive delivery may be symptomatic of cortical disturbance or bulbar involvement. In some cases, if the affecting lesion is not catastrophic, general improvement without therapy may be expected. Speech therapy and other remedial measures can, however, hasten improvement. Treatment

should utilize to the fullest extent all residual function.

## AUDITORY DISORDERS

Auditory disorders are responsible for certain defective speech characteristics. When there is definite hearing loss throughout the auditory range, certain deficiencies in speech may be expected. There will be a harsh, monotonous metallic quality to the child's voice, accompanied by little inflection and emphasis, and poor articulation. The deafened child rarely uses his voice for pleasure or ideational communication. He uses it to call attention to himself, and the product is impelled by fear, anger or discomfort. The greater the hearing loss, the more the child's speech is disturbed. When the hearing loss involves high frequency sounds, the child's speech will be defective through errors of omission such as of sibilants and soft sounds in words. There will also be poor differentiation of short vowel sounds. With low frequency deafness vowels and the deeper speech sounds will be faulty. Auditory evaluation should precede any speech therapy. Successful speech therapy depends on the skill of the therapist, on the psychologic status of the child, on his environment, and on whatever can be done to compensate for his auditory dysfunction.

## STUTTERING

Stuttering is an inability to speak freely, owing to incoordinate and spasmodic action of the musculature involved in speech. Two types of spasm may be observed: the tonic, resulting in complete blocking of speech, and the clonic, producing a repetitive disturbance ("c-c-c-can't"). Both types are frequently intermingled, and the initiating motor impulse often overflows in comparable spasmodic action into other neuromuscular functions, such as jerky movements of the feet, hands, arms and shoulder. The muscular paroxysms usually occur simultaneously with the child's efforts to speak. In the tonic type, at the instant of relaxation, the "pent-up" word is exploded, followed by rapid speech. In the clonic type the sound which is being repeated is finally blended with the remainder of the word. Occasionally, whole words and phrases are repeated. There are frequent periods, particularly in the milder cases, when the child can speak freely and naturally.

Stuttering occurs in approximately 1 per cent of all children of school age. It is the

most common functional speech disturbance and has a greater incidence among boys than girls, the ratio being about six to one. It occurs at any level of intelligence, appearing between the ages of two and ten years. It is at times accompanied by functional difficulty in other language facets, such as reading, spelling and handwriting.

Until recent years there was no general agreement about the underlying causes of stuttering, but some unity about therapy. There is increasing evidence that stuttering is symptomatic of profound emotional disturbance, although some continue to assume that the emotional aspects are secondary to disturbances within the central nervous system. Proponents of each of these concepts achieve notable therapeutic success by means of treatment methods based on their particular beliefs, but many stutterers go through life with their defect.

Orton proposed the theory that stuttering is due to fluctuating failure in kinesthetic integration resulting from lack of unilateral cerebral dominance for language controls. He believed that mixed motor dominance signified some deviation in the individual's establishment of this unihemispheric mastery. Studies, however, do not support the contention that there is a significant disparity between stutterers and nonstutterers in laterality of handedness. Interference with the use of the child's favored hand may or may not bring about an onset of stuttering. Furthermore, such interference cannot be postulated to interfere with the inherent development of cerebral controls. It is the child's adverse emotional reaction to an enforced change of his natural pattern that may bring on stuttering. Parents should always be advised not to attempt to influence the development of handedness.

There are two somewhat arbitrary etiologic categories in stuttering. These are termed primary and secondary disturbances; both have to do with emotional factors. The primary disturbance appears when the child begins to speak; this designation is also assigned to children who stutter before the age of four or five years. There is considerable evidence that these children have an extremely deep emotional disturbance. The primary stutterers, without prolonged psychotherapy, have a poor prognosis. The disturbance of the secondary stutterer is more likely to be in the category of hysteria, his adjustments are not so deeply neurotic, and his prognosis is more favorable under psychiatric management.

Whether stuttering is considered neurogenic, psychogenic or complex in its etiology, the patient will be initially unaware of the mechanisms creating his disorder. He is conscious only that he stutters. There is thus set in motion a reactive anxiety which in itself disturbs his emotional balance and contributes to the chronicity of his disorder.

There are many schools devoted to the stutterer. Much of the therapy is functional, being aimed at turning the person toward voluntary control of the speech apparatus. Most often such treatment is of only temporary benefit. The obvious reason for such disappointing results is failure to take into account the underlying psychologic disturbance.

**Treatment.** Before a rational plan for the treatment of stuttering can be devised, the child's behavior pattern must be thoroughly understood. Such an appraisal requires evaluation of his physical, intellectual and emotional status in relation to the many inherited and environmental factors which have been responsible. Whenever possible, it is recommended that evaluation comprise both verbal and nonverbal psychometric and standardized tests of educational achievement, analysis of language function and personality inquiries, such as the Rorschach and other projective tests. In evaluating the child's personality the physician should not accept the results of the usual questionnaire type of "inventory," since they may be misleading.

In therapy first consideration should be given to the prevention or alleviation of reactive anxiety. In the very young no attention should be paid to stuttering. There must be no nagging or ridicule, no undue sympathy or special attention. Everything possible should be done to eliminate adverse psychologic conditions in the home environment. Parents should be guided toward a better understanding of the disorder and of their contributions or reactions to it, so that they may assist, either directly or indirectly, in therapy. In school, regardless of a possible ebullience on the part of the stutterer to answer questions, it is usually wise to curtail, but not eliminate, oral recitation until the child has shown considerable improvement. On the other hand, participation in dramatics, in which parts are memorized and adverse reactions are not apparent, is sometimes therapeutic.

Most therapy is threefold: physical, emotional and functional. Optimal results are usually obtained through coordinated efforts



in these areas. Prompt attention should be given to defects in general health. The young stutterer usually has a low threshold of nervous fatigue, and needs help in planning his daily regimen, with particular attention to diet, exercise and rest. Factors in the environment which produce undue emotional reaction or exciting situations and which act as a drain upon nervous energy should be reduced to a minimum.

In general, psychologic management should be aimed at creating in the patient insight and understanding of his disorder. The physician should be on guard against the amateur mental hygienist in such cases. When there is obvious psychopathology, the stutterer should be treated by an experienced psychiatrist. Speech therapy is contraindicated in such cases until the psychiatrist feels it is warranted. The speech correctionist should always be chosen for experience, personality and philosophy.

## READING DISORDERS

Reading is the most complex facet of language function. It is not an isolated entity. It calls upon the integrity and precise association of the major portions of the cerebral organization. It is a perceptual, creative, interpretive enterprise commanding the positive use of an inquiring intelligence. Emotional, mental and physical health immediately influence, or are affected by, success or failure in reading. The most important concept about reading is the fact that it is a dynamic expression of the entire personality function.

A reading disorder may be defined as an inability to read with skill and effective understanding at a level commensurate with the person's experience and general intelligence. The degrees of difficulty range from mild retardation to total failure. Rarely is it a pure syndrome; poor spelling, vocabulary deficiencies and handwriting problems are often associated. There is usually an accompanying lag in those school subjects dependent on reading. Children thus handicapped are frequently able, however, to do relatively well in arithmetic computation and other non-reading areas.

Difficulties in the achievement of reading efficiency have the greatest incidence among children with language function disorders. It is reported that 10 per cent of the school population are handicapped in varying degrees by dysfunction in this sphere. There is

an unequal sex distribution, the male to female ratio appearing as 6:1. The largest number of cases appear in the years from seven to fourteen, from the second to the eighth grade. When comprehensive diagnosis is achieved, over 75 per cent of reading disorders reveal causative personality imbalances, about 10 per cent are related to faulty educational procedures, from 2 to 3 per cent are neurogenic, and the balance result from combinations of these and other conditions. Evidence in support of Orton's theory that delayed establishment or instability of unilateral cerebral dominance as a major cause of reading disability is dwindling. No longer are mixed motor dominance, left-eyedness and right-handedness, for example, considered important symptoms in these cases.

Adverse personality factors are becoming recognized as an important cause, not necessarily a secondary result, of reading disabilities.

For the preschool child the average American home is a matriarchy. The major portion of the early training efforts, cultural atmosphere and emotional climate are influenced by the mother. The child's primary struggle for selfhood must, of necessity, be with the mother, owing to the father's daily absence. The child's initial school years are an extension of this situation; when these early relationships are reasonably healthy for the child, he usually does not present learning problems. When they are adverse, he lags in learning, and generally his chief deficiency is in acquiring reading ability. It is notable that these conditions appear with slightly higher incidence in the moderate and upper income brackets than in the lower brackets. Influences appearing frequently are premature weaning and intense struggles of 'will over early feeding. Overstrict socialization efforts, through the "mother knows best" attitude, appear in over 15 per cent of these cases. Prolonged babying is likewise a factor. The mother who domineers through emotionalism, possessiveness or intellectualism, who criticizes the child for failure to meet her standards, who frequently admonishes, "You could do better," is contributing to a probable reading retardation. Teachers may do likewise.

Children with reading disorders are less well adjusted socially than successful readers. The psychologic factors responsible for the reading failure, not the deficiency itself, are usually at fault. There are four patterns of behavior among these children: the crushed, inhibited, unspontaneous, plastic child; the

hyperactive, thumb-sucking, enuretic immature child; the subtly negativistic, willful non-conformist; and the "I can't because I'm too dumb" type. They all proclaim their desire to succeed with reading. Accompanying psychosomatic complaints are frequent, such as allergies, colitis, erratic appetite and untoward irritability. Everyone is worried about the child and brings a great deal of pressure, consciously or otherwise, to overcome his learning problem.

The functional *symptoms* may vary, but most typical are the perceptual errors, appearing in oral reading and spelling, of transposition or reversal of letter orientation and sequences in words ("was" for "saw," "god" for "dog," "post" for "stop"). Accompanying confusions of letter-sound associations are prevalent. There is no regularity to the child's production of these errors; he will commit them repetitively, capriciously and spasmodically. He will demonstrate no ostensible control over his confusions. These are perceptual errors and are often referred to as "mirror vision," "mirror reading," alexia or "associational reading difficulty," and were termed by Orton "strophosymbolia." These errors do not stem from peripheral visual anomalies. They are of "central" origin, and their etiology is more likely to be psychogenic than neurogenic.

Other significant error patterns may predominate in oral reading. The child may offer "wild guesses" having little relation to a given word configuration or its relation to the context. He may omit words, or substitute one more personally familiar to him than the one in print ("boat" for "ship," "come" for "go"). Again, he may add words of his own to embellish the context. When these errors predominate, there is the possibility of faulty educational training, but more probably the pattern is symptomatic of psychologic maladjustment. When these "symptomatic" errors are not readily observable, and yet the child does not grasp what he reads, inadequate method and narrow vocabulary may be suspected. The child may be facile at pronouncing words with little recognition of their meaning or be limited in his facility to put words together into meaningful concepts. Here, again, adverse personality and educational factors may be presumed.

*Differential diagnosis* of reading disorders is imperative. Ophthalmologic studies should be required. The general health status should be examined; if neurologic study seems indicated, the inclusion of an electroencephalo-

gram should be considered. The pediatrician, in referring his patient to a reading clinic, should insist upon a thorough psychologic evaluation. Such a study must include a test of general intelligence by the revised Stanford-Binet scale, the Wechsler intelligence scale for children or the Wechsler-Bellevue intelligence scale. Secondly, educational achievement testing should contain quantitative and qualitative analyses of both oral and silent reading, of vocabulary levels, spelling, arithmetic computation and problem solving. Functional tests of visual and auditory perception are useful. Personality evaluation by "projection" tests such as the Rorschach and Szondi tests and the apperception instruments are imperative; interpretation by means of questionnaires or "inventories" can only be superficial. The results of these tests should be interpreted by a qualified person. Without integrated information from each of these categories the child may be given only perfunctory treatment and ultimately have serious difficulties inimical to his own welfare and that of the community as well.

*Treatment* should be based on the diagnostic findings and be planned in relation to the child's *total* situation. Some reasonable explanation to the child of his difficulty is essential. Reassurance of the parents and a lifting of their anxious pressure on the child are important. Both mother *and* father should be given as clear and practical an understanding of the nature of the problem and of the therapy as is possible. There is no case of reading disorder wherein this is not a primary need. This is particularly imperative when psychiatric management is indicated. Psychotherapy and concomitant parental guidance will be more effective if wanted by all concerned. Such treatment is likely to be less efficient, and may even fail, if approached with reluctance and hostility by either child or parents.

A variety of effective educational techniques are applicable to these deficiencies. None of these methods will lead to achievement if the remedial reading teacher stresses adherence to procedure and forgets that a good relationship with the child is vital to the success of the method. This fact is often forgotten by the eagerly striving educational specialist. If the pediatrician is treating the child concomitantly for psychosomatic complaints, he would do well to evaluate this factor and advise accordingly.

Remedial reading techniques may consist



in the kinesthetic, whole-word "tracing" procedures devised by Fernald. Phonetic systems are also useful in many cases. In neurogenic problems the Fernald system or the methods of Goldstein, Strauss and Lehtinen or of Benda may be utilized. Choice of method should be the decision of the therapist in relation to the diagnosis and the child as a person.

Often retardation in reading is used as an explanation for the child's failure in school subjects dependent on reading. The child, parents and teachers all expect academic success with the acceleration of reading proficiency. Experience reveals that this does not always occur. In such cases the disorder was initially a symptom of psychologic maladjustment; although the patient responded to the symptomatic treatment, he may still be unable to achieve initiative and perseverance in academic areas.

With comprehensive, differential diagnosis and appropriately designed treatment, most psychogenic reading disorders can be successfully overcome. The time required is variable,

ranging from six months to two years with a minimum of two treatment hours per week. The disorders resulting from organic factors do not respond rapidly to therapy, and the prognosis as to the child's eventual efficiency must be guarded.

E. GILLET KETCHUM

REFERENCES

Benda, C. E.: *Developmental Disorders of Mentation and Cerebral Palsies*. New York, Grune & Stratton, Inc., 1952.  
Fernald, G. M.: *Remedial Techniques in Basic School Subjects*. New York, McGraw-Hill Book Company, Inc., 1943.  
Goldstein, K.: *Language and Language Disturbances*. New York, Grune & Stratton, Inc., 1948.  
Gray, W. S.: *On Their Own in Reading*. New York, Scott, Foresman & Company, 1948.  
Orton, S. T.: *Reading, Writing, and Speech Problems in Children*. New York, W. W. Norton & Company, Inc., 1937.  
Strauss, A. A., and Lehtinen, L. E.: *Psychopathology and Education of the Brain-Injured Child*. New York, Grune & Stratton, Inc., 1947.

NUTRITIONAL REQUIREMENTS

A clear understanding of the fundamentals of nutrition is basic for the adequate medical supervision of children.

WATER

Water is second only to oxygen as an essential for existence; lack of it results in death in a matter of days. The water content of infants is relatively higher (75 to 80 per cent of the body weight) than of adults (65 per cent). Assuming that body water comprises 70 per cent of the body weight, 5 per cent is blood plasma, 15 per cent is interstitial fluid, and 50 per cent is intracellular fluid. Fluids provide the principal source of water; some is obtained from the oxidation of foods (mixed diets yield about 12 gm. of water per 100 calories) as well as of body tissues.

Requirements for water are related to caloric consumption and to the specific gravity of the urine. It is necessary for the infant to consume much larger amounts of water per unit of body weight than the adult, but when calculated per 100 calories of intake, the amounts required are practically the same (see Table 14). The daily consumption of fluid by the healthy infant is equivalent to 10

to 15 per cent of his body weight in contrast to only 2 to 4 per cent by the adult. Perhaps more than by chance, the natural food of infants and children is high in water content, most of the solid food in the child's diet containing 60 to 70 per cent water, and many of the fruits and vegetables, 90 per cent.

Little if any water is absorbed directly from the stomach, but absorption continues through the entire intestinal tract. Some water may go directly into the lymph stream, but most is taken into the blood stream. The quantity of water in the interstitial compartment changes

Table 14. Water Requirements

Urine Sp. Gr.	Infant—3 Kg. 300 Calories Intake			Adult—70 Kg. 3000 Calories Intake		
	Water Intake			Water Intake		
	Gm.	Gm./100 Cal.	Gm./Kg.	Gm.	Gm./100 Cal.	Gm./Kg.
1.005	650	217	220	6300	210	90
1.015	339	113	116	3180	106	45
1.020	300	100	100	2790	93	40
1.030	264	88	91	2430	81	35

Table 15. Range of Average Water Requirement of Children at Different Ages under Ordinary Conditions

Age	Average Body Weight in Kg.	Total Water in 24 Hours, Ml.	Water per Kg. Body Wt. in 24 Hours, Ml.
3 days.....	3.0	250- 300	80-100
10 days.....	3.2	400- 500	125-150
3 months...	5.4	750- 850	140-160
6 months...	7.3	950-1100	130-155
9 months...	8.6	1100-1250	125-145
1 year.....	9.5	1150-1300	120-135
2 years.....	11.8	1350-1500	115-125
4 years.....	16.2	1600-1800	100-110
6 years.....	20.0	1800-2000	90-100
10 years.....	28.7	2000-2500	70- 85
14 years.....	45.0	2200-2700	50- 60
18 years.....	54.0	2200-2700	40- 50

kidney produces a solution with a greater osmotic pressure than that of the internal environment, it is able to preserve the fluid and electrolyte equilibrium of the body; only 1 per cent of the filtrate of the kidneys enters the bladder.

CALORIES

The unit of heat in metabolism is the large calorie (C), defined as the amount of heat necessary to raise the temperature of 1 kilo-gram of water from 15° to 16° C. The pro-duction of heat varies with the oxidation of different foods, so that measuring the amount of oxygen consumed is the common method for measuring the amount of food oxidized and the heat produced. Estimates of heat pro-duction obtained from measurements of the end products of oxidation, carbon dioxide and water approximate those obtained by direct calorimetry.

There is great variation in the energy needs of children at different ages and under vari-ous conditions (see Fig. 21 and Table 17). The average expenditure of energy by the child of six to twelve years of age is approxi-mately as follows: maintenance of basal metabolism, 50 per cent; specific dynamic action of food, 3 per cent; growth, 12 per cent; physical activity, 25 per cent; and loss by way of feces, about 10 per cent.

Basal metabolism is measured at room

considerably in order to maintain homeo-stasis within the intracellular and vascular compartments. The interchange of water among these compartments is dependent on their respective protein contents and electro-lyte concentrations.

Depending upon the rate of growth, about 0.5 to 3 per cent of the fluid intake is re-tained. Somewhat less than 50 per cent of it is estimated to be eliminated through the kidneys, 3 to 10 per cent through the intes-tinal tract and 40 to 50 per cent by evapora-tion through the lungs and skin. Because the

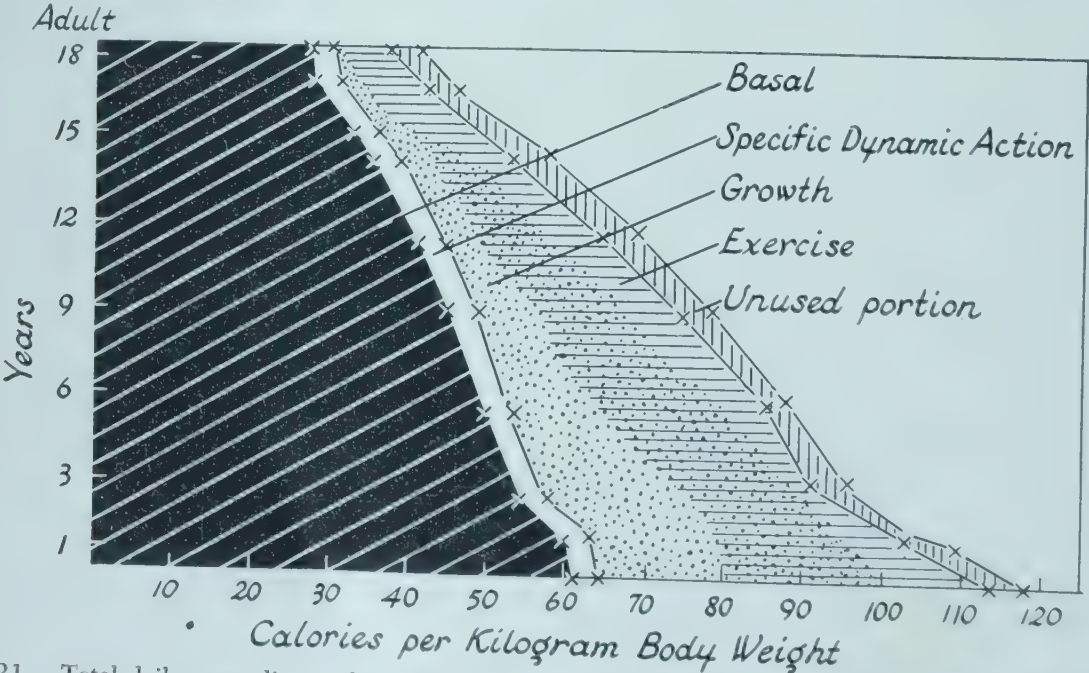


FIG. 21. Total daily expenditure of calories with approximate distribution between individual factors in relation to age and weight



temperature (20° C.) ten to fourteen hours after a meal, with the patient physically and emotionally quiet. For each degree (centigrade) of fever the basal metabolism is increased approximately 10 per cent. The basal requirement in infants is about 55 calories per kilogram of body weight per day and decreases to 25 to 30 calories at maturity. The term *specific dynamic action* (SDA) refers to the increase in metabolism over the basal

rate brought about by the ingestion and assimilation of food. Protein may increase the metabolism as much as 30 per cent above the basal level (except when protein is being deposited in tissues), whereas fat and carbohydrate, which have a "sparing" effect on the SDA of protein and upon each other, cause an increase of only 4 to 6 per cent, respectively. Practically, the theoretic SDA is probably never attained. In infants about 7 to 8

Table 16. Function, Effects of Deficiency and Excess, Requirements and Sources of Water, Calories, Proteins, Carbohydrates and Fats

Type of Nutrient	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
Water	Structure of cells; matrix for cellular changes; medium for ions; transport of nutrients and waste products; regulation of body temperature	Thirst, dryness of tongue, dehydration, anhydremia, high sp. gr. of urine, loss of kidney function (acidosis, uremia, anuria, death)	Abdominal discomfort, headache, cramps (water without salt), intoxication, convulsions, edema and circulatory failure	See Tables 15 and 17 Related to calories consumed; greater in hot weather	Water as such All foods
Calories	Energy for basal metabolism (body temperature, muscle tonus, circulation, respiration, peristalsis, glandular function, vegetative function); specific dynamic action of food; growth and physical activity	Underweight, malnutrition	Overweight	See Figure 21 and Table 17 Varies with body surface (weight and height) and age	4 C./gm. CHO 4 C./gm. Prot. 9 C./gm. Fat
Proteins	Supply amino acids for growth and repair of tissue cells; sols for osmotic equilibrium; ions in acid-base balance. With prosthetic groups to form hemoglobin, nucleoproteins, glycoprotein and lipoproteins. Enzymes, hormones, cellular respiratory substance, antibodies. Protective structures (nails and hair). Source of energy	Lassitude, abdominal enlargement, edema; depletion of plasma proteins, negative nitrogen balance (no clinical syndrome due to lack of specific amino acid)	Prolonged high protein intake not harmful	See Table 17 4 to 6 times greater per unit body wt. for infant than adult. See footnote (p. 101) for requirements of essential amino acids	Milk, eggs, meat, fish, cheese, soy beans, peas, beans, cereals, nuts, lentils
Carbohydrates	Readily available source of energy (body heat and muscular work), antiketogenic, structure of cells, antibodies, source of stored calories, conversion to fat, resynthesis of amino acids, roughage	Ketosis (if protein intake less than 15% of calories or in starvation); underweight, if total calories are low	Overweight; galactosemia (if unable to metabolize galactose)	To supply 25 to 55% of calories	Milk, cereals, fruits, sucrose, syrups, starches, vegetables

Table 16 (Continued)

Type of Nutrient	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
Fats	Concentrated reserve energy; physical protection for vessels, nerves, organs; insulation against changes in temperature; structure of body tissues, cell membranes and nuclei; vehicle for absorption of vitamins (A, D, E and K); stimulates appetite; aids satiety (delays emptying time of stomach); avoids necessity of ingestion of large bulk of foods; spares protein, vitamins A and B <sub>1</sub> ; supplies essential fatty acids	Lack of satiety (craving for fat), underweight	Overweight	Minimal not known, usually supplies 35% of calories Perhaps 2-3% of calories as linoleic acid	Milk, butter, egg yolk, lard, bacon, meat, fish, cheese, nuts, vegetable oils

per cent of the total caloric intake goes to SDA, whereas in older children on an ordinary mixed diet it is not likely to be more than about 5 per cent of total intake. The energy necessary to build body tissue (*growth*) is estimated to be the difference between the calories ingested and those expended for other purposes. The average requirement for *physical activity* is 15 to 25 calories per kilogram of body weight per day, peak utilizations being as high as 50 to 80 calories for short periods of time. The amount of energy-producing food lost in the stools (*unused portion*), except when absorption is impaired, is not more than 10 per cent of the intake.

Although caloric requirements can best be predicted from the surface area rather than from age or weight, the final criteria for meeting the child's needs depend upon the growth pattern, the sense of well-being and satiety. As indicated in Figure 21, the daily requirement is approximately 100 to 120 calories per kilogram of body weight for the first year of life, with subsequent decreases of about 10 calories per kilogram for each succeeding three-year period. Periods of rapid growth and development near puberty require increased caloric consumption. The average distribution of calories in a well balanced diet is as follows: protein, 15 per cent; fat, 35 per cent; carbohydrates, 50 per cent.

Table 17. Approximate Daily Requirements of Children for Calories, Protein and Water

Age in Years	Calories*		Protein	Water*	
	Per Kg.	Per Lb.	Gm./Kg.†	Ml./Kg.	Oz./Lb.
Infancy. ‡	110	50	3.0±	150	2¼
1-3.	100	45	2.5-3.5	125	2-
4-6.	90	41	2.5	100	1½
7-9.	80	36	2.5	75	1.0+
10-12.	70	32	2.0	75	1.0+
13-15.	60	27	1.5	50	¾
15+	50	23	1.0+	50	¾
Adult	40	20	1.0	50	¾

\* At least 10 per cent variation.

† To convert gm./kg. to gm./lb., divide by 2 and subtract 10 per cent of the quotient. Thus 4 gm. kg. is equivalent to 1.8 gm./lb.

‡ First month lower; first 6 months relatively higher than last 6 months. Breast-fed infants require lesser amounts of protein.



## PROTEINS

Protein, the predominant solid structure of the body, constitutes about 20 per cent of the body weight of the adult. An essential nutrient in the formation of cell protoplasm, it is found principally in the muscular and nervous systems and in the visceral and glandular tissues. It forms an integral part of most body fluids and secretions.

The kind, number and arrangement of the amino acids in a protein molecule determine the characteristic of the protein. Twenty-two amino acids have been identified; at least eight have been found to be essential for infants: threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine and methionine. From animal studies, histidine and arginine also appear to be essential.\* If protein is replaced by a mixture of amino acids in the diet, there is an increased need for calories. New tissue cannot be formed unless all the essential amino acids are present in the diet. Hence the absence of only one essential amino acid will result in a negative nitrogen balance.

Complex protein structures are broken down to proteoses, peptones, simple peptids and finally to amino acids in the digestive process. The hydrochloric acid of the stomach acts upon the protein to form acid metaprotein, which is soluble in an acid medium and can be readily acted upon by rennin and pepsin. Rennin changes casein of milk to paracasein, which pepsin hydrolyzes along with other proteins to proteoses and peptones. In the alkaline medium of the intestine, trypsin from the pancreas hydrolyzes these proteoses and peptones to dipeptids, tripeptids and tetrapeptids and to some amino acids, and peptidase from the intestinal juices carries digestion of these to the amino acid stage.

\* Studies with infants indicate the minimum requirements for the amino acids to be as follows: tryptophane, 30 mg. per kilogram for growth and nitrogen retention in infants; isoleucine, 90 mg. per kilogram for nitrogen balance in infants; methionine, 100 mg. per kilogram; threonine, 45 to 58 mg. per kilogram; phenylalanine, 90 mg. per kilogram; leucine, 200 mg. per kilogram; histidine, 30 mg. per kilogram. Data regarding lysine are not as adequate, but the requirements may approximate 100 mg. per kilogram per day.

As might be expected, the requirements for infants per unit of body weight are much greater than for adults and are greater for men than for women. Approximate minimum daily requirements for the essential amino acids in terms of grams per day for men and women respectively are: tryptophane, 0.25, 0.16; phenylalanine, 1.10, 0.22; lysine, 0.80, 0.50; threonine, 0.50, 0.31; valine, 0.80, 0.65; methionine, 1.10, 0.55; isoleucine, 0.70, 0.45.

Minute amounts of certain proteins may be absorbed unchanged as evidenced by immunologic reactions, but it is the hydrolytic products, the amino acids, which are normally absorbed through the intestinal mucosa. The amino acids are carried to the liver by the portal circulation and from there are distributed by the systemic circulation and are taken up rapidly by the tissues. Though amino acids are probably not stored as such, the excess absorbed and those from the breakdown of tissue proteins undergo deamination. The nitrogenous portions are converted to urea and are excreted by the kidneys. The carbon from amino acids is oxidized much as the carbohydrates. Some amino acids are glycolytic, others ketogenic. The absorption of protein is so efficient that little nitrogen is found in the stools.

The total plasma protein in the normal child ranges from 6 to 7.5 gm. per 100 ml., with somewhat lower values in newborn and premature infants. The albumin-globulin ratio is usually 2 to 1, fibrinogen varying from 0.1 to 0.4 gm. per 100 ml.

## CARBOHYDRATES

The greatest portion of the caloric needs of the body is supplied by carbohydrates, which also supply the necessary bulk of the diet. Carbohydrates are stored chiefly as glycogen in the liver and muscles, but probably make up not more than 1 per cent of the body weight. The infant's liver is one tenth that of the adult and the muscle mass one fiftieth; hence the infant has only a small fraction (approximately one twenty-sixth) of the glycogen reserve of the adult.

Carbohydrate is utilized as dextrose (glucose), but is consumed in various forms: the monosaccharides (dextrose, fructose, galactose), the disaccharides (lactose, sucrose, maltose) and the polysaccharides (starches, dextrins, glycogen, gums, cellulose). Pentoses are poorly absorbed.

Through a series of enzymatic reactions in the digestive tract, carbohydrates are broken into simpler structures. Amylase of the saliva breaks starch molecules to dextrins and maltose. The hydrochloric acid of the stomach hydrolyzes disaccharides to monosaccharides. Pancreatic amylase hydrolyzes the polysaccharides, while the enzymes of the intestinal glands complete the splitting of disaccharides: maltose to two molecules of dextrose; sucrose to dextrose and fructose; lactose to dextrose and galactose. The monosaccharides are rap-

idly absorbed. During absorption the phosphoric acid radical combines with hexose sugars in the intestinal mucosa and the hexose-phosphates formed are again broken into their component parts. Some dextrose may be oxidized directly, as in the brain and heart, but the absorbed monosaccharides are carried to the liver in the portal circulation and then to the systemic vascular system.

Most of the absorbed sugar is converted to glycogen in the liver, although glycogenesis also occurs in other tissues of the body. Up to 15 per cent (usually about 10 per cent) of the weight of the liver and 3 per cent of the muscle may be glycogen; there are also small amounts in the skin and in practically all other organs of the body. Glycogenolysis in the liver yields glucose as the chief product, whereas glycogen breakdown (glycolysis) in the muscle yields lactic acid. The over-all oxidation of glucose is complicated, having two phases, the anaerobic (glycolysis) and the aerobic (tricarboxylic acid cycle). In the former, glucose is broken down to pyruvic acid; in the aerobic cycle pyruvic acid is completely oxidized to carbon dioxide and water. Insulin, as well as pituitary and adrenal hormones, is involved in these processes, and nicotinic acid, thiamine and pantothenic acid take part in the enzymatic reactions. Carbohydrate which is not oxidized or stored as glycogen is converted to fat.

The major carbohydrate metabolic disorders are diabetes mellitus, glycogen storage disease and galactosemia.

## FATS

### (LIPIDS)

*Simple lipids*, esters of fatty acids with various alcohols, are the most abundant fats in the body and in food, the most common being triglycerides. *Compound lipids* (lecithin, cephalin, sphingomyelin, cerebrosides, sulfa and amino lipids) contain nitrogen bases, phosphoric acid, sugar, sulfur or amino groups with fatty acids and alcohol. *Derived lipids* from these two groups are separated out by hydrolysis; they include cholesterol, choline and saturated and unsaturated fatty acids.

Alkaline secretions with small amounts of free fatty acids and bile salts, together with motions of the intestinal tract, emulsify fat in the intestine. The lipolytic enzymes of the intestinal tract and pancreas hydrolyze the emulsified fat to fatty acids, glycerol and monoglycerides and diglycerides. The latter,

with bile salts, assist in absorption. Resynthesized fat passes directly into the lymph system and empties into the venous circulation by way of the thoracic duct. Naturally occurring fats contain straight-chain fatty acids, both saturated and unsaturated, varying in length from four to twenty-four carbon atoms, most of them containing sixteen or eighteen. The degree of absorption varies in general with the melting point and the degree of unsaturation.

**Essential Fatty Acids: Linoleic and Arachidonic Acids.** Human beings do not synthesize fatty acids with two double bonds. In healthy children dienoic, trienoic and tetraenoic acids constitute, on the average, 30.9, 1.9 and 12.7 per cent of the total fatty acids. In severely malnourished children these values average 11.6, 2.5 and 8.0, respectively. Hansen and co-workers observed that young infants on diets lacking linoleic acid frequently exhibit changes in the texture and appearance of the skin and an increased frequency of stools. When fat is absent from the diet, both man and experimental animals require more calories. The serum levels for *dienes* (linoleic) and *tetraenes* (arachidonic) acids decrease significantly, whereas the *triene* (3 double bond) fatty acids increase as compared with these levels in infants receiving milk containing linoleic acid. They observed that the addition of only 1 to 2 per cent of the calories as linoleic acid caused a rapid clearing of the skin, a restitution of the blood serum pattern and a decrease in caloric consumption.

## MINERALS

The ash content of the fetus is low; at the time of birth it constitutes only about 3 per cent of the body weight. It increases continuously throughout childhood, both absolutely and relatively, so that in the adult the mineral content is forty times greater than in the newborn, whereas the body weight is but twenty-three times greater. In the adult the ash content is 4.35 per cent of the body weight, 83 per cent of which is in the skeleton and 10 per cent in the muscle. It has been estimated that for each gram of protein retained, 0.3 gm. of mineral matter is deposited. The important electropositive elements are calcium, magnesium, potassium and sodium; the electronegative, phosphorus, sulfur and chlorine; the important inorganic complexes, iron and iodine; and the trace elements,



Table 18. Function, Effects of Deficiency and Excess, Requirement and Sources of the Nutritionally Important Minerals

Name	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
Calcium	Structure of bone and teeth, muscle contraction, nerve cell irritability, coagulation of blood, cardiac action, production of milk	Osteoporosis and osteomalacia, rickets (related to phosphorus loss), tetany	Dietary excess not harmful	Related to phosphorus ratio and vitamin D intake and sunshine. Roughly 1.0 gm./day (50-70 mg./kg.) provides daily retentions of 10-20 mg./kg.	Milk, milk products, eggs; leafy vegetables (0.2-0.3 gm. daily)
Magnesium	Structure of bone, ionic balance (intracellular), enzyme metabolism, regulation of nerve impulses and muscular action	Low plasma magnesium tetany in rats, dogs, cattle and possibly in human beings	Not harmful	Unknown; average consumption 2-400 mg. daily; estimated requirement 13 mg./kg./day	Green vegetables (in organic combinations with chlorophyll), milk, meat
Potassium	Structural protoplasm; regulation of nervous and muscular activity; intracellular action in acid-base equilibrium	Deficiency only under abnormal conditions, e.g., diarrhea, burns, shock, alkalosis, ACTH and cortisone therapy, and familial periodic paralysis, abdominal distention, weakness, paralysis, cardiac irregularities and electrocardiogram changes suggest deficiency	Heart block at serum levels of about 10 mEq./L.; such levels unlikely with normal renal function. In Addison's disease, excess may precipitate crisis	1 to 2 gm. daily	Natural foods, as vegetables, meat, milk
Sodium	Ionic equilibrium, osmotic pressure, irritability of neuromuscular system, small amounts in muscle and cartilage cells	Dehydration, loss of renal function; muscular cramps with excessive sweating; low intake contributes to crisis in Addison's disease	Edema, if excessive administration of parenteral fluids, particularly in premature and small infants with immature renal function	Estimates for daily intake as NaCl by parenteral routes: Newborn... 0.25 gm. Infants... 1 gm. Children... 3 gm. Adolescents and adults... 6 gm.	Foods, table salt
Phosphorus	Structure of bone, muscle and nerve tissue; absorption of carbohydrates; intermediary mechanisms of muscle activity; absorption of fat; buffer in acid-base equilibrium; with cephalin in formation of thrombin in clotting of blood	Unknown; related with calcium and vitamin D to rickets, osteomalacia and osteoporosis	No harmful effects known with adequate renal function; possibility of tetany during recovery from rickets due to excess in diet	55 mg./kg. with adequate calcium and vitamin D allows for retention of 6 to 8 mg./kg. per day; daily intake of 1.5 gm. recommended for Ca:P ratio of 1:1.5; the ratio is lower in infancy	Milk, milk products, meat, beans, cereal grains

Table 18 (Continued)

Name	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
Sulfur	As a constituent of certain amino acids: in keratin, pigment of epidermal tissues (melanin), bile acids, mucous secretions and vitreous humor, connective tissue, endocrine secretions (insulin) and enzymes, heparin and glutathione; with sugars to form glycoproteins and with lipids in nervous tissue	Unknown	No known significance; urinary acidity due to sulfates	Intake of 0.5 to 1 gm./day; ideal intake not known	Protein-containing foods
Chlorine	Acid-base equilibrium, osmotic equilibrium	Deficiency occurs in severe diarrhea, vomiting or excessive sweating. Administration of parenteral fluids of glucose without saline may produce deficiency, particularly in treatment of burns	Not likely under ordinary dietary conditions. Excessive parenteral administration of NaCl may lead to edema formation	2-3 gm. daily. Greater in pathologic conditions associated with dehydration, acidosis and adrenal cortical hormone disturbances	Foods, table salt
Iron	Structure of hemoglobin and other iron-containing compounds, related to oxidation mechanisms	Anemia (iron deficiency type): hypochromic, microcytic	None from dietary excess. Poisoning by medicinal iron (p. 1389)	In early life 0.4 to 1.0 mg./kg./day. For the older child, 0.2 to 0.4 mg./kg./day. Intake recommended varies from 6 mg. daily for infants to 16 mg. for adolescents (Table 19)	Meat, eggs, liver, green leafy vegetables, whole grains, legumes, beans, peas
Iodine	Manufacture of thyroxine, which is essential for regulation of energy metabolism	Simple goiter, endemic cretinism	No clinical significance in man	Children, 40-100 micrograms daily; adults, 100-200 micrograms daily	Iodized salt, common table salt with 0.01% potassium iodide; supplements needed in goiter areas
Fluorine	Related to hardness of bone and teeth; possible suppression of bacterial action, especially <i>Bacillus acidophilus</i> in saliva	Tendency to dental caries	Mottling of teeth, fluorosis	In drinking water, 0.7 part per million is sufficiently high to prevent dental caries, but low enough to avoid mottling	



Table 18 (Continued)

Name	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
copper	Catalyst in hemoglobin formation	Occasionally hypochromic anemia	Not harmful	For infants and children the diet should contain about 0.1 mg. of copper per kg. body weight; adults, 2 mg. daily	
zinc	Presence in enzymes, carbonic anhydrase, uricase and insulin substantiates its essentialness	Unknown	Unknown	Unknown	Similar to iron, but more abundant in milk

fluorine, copper, zinc, manganese, cobalt, silicon, selenium, boron, nickel, aluminum and arsenic.

**Calcium.** The bones and teeth contain 99 per cent of the calcium of the body. Absorption of calcium takes place in the upper part of the small intestine and is influenced by the intake of phosphorus and vitamin D, by the pH of the intestinal contents and by the amount of fat and such radicals as oxalate in the intestinal mixture. Under usual circumstances deposition in bone is a rapid and active process, calcium being constantly withdrawn and redeposited. Normally the plasma calcium level is 5 to 6 mEq. per liter (10 to 12 mg. per 100 ml.). The hormones of the parathyroid glands directly influence calcium metabolism: hypofunction decreases the serum calcium and increases the serum phosphate, and hyperfunction has the opposite effect. Calciferol and irradiated 7-dehydrocholesterol probably affect the level of the serum calcium indirectly through their influence on phosphate resorption by the kidney tubules; dihydrotachysterol raises the level of the serum calcium directly. Thyroxin, estrogens and adrenal cortical hormones also have an effect on calcium metabolism. About 10 per cent of ingested calcium is excreted in the urine and about 70 per cent in the stool; 15 to 25 per cent is retained, depending upon the rate of growth.

**Magnesium.** About three fourths of the magnesium in the body is in the skeletal structure, with most of the remainder in the muscles; there are only small amounts in other tissues. In some respects it is related in its metabolism to calcium, and in others the actions are antagonistic. Most of the magnesium is in the cells of the body, and there are only small amounts in extracellular fluids.

In the growing child about one sixth of the intake is retained, about two thirds is excreted in the stool, and the remainder is excreted in the urine. The plasma level is 1 to 3 mEq. per liter (0.5 to 3.5 mg. per 100 ml.), and the intracellular magnesium concentration is about 40 mEq. per liter.

**Potassium.** The potassium within the cellular structure of an infant is estimated to be 100 times greater than that in the extracellular compartments; it is concentrated to the greatest extent in muscle cells and erythrocytes. Of the total intake, about 8 per cent is retained by the growing child, about 80 per cent is excreted through the kidneys, and the rest in the feces. About one third of that retained is gradually lost through the sweat glands, and at times even more may be lost by this route. The blood level is maintained between 4 and 5.5 mEq. per liter (16 to 22 mg. per 100 ml.).

**Sodium.** Sodium is almost completely absorbed from the gastrointestinal tract; when the daily intake is about 2 gm., about 10 per cent is retained; about 98 per cent of that excreted is found in the urine. Of that retained, about 12 per cent is eventually lost in sweat. The blood concentration is maintained at about 142 mEq. per liter (330 mg. per 100 ml.).

**Phosphorus.** Phosphorus is widely distributed in the body as inorganic phosphate and as organic compounds, about 70 per cent of it being in the skeleton. While it is readily absorbed in its organic form in the upper part of the intestinal tract, there is evidence that some is later excreted into the lower intestine. Ordinarily about 31 per cent of that ingested is excreted in the feces and about 55 per cent in the urine; average retentions during childhood are about 14 per

cent, with much greater retentions during periods of rapid growth. In breast-fed infants about 55 per cent of the ingested phosphorus is retained, and in artificially fed infants, owing to the higher phosphorus content of cow's milk, about 25 per cent. The level of inorganic phosphate in the serum of children is 2.2 to 3.7 mEq. per liter (4 to 6 mg. per 100 ml.), which is definitely higher than in adults. The organic phosphorus of whole blood (mainly in the erythrocytes) is 35 to 50 mg. per 100 ml. It is present as phospholipids, such as lecithin, cephalin and sphingomyelin, and as organic esters, such as glycerophosphates, phosphoglycerates and hexosephosphates, and in nucleic acid.

**Sulfur.** Sulfur, as a component of the amino acids with a sulfhydryl linkage (SH), methionine, threonine, cysteine and cystine, is an integral part of the proteins of the body. It is present in taurocholic acid, in the pigment melanin, in glycoproteins, in tendons, cartilage and connective tissue, in mucous secretions and vitreous humor, in endocrine secretions (insulin), in respiratory pigment (glutathione), in the nervous system (combined with lipids as sulfolipids and sulfatides) and in vitamins (biotin and thiamine). In organic form it plays a minor role in acid-base equilibrium and is also concerned with detoxicating mechanisms of the body.

**Chlorine.** About two thirds of the blood plasma anions is chloride, and about one eighth of the chloride present in the body is in the plasma. Chloride is abundantly supplied in food and table salt. Approximately 1 per cent of that ingested is lost through the feces, 91 per cent in the urine. The remaining 8 per cent is retained, about one fifth of it being gradually excreted with sodium and potassium through the skin. The chloride level of the blood serum is 99 to 106 mEq. per liter (350 to 380 mg. per 100 ml.).

**Iron.** There are approximately 3 gm. of iron in the body of the average adult, about 58 per cent of which is in the blood as hematin combined with globin to form hemoglobin; about 15 per cent serves functionally in the tissues such as in chromatin material and in cytochrome; approximately 20 per cent is stored, principally in the liver, spleen and bone marrow with smaller amounts in the kidneys and skin. Iron is ingested in both organic and inorganic forms, the inorganic form appearing to be more readily utilized. It is estimated that the child retains 0.6 mg. of elemental iron daily, or 4.5 gm. during his

entire growth period. Absorption appears to be dependent upon the body stores; most of that not absorbed is lost in the stool; very small amounts are present in the urine (0.02 mg. per liter) and lesser amounts in sweat and desquamated cells. The body's ability to conserve iron is amazing. The amount of iron in the blood serum is 50 to 180 microgram per 100 ml. Each gram of hemoglobin contains about 3.4 mg. of iron. Iron released from destroyed hemoglobin is used over and over again. Copper may act as a catalytic agent and may be essential for hemoglobin formation, particularly in fetal life. Other metals, such as arsenic, zinc, nickel, cobalt and manganese, have a similar influence.

**Iodine.** Iodine is present in the body in amounts of 20 to 50 mg. It is consumed in both organic and inorganic forms and is readily absorbed as iodide from the intestinal tract. It is selectively withdrawn from the blood by the thyroid gland, which is able to concentrate iodine to a degree 10,000 times greater than any other tissue. The gland contains about 0.4 gm. of iodine per 100 gm. of tissue (average weight of thyroid is 25 gm.). In the gland inorganic iodine is converted to protein-bound iodine.

About 40 to 80 per cent of ingested iodine (varies with iodine content of water and soil) is excreted through the kidney; a considerable amount may be lost in perspiration, and some through the lungs. The amount in the blood is 6 to 13 micrograms per 100 ml.

Marine's success in preventing goiter in the children of Akron by feeding them 0.2 gm. of sodium iodide daily for two weeks each spring and fall indicates that sufficient iodine can be stored to meet requirements for a relatively long time.

**Fluoride.** Fluoride is heavily concentrated in the enamel of teeth and to a less extent in bones. Carious teeth have a lower concentration than healthy teeth, and dental caries is less frequent in areas where mottling of teeth results from a heavy intake of fluoride. The addition of fluoride salts to communal water supplies is responsible for a definite decrease in the incidence of caries in children.

**Copper.** Though the exact role of copper is not known, in invertebrates it is present in hemocyanin, which has oxygen-carrying properties; in vertebrates it seems to act as a catalyst in the transformation of iron into oxygen-carrying hemoglobin. Copper is found in greater concentration in the very young than in older animals, and is stored princi-



pally in the liver. About 24 mg. per kilogram are present in the liver of an infant as compared with 4 mg. per kilogram in that of the adult. Excretion in the urine varies from a trace to 0.7 mg. in twenty-four hours. In adults the average amount in the blood is 0.132 mg. per 100 ml.

**Zinc.** Zinc, present in the human body to about the same extent as iron, is most abundant in the pancreas, liver and kidney, with a higher rate of storage in young than in older subjects. The average daily intake is 12 to 20 mg. in adults, nearly all of which is found in the feces, though small amounts are excreted in the urine. Balance studies with children show that there is a slight retention, suggesting that there may be actual requirements for zinc. Rats show evidence of deficiency by impaired growth with definite changes in the skin and fur.

**Manganese.** Studies with rats and chickens indicate that manganese plays an essential role in the activation of enzymes and of certain catalytic actions. Manganese, whether given orally or parenterally, is excreted mostly in the feces. Balance studies suggest that the diet of preschool children should contain 0.2 to 0.3 mg. per kilogram of body weight per day.

**Cobalt.** Though it is not known whether cobalt deficiency produces any symptoms in a human subject, in sheep and cattle characteristic symptoms of emaciation and anemia develop. Man's requirement is not known; there is some increased erythrocyte formation after the administration of cobalt in the treatment of patients with anemia, particularly in that associated with infection.

**Silicon.** Silicon is present in all tissues, constituting as much as one ninth of the total ash. Because the amount present in the skin decreases with age, it is believed to be related to its elasticity. Blood levels in man are as high as 16 mg. per 100 ml. Some silicon is excreted in the urine, but most in the feces. Silicosis has not been known to result from a dietary source.

**Selenium.** There has been some interest in this element because in areas where there is high concentration of selenium in the soil and food, animals have severe nutritional disturbances. The significance in human beings is not known.

**Boron, Nickel, Aluminum, Bromine, Arsenic.** These elements exist in minute traces in man, but have not been shown to be significant in either human or animal nutrition. Boron is essential for plants; nickel delays insulin hypoglycemia; aluminum in excess may interfere with absorption of phosphorus; and bromine and arsenic are important pharmacologically.

VITAMINS

**Vitamin A.** Vitamin A and its precursors, the carotenoid pigments, are abundantly supplied in the average diets of children. Vitamin A ( $C_{20}H_{29}OH$ ) is a primary aliphatic alcohol of high molecular weight with an optically inactive beta-ionone ring. Vitamin  $A_1$  predominates in the tissues of salt-water fish; vitamin  $A_2$ , in fresh-water fish. They are formed in the animal organism from the precursors or the provitamins obtained from plants. The most important of the carotenoid

Table 19. Recommendations for Minerals and Vitamins

Age	Minerals				Vitamins					
	Ca	P	Fe	I <sub>2</sub>	A	Thiamine	Ribo- flavin	Niacin	Ascorbic Acid	D
	Gm.	Gm.	Mg.		I.U.	Mg.	Mg.	Mg.	Mg.	I.U.
Infancy.....	1.0	1.5	6	Trace	2000	0.4	0.6	6	30	400
1 to 3.....	1.0	1.5	8	Trace	2500	0.6	0.9	8	40	400
4 to 6.....	1.0	1.5	10	Trace	3000	0.8	1.2	10	50	400
7 to 9.....	1.0	1.5	12	Trace	3500	1.0	1.5	12	60	400
10 to 12.....	1.0+	1.5+	14	Trace	4000	1.2	1.8	14	70	400
13 to 15.....	1.0+	1.5+	16	Trace	4500	1.4	2.0	16	80	400
15+.....	1.0+	1.5+	16	Trace	5000	1.6	2.2	18	90	400

Tables 17 and 19 are adapted from recommendations by the Food and Nutrition Board of the National Research Council. Slight variations were made in order to state the amounts necessary for each 3-year period after infancy in direct arithmetic progression.

*Table 20. Functions, Effects of Deficiency and Excess, Requirements and Sources of Nutritionally Important Vitamins*

<i>Name</i>	<i>Function</i>	<i>Effects of Deficiency</i>	<i>Effects of Excess</i>	<i>Requirements</i>	<i>Sources</i>
Vitamin A	Supplies complex which unites with protein to form rhodopsin (visual purple) and iodopsin (visual violet), substances in the retinal cones and rods; development and maturation of epithelial cells	Nyctalopia (night blindness) and hemeralopia (inability to see in bright light): stratified, cornified epithelium with keratinized surface resulting in xerosis, Bitot's spots, xerophthalmia and ultimately keratomalacia; phrynoderma and keratosis pilaris	Hypervitaminosis A: bone changes, liver and spleen enlargement, anemia, drying and peeling of skin; lipemia when given in excess amounts as vitamin concentrates; carotenemia from excess carotenoid pigments (xanthosis cutis)	2500-5000 I.U. daily. Requirements greater in children having faulty fat absorption or liver disease (see Table 17)	Milk, milk products, egg yolk, beef, mutton, fats, liver, fish, and liver oils (percomorph, halibut, burbot, tuna, shark, cod), apricots, carrots, peaches, tomatoes, sweet potatoes
Thiamine	Combines with phosphates to form thiamine pyrophosphate, a coenzyme (cocarboxylase) which readily removes pyruvic acid	Accumulation of pyruvic acid in tissues and blood; diminution of the coenzyme cocarboxylase. Degeneration of the myelin sheath of nerves with fragmentation of the axis cylinder and wallerian degeneration: loss of striations and cloudy swelling or degeneration of the muscles supplied by these nerves; beriberi	Unknown	0.4 to 1 mg. (see Table 17)	Milk, liver, pork, other meats, fish, eggs, cheese, green vegetables, fruits
Riboflavin	Respiratory enzyme system in combination with phosphoric acid and protein; these enzymes include cytochrome reductase, d-amino acid oxidase; probably plays a role in metabolism of iodopsin	Decrease in the concentration of enzymes which contain riboflavin; symptoms include vascularization of the cornea, glossitis, cheilosis and sebaceous eruption about nose	Unknown	0.6 mg. for infant to 2.0 mg. for adolescent (see Table 17)	Milk, liver, pork, other meats, fish, eggs, cheese, green vegetables, fruits
Niacin	Coenzyme (1) diphosphopyridine nucleotide, also known as coenzyme I or cozymase, and (2) triphosphopyridine nucleotide, coenzyme II or coferment	Pellagra	Produces no untoward symptoms	4-16 mg. from infancy to adolescence (see Table 17)	Liver and meat, best sources; milk small amount; plants, poor sources, except whole wheat and peanuts



Table 20 (Continued)

Name	Function	Effects of Deficiency	Effects of Excess	Requirements	Sources
Vitamin C	Necessary for structure of intercellular ground substance; the reversible oxidation-reduction reaction concerned with cellular respiration; metabolism of aromatic amino acids in growing organisms	Abnormalities in the collagen of all fibrous tissue, in the matrix of bone, dentin and cartilage and all non-epithelial cement substances, including the vascular endothelium, scurvy	Unknown	Artificially fed infants need vit. C. Breast milk contains 4-7 mg. of ascorbic acid per 100 cc. Requirement varies with age of patients (see Table 17)	Citrus fruits, tomatoes and other fruits and vegetables
Vitamin D	Metabolism of phosphorus and calcium by making them available to skeletal tissue	Rickets, osteomalacia, osteoporosis, infantile tetany and possibly dental caries	As dietary supplement: excess of concentrates may produce toxic symptoms as well as excessive calcification of soft tissues, including kidneys, with consequent renal damage	400 800 I.U. (see Table 17)	Fish liver oils, "concentrates," irradiated foods; sunshine or ultra-violet irradiation to the body
Vitamin K	Essential part of prothrombin formation, hence of blood coagulation	Prolonged prothrombin time, resulting in bleeding	Not important	None under usual circumstances; necessary with liver disease when lack of bile in intestinal tract and in faulty fat absorption	Chlorophyll, present in many green leafy vegetables; hemp seed, soy bean oil, rice bran

pigments are beta-carotene (one molecule of which can form two molecules of vitamin A), alpha-carotene, gamma-carotene and cryptoxanthin. Vitamin A is absorbed with greater ease than the carotenoid pigments, absorption being influenced by such features as the amount of fat in the diet and of bile in the intestine. Part of the absorbed vitamin A is transported by the lymph system to the venous blood, and some appears to go directly to the liver, where the greater part is stored (about 95 per cent of the vitamin A in the body). Rhodopsin in the rods is broken down in bright light into vitamin A aldehyde (retinene) and protein; part of the complex is destroyed. In the dark, visual purple is resynthesized, in part from the old products and in part from new vitamin A.

**Vitamin B Complex.** A group of so-called water-soluble vitamins have come to be known as members of the vitamin B complex. Of these, niacin, riboflavin and thiamine, which tend to be found together in nature, are essen-

tial in the nutrition of children. The component members of the vitamin B complex supply a necessary prosthetic group to form one or more of the coenzymes which function in enzyme systems concerned with cellular respiration and with carbohydrate, protein and fat metabolism.

**Thiamine.** The hydrochloride of thiamine is a pyrimidine-thiazole compound ( $C_{12}H_{17}N_4OS.HCl$ ). Thiamine, the first discovered component of the vitamin B complex, is known as vitamin B<sub>1</sub>. It is found in the circulating blood, is readily excreted in the urine and feces, but is stored in the body only to a limited extent. There is some evidence that synthesis in the intestinal tract may occur, at least in certain species.

**Riboflavin.** Riboflavin is the only vitamin discovered and isolated before a clinical entity due to its lack was described; hence this entity bears the name ariboflavinosis. A pigment showing a greenish-yellow fluorescence in water solution, riboflavin ( $C_{17}H_{20}N_4O_6$ ) has

a side chain ribityl radical derived from the alcohol d-ribitol. Its oxidation yields d-ribose (adonitol). The other part of the complex is iso-alloxazine. Riboflavin in nature may be combined with phosphate, or with adenine as flavin adenine dinucleotide; both forms of riboflavin are coenzymes in many metabolic reactions.

**Niacinamide.** Niacin ( $C_6H_5O_2N$ ) (3: pyridine carboxylic acid) as the amide combines with phosphoric acid, adenine and ribose to form two coenzymes used for transferring hydrogen in the fundamental oxidative life processes in the cells of the body. It is stored in the tissues of the body, principally the liver, and is excreted in the urine as the methyl derivative.

**Vitamin C.** Ascorbic acid, a 2, 3-dienol-L-gul furano lactone ( $C_6H_8O_6$ ), is the chemical name for vitamin C, which is found in the blood in concentrations from 0.4 to 1.2 mg. per 100 ml. of plasma when the dietary intake is adequate. A certain amount, related to its concentration in the tissues, is continuously excreted in the urine. Ascorbic acid is necessary for the structure of intercellular ground substance in which tissue cells are embedded and cemented together.

**Vitamin D.** The natural diet of the child is more likely to be lacking in vitamin D than in any other food essential. There are, perhaps, ten or so sterols which have vitamin D activity, the most important of which are activated ergosterol (vitamin D<sub>2</sub>, viosterol, calciferol) from vegetable sources and irradiated 7-dehydrocholesterol (vitamin D<sub>3</sub>), a naturally occurring vitamin from animal sources. The body is able to activate its own precursors by exposure to sunlight.

Vitamin D is fat-soluble and is absorbed with fat from the intestines, its absorption being influenced by the fat of the diet as well as by bile salts. Vitamin D is especially concerned with phosphate metabolism, and there is some evidence that it may also have a direct effect on calcium metabolism.

**Vitamin K.** Vitamin K is concerned with prothrombin production. A number of substances with a quinoid structure have vitamin K activity. Vitamin K<sub>1</sub> ( $C_{31}H_{46}O_2$ ) (2-methyl-3-phytyl-1, 4-naphthoquinone) has been isolated from alfalfa, and vitamin K<sub>2</sub> ( $C_{41}H_{56}O_2$ ) (2-methyl-3-difarnesyl-1, 4-naphthoquinone) has been isolated from putrefied fish meal. A synthesized compound, 2-methyl-1, 4-naphthoquinone, under the nonproprietary name of menadione, appears to have the greatest antihemorrhagic activity.

In its naturally occurring form it is fat-soluble and apparently is absorbed readily from the upper part of the jejunum. Lack of bile predisposes to a deficiency. The small amount stored is in the liver. Vitamin K is apparently synthesized in the gastrointestinal tract, probably by bacterial action.

**Pyridoxine.** This vitamin (also known as vitamin B<sub>6</sub>;  $C_8H_{12}O_3NCl$ ) is a complex which includes pyridoxine, pyridoxal and pyridoxamine. The phosphorylated forms of the latter two are the active coenzymes for certain transaminations and decarboxylations. Convulsions in infants may be associated with low intakes of pyridoxine. It is fairly abundant in ordinary diets, but little is known of actual human requirement.

**Pantothenic Acid.** Pantothenic acid ( $C_9H_{17}O_5N$ ) occurs in bound form in many tissues in the body and functions as coenzyme A in acetylation reactions and in certain key reactions of the oxidative phase of metabolism. Because of its wide distribution in tissue cells and its importance in animals, it is undoubtedly essential for man; however, no symptoms due to its lack have been described in infants and children. Apparently it is abundant in average diets.

**Biotin.** A cyclic derivative of urea, biotin ( $C_{10}H_{16}O_3N_2S$ ) on oxidation yields adipic acid. It has been referred to as the universal vitamin, since it is found in all living tissue. Biotin deficiency has been produced experimentally in man with a diet containing 30 per cent of the calories as desiccated egg white. Biotin is abundant in the average diet; actual requirements are not known.

**Choline.** The basic substance choline ( $C_5H_{15}O_2N$ ) is present in lecithin and is believed to be a factor in the mobilization of fatty acids in the body. Methionine and betaine are closely related to choline physiologically and also act as a source of labile methyl groups, especially in the absence of choline. These substances are known as lipotropic factors in the prevention of fatty degeneration in the liver.

**Inositol.** Hexahydroxycyclohexane, inositol ( $C_6H_{12}O_6$ ), is combined in plants as phytin, a calcium magnesium salt of inositol phosphoric acid. It is found in body tissues and fluids. Its function appears to be related to that of fat; it may act as a lipotropic substance in the prevention of certain types of fatty liver in the rat. Little is known about human requirements for it, although it is abundant in the usual diet.

**Para-aminobenzoic Acid.** Para-aminoben-



ic acid ( $C_7H_7O_2N$ ) is a constituent of folic acid.

**Pteroylglutamic Acid (Folic Acid).** Pteroylglutamic acid, sometimes called the *L. casei* factor, was formerly known as vitamin  $B_c$  and vitamin M. It has clinical significance in the development and treatment of a macrocytic type of anemia in infants. There are indications that a derivative of this vitamin, formyl folic acid (citrovorum factor; folinic acid), may be the metabolically active form of the vitamin. Aminopterin, a biologic antagonist of folic acid, is used to prolong remissions in leukemia.

**Vitamin  $B_{12}$ .** Vitamin  $B_{12}$  (cyanocobalamin) has been isolated from refined liver extract and appears to be the antipernicious anemia factor of the liver. It appears to be necessary for "labile methyl" metabolism. In animals it stimulates growth, but no conclusive evidence for a similar effect in children has been demonstrated.

**Vitamin E.** Alpha tocopherol ( $C_{29}H_{50}O_2$ ) is the most important of the substances having vitamin E activity, which include beta, gamma and delta tocopherols. The relation of vitamin E to human nutrition is not known, but limited evidence suggests that tocopherol may be related to muscle metabolism in man.

**Citrin.** Formerly called vitamin P, citrin is found in paprika and the rind of citrus fruits. It consists of two compounds, hesperidin and eriodictin, and is said to be concerned with capillary resistance, but its significance in man is not known.

## MISCELLANEOUS FACTORS

**Roughage.** Roughage is indigestible vegetable fiber. Macy found that amounts as high as 170 to 300 mg. per kilogram per day appeared to cause no difficulty. Most children who receive average well-balanced diets obtain sufficient amounts of roughage.

**Digestibility.** The relative amount of a given food available for assimilation by the body is high in most of the common food classes: carbohydrate is 97 per cent; fat, 95 per cent; and protein, 92 per cent. Vegetable fats and proteins have lower values. Cooking is a factor in digestibility. For example, the boiling of milk reduces the size of the protein curd and renders it more digestible for infants; by contrast, heating destroys vitamin C activity.

**Satiety.** The ingestion of a meal should provide a sense of well-being. Whole milk, cream, eggs and fatty foods have a high satiety

value; sugar increases the flow of gastric juice and delays emptying of the stomach, thus also increasing satiety. Bread and potatoes have relatively low satiety values, as do lean fish, vegetables and many fruits.

**Availability.** Low economic status, more than any other factor, limits the availability of essential foods and is probably the greatest single cause of malnutrition in children. Diets of families in the lower income brackets are likely to be deficient in milk, fruits and vegetables. A suggested method for planning low cost meals is to divide the money available for food into fifths: one fifth each for vegetables and fruits; milk and cheese; meats, fish and eggs; bread and cereals; and fats, sugar and other food adjuncts.

Geographic distribution also influences the availability of foods, the tendency being for a population to consume foods indigenous to

Table 21. Recommendations for the Content of the Daily Diet of the Healthy Child

Proteins	2 gm. per kg. of body weight
Fat	} ... Sufficient to meet caloric needs
Carbohydrate	
Minerals	
Calcium	1.0 gm.
Phosphorus	1.5 gm.
Iron	16.0 mg.
Iodine	Trace
Vitamins	
A	5000 I.U.
Thiamine	1 mg.
Riboflavin	2 mg.
Nicotinic acid	10 mg.
Ascorbic acid	60 mg.
D	400 to 800 I.U.

### COMPOSITION OF THE SATISFACTORY DAILY DIET

Milk	¾ to 1 quart
Meat, poultry or fish	1 serving (5 to 6 per week)
Liver	1 serving or more per week
Eggs	1 daily (5 to 6 per week)
Vegetables (1 raw, 1 pigmented)	2 or more servings
Fruits (1 fresh; noncitrus, and 1 citrus or tomato juice)	2 or more servings
Butter	2 to 4 tsp. or more
Bread and cereals (whole grain or reinforced)	Sufficient to meet caloric needs
Vitamin D concentrate	400 to 800 I.U.
Salt (iodized)	For seasoning

Adapted from the Food and Nutrition Board of the National Research Council.

its own area. The effect of geographic factors on deficiency diseases is evidenced in the high incidence of goiter owing to a deficiency of iodine in certain areas and by the relationship between dental caries and fluorine in communal water supplies.

ARILD E. HANSEN

## REFERENCES

### General

- Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*. 6th ed. Baltimore, Williams & Wilkins Company, 1955.
- Luck, J. M., and others: *Annual Review of Biochemistry*. Stanford, California, Vol. 22-25, 1953-1956.
- Macy, I. G.: *Nutrition and Chemical Growth in Childhood*. Vol. 1, Evaluation, 1942. Vol. 2, Original Data, 1946. Vol. 3, Calculated Data, 1951. Springfield, Ill., Charles C Thomas.
- McLester, J. S., and Darby, W. J.: *Nutrition and Diet in Health and Disease*. 6th ed. Philadelphia, W. B. Saunders Company, 1952.
- Nutrition Reviews*: Nutrition Foundation, New York, Vol. 10-14, 1953-1956.
- Recommended Dietary Allowances*, Revised. National Research Council, 1953.

### Protein

- Greenberg, D. M.: *Amino Acids and Proteins*. Springfield, Ill., Charles C Thomas, 1951.
- Pratt, E. L., Hansen, A. E., and others: The Threonine Requirement of the Normal Infant. *J. Nutrition*, 56:231, 1955.
- Rose, W. C.: Amino Acid Requirements in Man. *Federation Proc.*, 8:546, 1949.
- Snyderman, S. E., and others: The Phenylalanine Requirement of the Normal Infant. *J. Nutrition*, 56:253, 1955.

### Carbohydrates

- Cori, G. T.: Glycogen Structure and Enzyme Defi-

ciencies in Glycogen Storage Disease. *The Harvey Lectures 1952-3*. Series XLVIII. New York, Academic Press, Inc., 1954.

- Illingworth, B., Cori, G. T., and Cori, C. F.: Amylo-1, 6-Glycosidase in Muscle Tissue in Generalized Glycogen Storage Disease. *J. Biol. Chem.*, 218:123, 1956.

### Fats (Lipids)

- Bloor, W. R.: *Biochemistry of the Fatty Acids*. New York, Reinhold Publishing Corporation, 1943.
- Hansen, A. E., and Wiese, H. F.: Essential Fatty Acids and Human Nutrition. II. Serum Level for Unsaturated Fatty Acids in Poorly Nourished Infants and Children. *J. Nutrition*, 52:367, 1954.
- Wiese, H. F., Gibbs, R. H., and Hansen, A. E.: Essential Fatty Acids and Human Nutrition. I. Serum Level for Unsaturated Fatty Acids in Healthy Children. *J. Nutrition*, 52:355, 1954.

### Minerals

- Darrow, D. C.: Disturbances in Electrolyte Metabolism in Man and Their Management. *Bull. New York Acad. Med.*, 24:147, 1948.
- Sherman, H. C.: *Chemistry of Food and Nutrition*. 8th ed. New York, Macmillan Company, 1952.
- Shohl, A. T.: *Mineral Metabolism*. Am. Chem. Soc., Monograph Series. New York, Reinhold Publishing Corporation, 1939.

### Vitamins

- Bessey, O. A., Adam, D. J. D., and Hansen, A. E.: Intake of Vitamin B<sub>6</sub> and Infantile Convulsions: A First Approximation of Requirements of Pyridoxine in Infants. *Pediatrics*, 20:33, 1957.
- Nitowsky, H. M., Gordon, H. H., and Tildon, J. T.: Studies of Tocopherol Deficiency in Infants and Children. IV. The Effect of Alpha Tocopherol on Creatinuria in Patients with Cystic Fibrosis of the Pancreas and Biliary Atresia. *Bull. Johns Hopkins Hosp.*, 98:361, 1956.
- Sebrell, W. H., Jr., and Harris, R. S.: *The Vitamins: Chemistry, Physiology, Pathology*. New York, Academic Press Inc., 1954, Vol. I-III.

## FEEDING OF INFANTS

The successful management of infant feeding requires practical interpretation of specific nutritional needs and of the widely varying limits of the normal baby's appetite and behavior with regard to food. Since the establishment of feeding habits as well as personality patterns begins at birth, and since the newborn period is a time of great emotional tension for the mother, it is important that she be helped to understand his needs as well as her own.

Fathers and other members of the household are too often neglected by physicians in

their approach to the problems of infant care. Time is rewardingly spent in conferences at the hospital or at home with emphasis on reassurance, on explanation of simple procedures, and on the philosophy of adjusting the family's activities, within reasonable limits, to the infant's needs. The physician can learn much about the personality and expectations of both parents which is invaluable in helping to avert physical and psychological problems centered around feeding.

The majority of feeding difficulties of the first few years of life are the result of abnor-



nal and unpleasant child-parent relationships, most of which are avoidable.

With the present emphasis on "self-regulating" infant feeding schedules, it is natural that uncertainties result concerning the extent to which the infant shall determine his routine. There is reasonable agreement that better child-parent relationships develop when the infant's natural habits serve as the basis for determining his daily habits, but there remains a need for the experienced physician to guide the parents.

The emptying time of the infant's stomach varies from one to four hours. Thus there is considerable individual variation in the desire for food, even in the same infant at different times of the day, and ideally the feeding schedule should be planned accordingly. With such a plan of "self-regulation" irregularity in the intervals between feedings and in the amounts taken per feeding can be expected the first few weeks, but by the end of the first month over 90 per cent of infants will have established a fairly definite schedule.

The advantages to the infant in supplying his needs as they are expressed are tremendous: he is not immediately forced into conflict with his environment; his physiologic needs are promptly met; he does not learn to associate prolonged discomfort as expressed by crying with feeding; he does not learn to gulp his food, or to take just a little, or to refuse some feedings completely. A reasonably regular schedule is soon established, which is essential to the family in assuming their normal activities. Such a schedule requires more understanding on the part of the parents as well as more time from the physician than does an arbitrary three- or four-hour feeding schedule.

Most healthy full term infants will want from six to ten feedings a day during the first week of life. By the time the mother's milk supply is established the majority will take enough at one feeding to satisfy them for approximately four hours; some who are smaller or whose gastric emptying time is more rapid will want food about every three hours. Consistent crying at shorter intervals should raise the question of an inadequate milk supply, mechanical difficulties associated with feeding, or discomfort from some cause other than hunger. Most infants will not awaken for the middle of the night feeding after three to six weeks of age; some may never need it. The majority will skip the late

evening feeding between four and eight months of age and will be satisfied with three major feedings per day by nine to twelve months.

In helping a mother to establish a schedule geared to the infant's needs and behavior, it is important to point out that he may cry for reasons other than hunger and that he need not be fed every time he cries; some infants are placid, some active, some irritable, and a sick one is usually apathetic about food. The habit of offering frequent small feedings or of holding and feeding to pacify all crying is to be avoided. Too much clothing, wet, tight or uncomfortable clothes, an environment that is too hot or cold, swallowed air, colic, illness or discomfort from any cause and lack of sufficient attention are the most frequent reasons other than hunger for an infant's crying. Infants who stop crying when they are picked up or held are usually not in need of food, nor are those who do not stop crying when food is offered.

After the first two or three weeks a "self-regulated" schedule for the infant need not interfere too much with the rest of the family's activities. Individual feedings or the whole day's schedule can be moved ahead or delayed sufficiently to avoid conflicts with the family mealtimes, bedtimes and other activities essential to family living.

Some mothers will not understand the goals of self-regulation by the infant, some will misinterpret the physician's instructions, and others may not have the capacity to adjust themselves to the regimen of the infant. The orderly, overanxious and compulsive type of parent will do better with a more specific outline for the infant's activities.

## BREAST FEEDING

See page 121 for composition of human and cow's milk.

**Colostrum.** The secretion of the breasts for the first two to four days after delivery is termed "colostrum." It has a deep lemon-yellow color, its reaction is alkaline, and its specific gravity is 1.040 to 1.060, in contrast to an average specific gravity of fresh breast milk of 1.030. Colostrum contains several times as much protein as does breast milk, but less carbohydrate and fat. The total amount of colostrum secreted daily is not large (10 to 40 cc.). Subsequent to the changes after the first few days of lactation from colostrum to milk, there is a further gradual transition

during the next two or three weeks until characteristic breast milk is secreted.

**Advantages of Breast Feeding.** Breast milk is not only the natural but also the ideal food for full term infants during the first few months of life. It can scarcely be said that the milk of various mammals is specific for the species in the sense that the young of one species cannot be nourished by the milk of another. There are, however, quantitative differences in the content of protein, carbohydrate, fat, minerals and vitamins in the milk of various species, and the nurslings of the various species do well on their natural milk supply. During the first three or four months of life the infant who is successfully breast-fed by a mother whose diet is quantitatively adequate and properly balanced will receive the necessary nutrients, with the exception of vitamin D and possibly of C. Though breast milk is low in iron, that stored during the latter part of fetal life will supply the requirements for the first three or four months.

The practical aspects of breast feeding are apparent. Human milk is always readily available at the proper temperature wherever the mother may be. It is always fresh and free of contaminating bacteria, and errors in preparation of formulas are avoided, so that the chances of gastrointestinal disturbances are greatly reduced.

In the past there was a much higher mortality rate among artificially fed infants than among breast-fed ones. It now appears that there may be little, if any, difference in the mortality rates of artificially fed and breast-fed infants when they receive good pediatric care. Among the lower socio-economic groups or where sanitary conditions are poor the breast-fed infant continues to have a much better chance of survival.

There are fewer and less serious feeding difficulties among breast-fed than among artificially fed infants. There is some evidence that breast-fed infants may acquire greater passive immunity than artificially fed ones. In a group of infants receiving good pediatric care Stevenson found a higher incidence of respiratory infections during the second six months of life in artificially fed than in breast-fed infants. The incidence of atopic eczema is about seven times greater in artificially fed infants.

It has been suggested that the intestinal flora of infants fed human milk provides special benefits. The stool of the breast-fed infant has a lower pH than that of an infant fed cow's milk, and the bacterial content is pre-

dominantly of the lactobacillus group in contrast to a predominance of the coliform group in artificially fed infants. György demonstrated that a strain of *L. bifidus* requires a "growth factor" contained in milk for its propagation. This factor appears to be abundant in human and rat milks, but present in only slight amounts in the milk of cows, goats and sheep.

Much has been said about the psychologic effects of breast feeding on the infant and on the mother. Certainly successful breast feeding is a satisfactory experience for both. For the mother there is the sense of accomplishment and of essentialness; however, the mother who wishes but is unable to nurse her infant need have no less a sense of affection for him. Though it has been suggested that the breast-fed infant will be emotionally more stable than the bottle-fed infant, it would seem that the latter, provided he is a "wanted baby," would receive adequate protection and affection from the mother. In a world that needs stability there seems to be no justification for projecting a new "fear neurosis." The theory that emotional instability is likely to be an aftermath of bottle feeding requires confirmation which is not available, and until it is, it should be emphasized that security and affection can be given to a bottle-fed infant.

**Disadvantages and Contraindications.** For the average, healthy, full term infant there are no disadvantages to breast feeding, provided the mother's milk supply is ample and her diet contains sufficient amounts of protein and vitamins. Infrequently, allergens to which the infant is sensitized may be conveyed in the milk. In such instances an attempt should be made to find the specific allergen and to remove it from the mother's diet; the presence of such allergens rarely becomes a valid reason for weaning the baby.

The infant who is too weak to nurse because of prematurity, general debility or illness, or unable because of a cleft lip or palate, should receive milk, when available, that has been pumped or expressed from the breasts.

From the standpoint of the mother there are temporary or permanent contraindications to breast feeding. Fissuring or cracking of the nipples is an indication for temporary cessation of nursing when the use of a nipple shield is unsatisfactory. Mastitis necessitates discontinuance of nursing, although, when treatment is rapidly effective, breast feeding may be resumed after several days. Acute illness in the mother may be considered a contraindication to breast feeding if the in-



infant does not have the same infection; otherwise there is no need for cessation of nursing unless the condition of either makes it mandatory. When the infant is not affected and the mother's condition permits, the breasts should be emptied, and the milk may be sterilized and given to the infant.

Severe disturbances such as septicemia, nephritis, eclampsia, severe hemorrhage, active tuberculosis, typhoid fever or malaria are permanent contraindications to nursing, as are chronic poor nutrition, debility, epilepsy, insanity, neurosis, postpartum psychosis and regnancy.

When the mother is repulsed by the thought of nursing her infant, it is probably wise to avoid an issue which might further disturb the mother-infant relationship.

The onset of menstruation is not a contraindication to continued nursing, although there may be changes reflected by different behavior of mother or baby which necessitate reassurance that they are temporary.

Erythroblastosis fetalis is not a contraindication to breast feeding, if the infant's general condition warrants it, since antibodies in the mother's milk are inactivated in the intestinal tract and do not contribute to further hemolysis of the infant's red blood cells.

**Preparation of the Prospective Mother.** Despite the fact that breast milk is the natural food for infants, many receive little or none of it. Some mothers are not good milk producers and are unable to provide an amount sufficient to justify even partial feeding of their infants (combined breast and supplemental milk feedings). Great improvement in the quality of artificial feeding has been a large factor in the decreased incidence of breast feeding; "emancipation of women" and the tempo of modern living are also contributing elements. Some groups do not consider breast feeding a socially acceptable procedure. Employment of women outside the home necessitates artificial feeding in many instances. Many mothers are reluctant to nurse their infants because of the limitation on their social activities or because of the fear of loss of physical attractiveness, especially through gain in weight and loss of breast tone.

To permit the mother greater freedom of activity outside the home, a daily bottle of formula can be substituted for one of the breast feedings by the time she is ready to resume her normal activity. Actually, there are advantages in such an arrangement. The psychologic effect on the mother is perhaps the most important, but there is also training

of the baby in feeding from the bottle so that weaning at the usual time is facilitated. The mother may be reassured that she need not gain or lose weight if her diet is adequate. Both mother and father should be reassured that breast tone may be preserved by the use of a properly fitted brassiere to support the breasts, especially before delivery and during the nursing period.

The advantages of breast feeding must be explained to the prospective mother early in her pregnancy. It might even be pointed out during puberty or before that the primary physiologic function of a woman's breasts is to feed her children. Physical factors consist in establishing and maintaining a healthy status by properly balanced rest and exercise, freedom from worry, early and adequate treatment of any intercurrent disease and adequate nutrition. Nutritional deficiencies are one of the causes of premature birth and of increased infantile morbidity, and are possibly contributory factors to infantile mortality and to inadequate lactation.

There does not appear to be any advantage in the use of the so-called hardening processes designed to toughen the nipples. Such procedures may increase the likelihood of cracking or fissuring. Retracted nipples may be benefited by daily manual or breast pump traction during the latter weeks of pregnancy, but true inverted nipples are not helped.

#### ESTABLISHMENT AND MAINTENANCE OF THE MILK SUPPLY

**Psychologic Factors.** Attention to the details of maternal hygiene are paramount. No factor is more important than a happy, care-free state of mind; worry and unhappiness are the most effective means for decreasing or abolishing breast secretion.

Mothers worry that their babies are abnormal when they cry, when they are drowsy, when they sneeze or eructate a mouthful of milk. Mothers are upset about any suggestion that their milk may be lacking in quantity or quality. They are disturbed at the thin appearance of colostrum, at tenderness of the nipples and at the fullness of the breasts on the fifth day. Many mothers cannot feel comfortable trying to nurse in an open ward or even with one person in the room. Most mothers worry about what is going on at home while they are hospitalized and about what is going to happen when they arrive home. An alert nurse or physician is conscious of these worries, particularly if the baby is a first-born, and by tactful reassurance and ex-

planation can help to prevent or minimize worry and thus contribute to successful breast feeding.

**Fatigue.** Avoidance of fatigue is important, but the mother should have sufficient exercise to promote a sense of physical well-being.

**Diet.** The diet should contain enough calories to compensate for those contained in the secreted milk as well as those required for its production. A diet adequate to maintain weight and relatively high in protein, fluid, vitamins and minerals will suffice. However, the mother should have the benefit of instruction in the make-up of her diet. Milk is important, but should not replace other essential foods. When the mother is allergic or has an aversion to milk, 1 gm. of calcium may be added to her daily diet. The fluid intake should approximate 3 quarts daily.

There are mistaken ideas that such substances as milk, beer, oatmeal and tea are galactogenic. There is no objection to small amounts of alcoholic beverages or to smoking in moderation if they contribute to the mother's peace of mind and sense of well-being. Seldom does a particular food in the mother's diet have a disturbing influence on the breast-fed infant. Occasionally, however, some items in the maternal diet, such as certain berries, tomatoes, onions, members of the cabbage family, chocolate, spices and condiments, may cause gastric distress or loose stools in the infant. No food should be withheld from the mother's diet unless it causes distress to the infant. It is better to control the mother's constipation by inclusion in the diet of raw and cooked fruits and vegetables, whole wheat bread and an adequate amount of water than by the use of laxatives. Certain drugs, such as the barbiturates, bromides, iodides, salicylates, opium, atropine, sulfonamides and cascara, may be transmitted through the milk and exert an effect on the infant.

**Hygiene.** The nipples should be washed with water before and after each nursing and once or twice a day with soap and water. As a rule, no other care is needed; the important factor is to keep the nipple dry. The use of boric acid should be avoided. Care should be taken to prevent irritation and infection of the nipples by prolonged initial nursing, maceration from wetness of the nipple, irritation of clothing, or difficult nursing associated with engorged or overdistended breasts. Serious difficulties can usually be avoided by taking the infant off an affected breast temporarily and expressing the milk manually.

Occasionally nipple shields may be of help. The infant should be returned to breast feeding as soon as the nipple has healed.

A properly fitted brassiere should be worn day and night. A piece of clean cloth may be placed inside the brassiere to absorb any milk which leaks out.

*Manual expression of breast milk* is achieved by two movements. The first is compression of the whole breast between the hands, starting at the base and continuing toward the areola. Firm pressure is maintained throughout the movement, which is repeated several times. The purpose is to impel milk to the lacteal sinuses. The second movement should empty the sinuses. The breast is supported with one hand while the tissue just behind the areola is repeatedly compressed between the thumb and first finger of the other hand. The direction of the force is backwards toward the center of the breast rather than toward the nipple. The fingers are not moved from this initial position, nor is the skin rubbed over the breast tissue. The procedure should not be painful even though the nipples are sore and cracked.

**Stimulation.** It is essential in establishing an adequate milk supply for the breasts to be stimulated. The only known satisfactory stimulus to the secretion of human milk is regular and complete emptying of the breasts. There are many reasons for incomplete nursing, but the principal ones are weakness of the infant and failure of initiation of a natural hunger cycle. When the breasts are not emptied completely by the infant during the early days of nursing, they should be emptied regularly by artificial means. This is sometimes necessary on the fifth day to relieve overdistention of the breast so that the infant is able to grasp the mother's nipple. A hand breast pump or a water suction pump may be used, or the mother may be taught manual expression. Every effort should be directed toward the establishment of natural, vigorous nursing. This is accomplished by letting the infant empty the breasts frequently during the time when colostrum is being formed. The infant should be allowed to nurse when he is hungry whether or not there appears to be any milk. It is probably unimportant whether he be put to breast shortly after delivery or after a lapse of twenty-four hours, but early acquaintance with his mother's breast is much more important than prelacteal feedings.

Centralized nurseries in busy maternity services necessitate a fairly rigid schedule of infant feeding. Infants seem to do fairly well



Under such circumstances if they are allowed to nurse twice or three times during the second day and every four hours thereafter. Sterile water or 5 per cent glucose solution may be offered after nursing if they still desire fluid. Nature never intended babies to be fed on an arbitrary schedule, and much can be said for the "rooming-in" plan. Breast feeding is more successfully established and maintained when the baby is allowed to nurse when he is ready than at prescribed times.

Though lactogenic hormones have been effective in certain mammals, there is no evidence that they are effective in the stimulation of breast secretion in the human being.

The first two weeks of the neonatal period is the crucial time for the establishment of breast feeding. Too much emphasis is put on daily weight gains. If early supplemental milk feedings are given to achieve this false goal, attempts at successful breast feeding are doomed to failure, since it is usually easier for the infant to get milk from a bottle than from the breast.

Supplemental milk should never be given before the fifth day and rarely before the end of the first week. An exception may be made on the day the mother is discharged from the hospital, particularly if her confinement is limited to four or five days. By that time lactation may not be well established, and the excitement of going home may not be conducive to an initial successful nursing experience there. A wise doctor may foresee this experience and supply the mother with enough isocaloric formula for complementary feedings for the rest of the day and evening, thus avoiding a discouraging situation that might well prejudice the success of further nursing. By his pointing out the effect that such excitement and unusual activity are likely to produce, she will not be so upset when her milk supply is temporarily decreased.

#### TECHNIQUE OF BREAST FEEDING

The technical aspects of breast feeding require careful consideration. It is not unusual for breast feeding to be deemed impossible simply because the attending physician fails to recognize that the difficulties are related to the manner of feeding and not to qualitative or quantitative inadequacies of the milk.

The infant should be hungry at feeding time, dry and neither too cold nor too warm. He should be held in a comfortable, semi-sitting position for his enjoyment and for facilitation of eructation without vomiting.

The mother, too, must be comfortable and completely at ease. When she is able to be out of bed, a moderately low chair with armrest is preferable, and a low stool is advantageous for resting her foot and raising her knee on the nursing side. The baby is supported comfortably with his face close to the breast by one arm and hand while the other hand supports the breast so that the nipple is easily accessible to the infant's mouth and yet does not obstruct his nasal breathing. The baby's lips should be well out over the areola of the breast.

Success in infant feeding depends to a great extent upon the adjustments during the first few days of life. Difficulties are likely to result when attempts are made to adapt the infant to the nursing procedure rather than to try to satisfy his natural desires. If he is put at the breast when there is normal hunger crying and if his appetite is satisfied, the fundamental requirements are met. Two difficulties in this respect are the rigid adherence to clock schedules in the hospital nursery and the mechanistic manner in which many infants are handled. Most of the difficulties can be avoided by conforming to the infant's natural pattern. Aldrich emphasized the natural initial responses to hunger; his account of one of them, the rooting reflex, is so well phrased



FIG. 22. Technique of nursing. (Lyon and Wallinger: *Mitchell's Pediatrics and Pediatric Nursing*.)

that we have taken the liberty of reproducing it here.

At the time he is born, the normal infant is equipped with several reflexes, or behavior patterns, which are designed to make him a successful feeder from the breast. The most obvious of these reflexes are those concerned with the actual getting of food—rooting, sucking, swallowing, and satiety reflexes.

The *rooting reflex* is the first one of these to come into play. When a baby smells milk, he moves his head around and attempts to find its source. If one cheek is touched by a smooth object, he will turn his mouth toward that object and open it in anticipation of grasping the nipple. This obviously gives a clue as to how milk should be given to the baby. His cheek applied to his mother's breast will start him rooting with his mouth for the nipple.

I can illustrate a mistake made in this regard by telling the . . . experience of a patient in one of our best hospitals. As I was making daily rounds, she said to me: "Your nurses don't know their stuff! . . . They don't know anything about the rooting reflex. They bring my baby in, place her beside me and with their hand on the baby's cheek try to push her head around to meet the nipple. The baby, feeling the pressure of the hand, tries to turn toward the nurse's palm instead of toward my breast. A fight ensues, and usually the natural response is prevented. I always tell the girls to go out of the room; that I can handle this myself if they just lay the baby down beside me. I touch her cheek with my breast and let her do the rest." This experienced mother had learned to respect her baby's ability in these basic matters. This is a highly important lesson for anybody to learn.

Mothers should know that if the infant is not hungry, he will not search for the nipple or suck. Infants are unusually sleepy for several days, and most are not initially avid suckers. Particularly on the third day, when there has been some weight loss, mothers are anxious about infants who do not seem particularly interested in eating. It is reassuring for them to know that most healthy babies "wake up" and become good eaters on the fourth day.

The "let-down" reflex, wherein milk flows from one nipple when the baby nurses from the other, is a sign of successful nursing rather than of an abnormality and is not present in a worried mother.

Some infants will empty a breast in five minutes; others will be more leisurely and nurse well for twenty minutes. The baby should be permitted to suck until he is satisfied. Efforts to wake up a sleepy baby and to "make him" nurse by snapping his feet, pinching or shaking him are rarely successful.

At the end of the nursing period the infant should be held erect over the mother's shoulder to eructate swallowed air; often this pro-

cedure is necessary at one or more intervals during the feeding as well as five to ten minutes after the infant has been put into the crib. It is an essential procedure during the early months. When nursing is completed, the infant should be placed in the crib on his abdomen or on his right side to facilitate emptying of the stomach into the intestine and to lessen the chances of regurgitation.

**One or Both Breasts per Feeding.** After the milk supply has been well established the breasts may be alternated at successive feedings, and the baby will usually be satisfied with the amount from one side. It is important that he empty at least one breast at each feeding; otherwise it will not be stimulated to refill. If the supply seems inadequate, it is advisable to offer both breasts at each feeding, alternating the one offered first, so that it will be completely emptied at each feeding. When the secretion of milk is too great, however, both breasts may be offered at each feeding and incompletely emptied with the intent of securing a partial decrease in lactation.

**Determination of Adequacy of Breast Supply.** If the infant is satisfied at the completion of the nursing period, sleeps for three to four hours thereafter, and gains weight satisfactorily, it can be assumed that the breast supply is adequate; weighing of the infant at other than weekly to monthly intervals is neither necessary nor desirable. If, however, the infant nurses avidly and is not satisfied after completely emptying both breasts, does not go to sleep quickly, sleeps fitfully and/or awakens after an hour or two and gain in weight is not satisfactory, it is probable that the milk supply is inadequate. The extent to which the mother's breasts become filled during the intervals between nursing is an additional measure of her capacity to produce milk.

Weighing a baby before and after nursing is generally an unsatisfactory way of judging adequacy of breast supply and is fraught with danger of misinterpretation. It wrongly focuses attention on how much the baby takes at a given time (this may normally vary from a fraction of an ounce to 8 to 10 ounces in the various feedings during a twenty-four hour period) and hence causes the mother to worry and the supply to diminish. She then wishes to give him a bottle so that she can see how much he gets and know that it is enough. Before it is assumed that the mother is unable to produce sufficient milk, three factors should be considered: (1) that tech-



cal faults are not responsible for the infant's inadequate progress; (2) that there are no medial maternal factors related to diet, rest and/or psychologic disturbances; and (3) that the infant has no physical disturbance which interferes with eating or otherwise with gain in weight.

**Supplementary Feedings.** One substitute feeding a day, after the first week or two and after the mother's milk supply has been adequately established, has the advantage of permitting the mother greater freedom in her activities and of familiarizing the infant with the bottle so that weaning will be facilitated later. If a baby who is otherwise normal and healthy is getting insufficient breast milk, he could be offered additional artificial feedings either immediately after or in place of one or more breast feedings. Any of the milk formulas described under Artificial Feeding may be used and should be offered to the baby in amounts sufficient to satisfy him.

If a formula is to be given after the baby has completed a breast feeding, the bottle should be warmed and handy so that it can be offered immediately after the infant has been given an opportunity to eructate any swallowed air. The holes in the nipple should not be so large that the baby gets this portion of his food without any effort, or he will quickly abandon any efforts to suck adequately at his mother's breast.

A replacement feeding is preferably substituted for the breast when the milk supply is observed to be scantiest, usually late in the afternoon. The infant is given as much as he wants of an isocaloric formula. It is frequently accepted better from a person other than the mother, from whom he is conditioned to nurse. Combined breast and bottle feedings may be continued as long as seems practical and satisfying to the mother and the infant.

**Breast Milk from Sources Other than the Infant's Mother.** With improvements in artificial feeding the use of breast milk from other than the maternal source has decreased. Direct wet-nursing, once widely used, is now a rarity. When a wet nurse is employed, she must be known to be free of all contagious disease, especially tuberculosis and syphilis. In some maternity hospitals it is common practice to collect excess breast milk by means of an electric breast pump for the feeding of weak or sick infants. A number of the larger cities have so-called breast milk stations where breast milk is collected, pasteurized, dried or frozen and dispensed. All women who con-

tribute milk must be in good health, and supervision must be maintained to prevent contamination or dilution of the milk.

## WEANING

Weaning is usually advisable when the infant is six to nine months of age, but should be avoided, if possible, during extremely hot weather. When a bottle feeding per day has been substituted for one of the breast feedings, as suggested previously, there is no difficulty in weaning. When the infant is not acquainted with the bottle, cup feeding may be tried. Not infrequently the cup is taken as readily as the bottle, and the subsequent transfer to cup from bottle feeding is avoided. In any event, when the mother's milk supply is abundant, the process of weaning should be sufficiently gradual to avoid causing her unnecessary discomfort and to let the baby learn to accept milk from a new source. Initially, one of the breast feedings is replaced by a bottle feeding. After several days another breast feeding is replaced, and so on until the baby is entirely weaned. The total time required is governed by the status of the maternal milk supply. One breast feeding a day may be continued for several weeks, if necessary, to avoid discomfort from engorged breasts.

When weaning is necessary at an earlier age because of illness of the mother or for other reasons, or if breast secretion is no longer needed because of the death of an infant, a tight breast binder may be used and ice bags applied for a day or so. The mother's fluid intake should also be restricted.

## ARTIFICIAL FEEDING

The term "artificial feeding" is used for non-breast milk feedings during the period when the infant would naturally receive human milk. Cow's milk in the fresh whole state or in some modified form is the basis for most formulas. There are, however, a number of milk substitutes for infants hypersensitive to cow's milk.

Artificial feeding, once a complicated procedure from the standpoints of calculation and preparation, is now a rather simple one. Sterilization of the formula and refrigeration of it until used, so that bacterial contamination is avoided, have been important factors in the reduction of morbidity and mortality from gastrointestinal infections in the first year of life. Though infants can now be fed reasonably well by artificial means, and it is

often impossible to distinguish those who are breast-fed from those who are artificially fed, there are strong arguments for breast feeding during the first months of life (p. 114).

#### TECHNIQUE OF ARTIFICIAL FEEDING

In principle, this is the same as that described for breast feeding. The infant should be hungry, fully awake, comfortably warm and dry. The mother should be in a comfortable position, pleasant, unhurried and free of distractions. The baby should be held just as though he were being nursed. The bottle should not be propped, even in a "safe" holder, since this deprives the infant of the comfort and security he can get from being held. It may be dangerous, particularly to a small baby, to leave him unattended even momentarily with a bottle in his mouth. The bottle should be held so that milk, not air, is channelled into the nipple.

The bottle of milk should be warmed to body temperature; it may be tested by dropping milk on the wrist. The sterile nipple should be applied without contaminating it. The holes of the nipple should be of such a size that the milk will drop slowly.

Especially during the first six or seven months of life, the eructation of swallowed air during feeding is important to avoid discomfort as well as regurgitation. Eructation is facilitated by holding the infant upright over the shoulder with or without gently rubbing or patting the back. A few relieve themselves best after being replaced in the crib. Lying on the abdomen or right side facilitates this procedure and makes it easier for the stomach to empty into the intestine. All babies will at times regurgitate or "spit up" a small amount of milk after feeding, a fact which the mother should know. It occurs more often in artificially fed than in breast-fed infants. Aspiration of this milk is less likely if the infant lies on his side or abdomen, rather than on his back.

A feeding may require from five to twenty-five minutes, depending on the vigor and the age of the infant. Since the appetite varies from feeding to feeding, each bottle should contain more than the average amount taken per feeding. In no instance should the baby be urged to take more than he desires. The excess milk should be discarded, and the bottle and nipple rinsed with cool water.

#### COMPARISON OF HUMAN AND COW'S MILK

Average values for the various constituents of human milk and whole fresh and evaporated

cow's milk are listed in Table 22. Human milk and cow's milk differ during the various stages of lactation, and there are some differences between the milks of individual women as well as of cattle. The initial secretion of each is known as colostrum, which is described on page 113. For women whose diets are adequate in protein, vitamins, minerals and total calories, the differences in the milks are insignificant.

**Water.** The relative amounts of water and solids in human and cow's milk are about the same, the water content of each being about 87 to 87.5 per cent, with a specific gravity in the range of 1.030 to 1.032.

**Calories.** Though there are slight variations in the energy value of each milk, for practical purposes each may be assumed to be equivalent to 20 calories per ounce.

**Protein.** There are both qualitative and quantitative differences between the proteins of the two milks. Human milk contains only 1 to 1.5 per cent protein, in contrast to about 3.5 per cent in cow's milk. The principal qualitative differences are the relative amounts of lactalbumin and casein. In human milk the protein consists of approximately 6 per cent lactalbumin and 40 per cent casein whereas in cow's milk there is about 85 per cent casein and 15 per cent lactalbumin. Each milk contains small amounts of other proteins, including lactoglobulin. The proteins of the two milks are essentially equivalent for infant nutrition.

**Carbohydrate.** The sugars of the two milks differ only quantitatively, both being lactose. Human milk contains from 6.5 to 7 per cent, and cow's milk about 4.5 per cent.

**Fat.** The fat content of milk is more variable than any other constituent. The average content of each is about 3.5 per cent. The amount of fat in human milk varies somewhat with the maternal diet. The fat content of the latter portion of milk obtained at a single nursing is higher than that of the first portion.

The milk of different breeds of cattle varies in its fat content. Most market milk in urban areas, however, is pooled and the fat content adjusted to a standard level, generally from 3.25 to 4 per cent. As a rule, milks with the lower fat content are preferable for the feeding of infants.

There are qualitative differences between the fats of human and cow's milks. The fats of each are composed principally of the triglycerides, olein, palmitin and stearin. Human milk, however, contains relatively larger



quantities of the more readily absorbed olein. The volatile fatty acids (butyric, capric, propionic and caprylic) account for only about 5 per cent of the fat of human milk, in contrast to about 27 per cent of that of cow's milk. Though the normal full term infant has no difficulty in digesting the fat of cow's milk, the premature or debilitated infant may have difficulties. In such instances it is well to keep the fat content of the milk formula relatively low or substitute a more readily assimilated fat such as olive oil.

**Minerals.** The total mineral content of human milk (0.15 to 0.25 per cent) is considerably less than that of cow's milk (0.7 to 0.75 per cent). With the exception of iron and copper, cow's milk contains considerably more of all the minerals. Neither milk contains an adequate amount of iron; the deficiency is compensated for in the first four

months or so of life by fetal stored iron. Although the need for calcium and phosphorus is relatively great during the periods of rapid growth, adequate balances are maintained on breast milk in spite of its comparatively low content of these minerals.

**Vitamins.** The vitamin content of each milk varies with the maternal intake. Each has relatively large amounts of vitamin A and small amounts of D. Human milk contains more C except when there is a deficiency in the maternal intake of vitamin C-containing foods. The maximum secretion of vitamin C is one and a half hours after ingestion. Cow's milk contains more thiamine and riboflavin than human milk and about an equal quantity of niacin. It is assumed that each milk contains adequate amounts of vitamin A and inadequate amounts of vitamins C and D for the nutritional needs of infants and adequate

Table 22. Comparison of Human Milk with Cow's Milk (Whole and Evaporated)

	Human Milk	Cow's Milk	
	(Per Cent)	Whole (Per Cent)	Evaporated (Per Cent)
Water.....	87.0-88.0	83.0-88.0	73.0-74.0
Protein.....	1.0- 1.5	3.2- 4.1	6.8- 7.0
Lactalbumin.....	0.7- 0.8	0.5	1.1
Casein.....	0.4- 0.5	3.0	5.7
Sugar (lactose).....	6.5- 7.5	4.5- 5.0	9.8-10.0
Fat.....	3.5- 4.0	3.5- 5.2	7.9- 8.2
	(More olein and less of the volatile fatty acids)		
Minerals.....	0.15 -0.25	0.7-0.75	1.5- 1.6
Calcium.....	0.034 -0.045	0.122-0.179	
Phosphorus.....	0.015 -0.040	0.090-0.196	
Magnesium.....	0.005 -0.006	0.013-0.019	
Sodium.....	0.011 -0.019	0.051-0.060	
Potassium.....	0.048 -0.065	0.138-0.172	
Chlorine.....	0.035 -0.043	0.098-0.116	
Sulfur.....	0.0035-0.0037	0.030-0.032	
Iron.....	0.0001	0.00004	
Copper.....	0.00003	0.00002	
Vitamins (per 100 cc.):			
A.....	60-500 I.U.	80-220 I.U.*	No loss
D.....	0.4-10.0 I.U.	0.3-4.4 I.U.*	No loss
C.....	1.2-10.8 mg.	0.9-1.4 mg.*	0.6 mg.†
Thiamine.....	0.002-0.036 mg.	0.03-0.04 mg.*	0.02-0.03 mg.†
Riboflavin.....	0.015-0.080 mg.	0.10-0.26 mg.*	No loss
Niacin.....	0.10-0.20 mg.	0.10 mg.	
Reaction.....	Alkaline or amphoteric	Acid or amphoteric	Acid or amphoteric
Bacteria.....	None	Present	None
Digestion.....		Less rapidly	
Emptying of stomach.....		Less rapidly	
Curd.....	Soft, flocculent	Hard, large	Soft, flocculent
Calories per fluid ounce.....	20	20	44‡

The data are assembled from a number of sources.  
\* Values are for pasteurized milk.  
† Evaporated milk reconstructed to dilution of whole milk.  
‡ In practice, commonly regarded as 40 calories.

amounts of vitamin B complex for the first few months of life before cereal and other foods are started.

**Bacterial Content.** Human milk is essentially free from bacterial contamination. When there is mastitis, pathogenic organisms in significant numbers may gain access to the milk. Both tubercle bacilli and typhoid bacilli may be found at times in the milk of women infected with these organisms. Cow's milk is regularly contaminated, but in most instances the bacteria are not especially harmful for man. Cow's milk, however, is a good vehicle and even a culture medium for pathogenic bacteria, and many infections are milk-borne. Such infections include streptococcal pharyngitis, scarlet fever, diphtheria, typhoid fever, salmonellosis, tuberculosis and brucellosis. Furthermore, certain bacteria which may not have any disturbing effect upon older children or adults may cause diarrheal disturbances in infants. For this reason, in most cities pasteurization of all market milk, even certified, is required. In addition, boiling of the milk immediately before mixing the infant's formula or terminal sterilization is advisable.

**Digestibility.** The emptying time of the stomach is more rapid for human than for cow's milk. This is apparently due to the higher buffer content of cow's milk, which requires more acid for its digestion, and to the larger amount of casein, which is responsible for the production of large tough curds in the stomach. By contrast, the curd of breast milk is fine and flocculent and readily broken down in the stomach. The curd of cow's milk is somewhat reduced in size by boiling and is made considerably less tough and much smaller by the heating required in the production of evaporated milk, by the addition of acid or alkali or by homogenization. The fat of cow's milk is less readily digested than that of breast milk.

#### FORMS OF COW'S MILK USED IN FORMULAS

**Raw Milk.** Most urban centers forbid the sale of milk in the raw state, even of unpasteurized certified milk. Raw milk is not advised for infant feeding because it is slowly digested, forms large curds in the stomach and is likely to be contaminated with pathogenic organisms.

**Pasteurized Milk.** Pasteurization destroys pathogenic bacteria and alters the casein to some extent, so that smaller and less tough curds are produced in the stomach. Pasteurization is accomplished by heating milk at a

specific temperature for a specific length of time, e.g., at 143° F. for thirty minutes. Standards for the bacterial content of pasteurized milk vary in different cities, being as high as 50,000 nonpathogenic bacteria per cubic centimeter; averages in many cities, however, are as low as 5000 to 10,000 bacteria. Pasteurized milk should be boiled when used for infant feeding. If allowed to stand in the refrigerator for as long as forty-eight hours, it can show a significant increase in the number of bacteria.

**Certified Milk.** Milk marketed under this designation must meet rigid requirements. The cattle must be examined at regular intervals for all types of illness, including tuberculosis and brucellosis. The barns must be constructed so that adequate cleaning is possible and must be screened. The milkers are also examined for disease at regular intervals. Each step in handling of the milk is guarded to avoid bacterial contamination. Immediately after milking, the milk is cooled to 45° F. and maintained at this temperature until delivery. Bacterial requirements vary, but not more than 10,000 bacteria per cubic centimeter are permitted in any city. Many cities require certified milk to be pasteurized. Boiling it for infant feeding is advisable in order to increase its digestibility.

**Homogenized Milk.** The processing of milk so that the fat globules are broken into minute particles is termed "homogenization." By one method, milk is forced through minute openings in a metal plate under high pressure. Owing to the decrease in size and the dispersion of the fat molecules, the cream does not separate. The principal advantage of homogenized milk lies in the smaller and less tough curd produced in the stomach.

**Evaporated Milk.** Evaporated milk has numerous advantages in addition to its almost universal availability. In the unopened can it will keep for months without refrigeration. The casein is altered so that the curd produced in the stomach is softer and smaller than that of boiled whole milk. The effect of homogenization on the fat molecules also contributes to the smaller curd formation. The lactalbumin appears to be less allergenic than that of fresh milk. The sugar is unchanged. It can be fed when necessary in higher concentrations than whole milk formulas.

The standard can contains 14.5 ounces avoirdupois or 13 fluidounces. In each fluidounce there are about 44 calories; in practice it is generally figured as 40 calories. Since more than one can of evaporated milk is



dom used for a daily feeding, whether it is uted with an equal quantity of water (13 nces) or reconstructed at a ratio of 1:1.2 5½ ounces), it is equivalent to only about ounces of whole milk. Vitamin D is added most evaporated milks in an amount so at each reconstructed quart contains 400 U.

**Condensed Milk.** About 45 per cent of ne sugar has been added in sweetened condensed milk, and it is impossible to dilute is without having a mixture disproportionately high in sugar and low in fat and otein. Although it is readily digestible, it is no use in infant feeding for more than ort periods when a high caloric diet is esired.

**Dried Milk. Whole milk.** Standard regulations govern the production of dried milk. he fat content of fluid milk is adjusted to 5 per cent, and the milk is evaporated with treme rapidity to powder form. Reconstructed dried milk has most of the advantages evaporated milk. Dried milk has its great usefulness in the feeding of infants in stitutions. It has limited keeping qualities hen exposed to air. In reconstructing dried milk to its original fluid state, 1 ounce by eight (3½ packed level tablespoonfuls) is added to 7 ounces of water.

**Dried skimmed milk.** Available with varying percentages of fat content up to about 1.5 er cent, dried skimmed milk has limited usefulness: (1) for infants with fat intolerance, (2) during convalescence from diarrheal diseases; and (3) for diets high in protein and low in fat for premature infants. n the reconstruction of dried skimmed milk, ounce by weight is added to 9 ounces of water.

**Acid Milk.** So-called acid milks are prepared by addition of acid or by fermentation by bacterial action. Such milks require less hydrochloric acid from the gastric juice for digestion. The casein is altered so that a smaller and less tough curd is formed in the stomach. These factors appear to be advantageous in the feeding of infants with digestive disturbances and of those convalescing from diarrheal disturbances. Acid milk does not appear to have decided advantages for healthy infants.

**Lactic acid milk.** Lactic acid, U.S.P. is added to previously boiled and cooled cow's milk formulas; the amount required varies with the fat content, those with the higher concentrations requiring more acid. Milks

containing 3.5 to 4 per cent fat require about 1½ fluid drams (6 cc.) to the quart. Reconstructed evaporated milk requires about the same amount. The acid is added drop by drop to the cooled milk formula with constant stirring with a wooden spoon to avoid curd formation. There are several commercial preparations of dried lactic acid whole and skimmed milk.

**Fermented milk.** This milk also contains lactic acid. Buttermilk, once widely used in infant feeding, is now rarely used, and most fermented milks are prepared by culture with a lactic acid-producing organism (*Lactobacillus acidophilus* and *L. bulgaricus*).

**Vitamin D Milks.** In addition to the wide availability of fortified evaporated milk (400 I.U. per reconstructed quart), fortified whole milk containing 400 I.U. of vitamin D per quart may be had in most cities. Homogenization of vitamin D milk is a distinct advantage, since it ensures even distribution of the fat which contains the vitamin D.

#### OTHER MILKS USED IN FORMULAS

**Goat's Milk.** The composition of goat's milk is similar to that of cow's milk: fat, 4 per cent; carbohydrate, 4.5 per cent; protein, 4 per cent. The curd tension of goat's milk is less than that of cow's milk. The goat seldom contracts tuberculosis, but is especially susceptible to brucellosis. In some countries goat's milk is widely used for the feeding of infants, but in this country is used chiefly for infants allergic to cow's milk. Evaporated goat's milk is available commercially. Fresh goat's milk should be boiled before use.

**Prepared Milks.** Table 23 lists the varieties of milks and milk substitutes available for infant feeding. Many of the commercially prepared ones require only the addition of water to make them ready for use. Those which have a relatively low fat and high protein content may be used satisfactorily for premature (p. 309) and debilitated infants, and for infants convalescing from diarrheal disease.

**Milk protein.** Powdered protein is used chiefly for increasing the protein content of dilute skimmed milk or other formulas for feeding during diarrheal conditions, or to premature or debilitated infants.

**Milk Substitutes and Hypoallergenic Milks.** There are a number of milks and milk substitutes for infants allergic to cow's milk. These include goat's milk, a preparation in which the protein is supplied by an amino

Table 23. Commercial Milks and Milk Substitutes Used in Infant Feeding

	Percentage Composition (Approximate)								Cals. Oz.		Normal Dilution <sup>a</sup>	Household Equivalents for One Dry Pound
	Dry or Undiluted				Normal Dilution				As Pack-aged	Normal Dilution		
	Protein	Carbo-hydrate	Fat	Min-erals	Protein	Carbo-hydrate	Fat	Min-erals				
Fluid Whole Milk												
Market milk, average	3.3	4.8	3.5	0.7	3.3	4.8	3.5	0.7	20	20	Not diluted	
Powdered Whole Milk												
Klim, Borden	26.7	38.0	28.0	5.8	3.2	4.5	3.3	0.7	145	18	1:7	3½
Evaporated Milk												
Many brands	7.0	9.9	7.9	1.5	3.5	5.0	4.0	0.75	44	22	1:1 <sup>b</sup>	
Lactic Acid Milk												
Powdered lactic acid milk no. 2, Mead	26.0	38.0	28.0	6.0	3.3	4.6	3.4	0.8	141	19	1:7	3½
Milks with Composition Similar to That of Breast Milk												
Bremil, powder, Borden	11.7	54.6	27.5	3.9	1.5	7.0	3.5	0.5	145	20	1:8	3½
Bremil, liquid, Borden	3.0	14.0	7.0	1.0	1.5	7.0	3.5	0.5	40	20	1:1	
Similac powder, Ross	13.75	53.4	26.85	4.0	1.7	6.7	3.4	0.5	145	20	1:7	4
Similac liquid, Ross	3.45	13.1	6.8	0.75	1.7	6.6	3.4	0.38	40	20	1:1	2
SMA powder, Wyeth	11.9	55.4	27.7	3.0	1.5	7.0	3.5	0.38	151	20	1:6½	3½
SMA liquid (concentrate), Wyeth	2.9	13.6	6.8	0.70	1.5	7.0	3.5	0.38	40	20	1:1	
Milks with Composition Similar to That of Breast Milk Except for Higher Percentage of Protein												
Lactum powder, Mead	19.0	54.5	19.5	4.5	2.7	7.8	2.8	0.6	133	20	1:6	3
Lactum liquid, Mead	5.4	15.6	5.6	1.2	2.7	7.8	2.8	0.6	40	20	1:1	
Modified milk (powder), Baker	16.7	52.3	24.7	4.3	2.2	7.0	3.3	0.6	142	20	1:7	3½
Modified milk (liquid), Baker	4.3	13.5	6.4	1.1	2.2	7.0	3.3	0.6	40	20	1:1	2
Varamel (formula base requires added sugar), Baker	4.9	8.3	5.8	1.2	2.5	4.3	3.0	0.6	32	16	1:1	
Milks with Relatively High Protein and Low Fat Content												
Alacta, Mead	33.0	46.5	12.0	7.0	4.2	5.9	1.5	0.9	121	15	1:7	3½
Dalactum, Mead	5.5	22.4	2.7	1.2	2.7	11.2	1.3	0.6	40	20	1:1	
Dryco, Borden	32.0	46.0	12.0	7.0	4.0	5.7	1.5	0.9	119	16	1:8	3¾
Hi-Pro, Jackson-Mitchell	41.0	35.0	14.0	6.5	4.6	3.8	1.5	0.73	121	14	1:9	3
Olac powder, Mead	23.0	51.4	18.5	4.9	3.4	7.5	2.7	0.7	134	20	1:6	3
Olac liquid, Mead	6.8	15.0	5.4	1.4	3.4	7.5	2.7	0.7	40	20	1:1	
Powdered protein milk, Mead	37.0	26.0	26.5	6.0	4.7	3.3	3.3	0.8	139	18	1:7	3½
Protein SMA, Wyeth	35.0	28.0	22.0	6.0	3.5	2.8	2.2	0.6	150	15	1:9	4
Powdered Skim (Nonfat) Milk												
Starlac (Borden), Carnation Instant, Pet Instant	37.0	51.0	0.8	8.0	3.3	4.8	0.05	0.7	100	10	1:10	c



Table 23. (Continued)

	Percentage Composition (Approximate)								Cals. /Oz.		Normal Dilution <sup>a</sup>	Household Equivalent for 1 Ounce Dry Powder
	Dry or Undiluted				Normal Dilution				As Pack- aged	Normal Dilution		
	Protein	Carbo- hydrate	Fat	Min- erals	Protein	Carbo- hydrate	Fat	Min- erals				
"Milks" for Children Allergic to Cow's Milk												
aporated goat's milk, Mey- nberg	7.01	8.41	7.2	1.6	4.02	4.22	3.6	0.9	38	19	1:1	3
poallergenic whole milk powder, Wyeth	26.0	39.0	27.0	6.0	3.3	4.7	3.5	0.7	142	19.5	1:8	4
ll-Soy, powdered, Borden	24.0	35.4	30.0	5.4	3.1	4.5	4.0	0.7	145	20	1:8	3½
ll-Soy, liquid, Borden	6.0	8.9	7.8	2.0	3.1	4.5	4.0	1.0	40	20	1:1	
tramigen powder, Mead	15.0	57.0	18.0	4.2	2.2	8.5	2.7	0.6	130	20	1:6	3
ee powder, Mead	22.4	53.1	17.9	3.4	3.2	7.7	2.6	0.5	132	20	1:6	3
ee liquid, Mead	6.5	15.5	5.2	1.0	3.2	7.7	2.6	0.5	40	20	1:1	
Special Therapeutic Product												
obana, powder, Mead <sup>d</sup> . . . .	27.0	51.0	14.0	4.0	3.9	7.3	2.0	0.6	125	19	1:7	3½
Powdered Protein												
sec powder, Mead	88.0		2.0	4.5	e				105			6
senamine, Winthrop	93.3				f			0.7	115			

<sup>a</sup> Number of ounces of milk product to number of ounces of water.  
<sup>b</sup> 1:1.2 (13 fl. oz. of milk and 15½ oz. of water) more nearly approximates whole cow's milk  
<sup>c</sup> Varies among different brands.  
<sup>d</sup> Contains protein milk, banana powder, dextrose and protolysate (casein hydrolysate).  
<sup>e</sup> 1 level tablespoonful is equivalent to 4 gm. of protein.  
<sup>f</sup> 1 level tablespoonful is equivalent to 8 gm. of protein.

acid mixture (casein hydrolysate), and non-milk foods in which the protein is derived from soy beans.

FORMULAS

Most methods for calculating milk formulas result in somewhat similar combinations of milk, water and sugar. No method stands out as definitely superior. In general, there has been increasing simplification in the construction of formulas. Some clinicians feel that the healthy infant's digestive capacity is adequate to handle such a variety of formulas, and that too much attention is paid to this aspect of infant feeding.

One result of an indifferent attitude toward the details of infant feeding is inadequate teaching of medical students, who thus have an insufficient background of the principles involved. Unless the student has a concept of the infant's nutritional requirements, of how they can be supplied, and of average eating habits at the various ages, he cannot expect to guide the mother in the establishment of a "natural regimen" for her infant. What follows represents the author's teaching to medical students. The student should realize that whatever method is used, the resultant formula is to be considered only a starting one.

Subsequent modifications must be made on the basis of the individual infant's response as determined by satisfaction of hunger, character of stools and satisfactory growth response.

The formula consists of milk, water and sugar. Some modification of the milk which results in smaller curd formation in the stomach is desirable and is achieved to some extent by boiling raw milk and to a greater extent by boiling previously pasteurized milk. Homogenization and evaporation alter milk in such a way that still smaller and less tough curd formation results. The addition of acids or alkalis has a similar effect. The choice of milk depends somewhat upon available supplies and upon individual preferences.

Caloric Requirements (see also p. 98). The average caloric requirements of full term infants are about 50 to 55 calories per pound, or 110 to 120 calories per kilogram of body weight, during the first few months of life; and about 45 calories per pound, or 100 calories per kilogram (or slightly less), by one year of age; individual variations are significant. As a general rule the formula should contain approximately 20 calories per ounce.

Fluid Requirements (see also p. 97). Though there is a lack of specific data, fluid

requirements are high during infancy. During the first six months of life they range from 2 to 3 ounces per pound, or 130 to 190 cc. per kilogram of body weight, per day. The requirements are relatively high during hot weather. As a rule the infant will regulate his own fluid intake, provided adequate amounts are offered. Most of the fluid requirement is in the formula, but some is supplied in orange juice and other foods and by water between feedings.

**Number of Feedings Daily** (see also p. 113). The number of feedings required per day decreases throughout the first year, so that by one year of age most infants are satisfied with three meals a day. The interval between feedings differs considerably among infants, but, in general, ranges from three to five hours during the first year of life, with an average of four hours for full term healthy infants. Small and weak infants may desire more frequent feedings at two to three hour intervals. For the first month or two, feedings are taken throughout the twenty-four hour period, but after this the infant will usually sleep from 10 or 12 p.m. to 6 or 7 a.m. Omission of the late evening feeding (10 to 12 p.m.) varies from the third to the eighth month.

**Table 24. Average Number of Feedings per 24 Hours**

Age	Average Number of Feedings in 24 Hours
Birth-1 week . . . . .	6-10
1 week-1 month . . . . .	6-8
1-3 months . . . . .	5-6
3-7 months . . . . .	4-5
4-9 months . . . . .	3-4
8-12 months . . . . .	3

**Quantity of Formula per Feeding.** Although the quantity taken at a feeding will vary with different infants of the same age and with the same infant at different feedings, it is necessary to know the average amounts taken at various ages. It is good practice to put more in each bottle than the infant is expected to take. A general rule for estimation of the quantity of the individual feeding to be offered during the first half year of life is to add the numeral 3 to the age in months. Estimates which more nearly reflect the average infant's intake are shown above. These "rules of thumb" are at best guides, and each infant must be given the major responsibility in determining the quantity of his intake. Rarely will an infant want to take more than 7 or 8 ounces of milk at one feed-

ing if his caloric and nutritional needs adequately supplied by other foods.

Age	Average Quantity Taken in Individual Feedings
1st and 2d weeks . . . . .	2-3 ounces
3 weeks-2 months . . . . .	4-5 ounces
2-3 months . . . . .	5-6 ounces
3-4 months . . . . .	6-7 ounces
5-12 months . . . . .	7-8 ounces

**Quantity of Milk.** The amount of whole milk usually taken daily in the first months of life varies from  $1\frac{3}{4}$  to 2 ounces per pound of body weight (evaporated milk approximately 1 ounce per pound). The relative requirements are somewhat less in the first two weeks than in the succeeding five six months. Subsequently milk, though of great value, has a decreasing importance in total nutritional requirements.

Rarely is it necessary to use more than a can (13 fluid ounces) of evaporated milk or a quart of whole milk per day. By the time the infant is taking these quantities, other foods will be added to the diet in increasing amounts.

**Water.** It is common practice to dilute cow's milk with water for the feeding of infants during the first few months of life. It has been demonstrated, however, that, with reasonable environmental temperature and humidity, infants will tolerate undiluted cow's milk or fully reconstructed evaporated milk after the first few days of life. There is a tendency with such feedings for a moderate elevation of the plasma nonprotein nitrogen level. With high environmental temperature or with vomiting or diarrhea such concentrations are higher. It would seem to be good judgment to add water and sugar to milk for infants up to four to six months of age to reduce the renal solute load so far as proteins and minerals are concerned. In the two weeks or so after birth, dilution of cow's milk should result in less chance of tetany by a reduction in the amount of phosphorus to be excreted. During periods of high environmental temperature, water should be offered between milk feedings, and additional water is needed when there are unusual losses as with vomiting or diarrhea.

**Sugar.** A number of sugars are used in infant feeding, and all seem to be satisfactory. Theoretically, it might seem that lactose, the sugar of milk, would be the one of choice; however, it appears to have no advantage over the others and may even cause an increased amount of flatulence owing to



greater degree of fermentation. Cane sugar has advantages of universal availability and low cost. Its only apparent disadvantage is a greater sweetness than the others. There are a number of dextrin-maltose preparations, several of which enjoy wide popularity. Their principal advantages are a slower rate of digestion and absorption and a less sweet taste. Honey is also used, but has no particular advantages. There are several rules for estimating the quantity of sugar. In our Clinic  $\frac{1}{2}$  ounce is added to the daily formula during the first week or so of life, then 1 ounce until about four or six months, when it is discontinued, usually in two equal steps at an interval of a week or so.

Table 25. Household Measures of Some Commonly Used Sugars

	Tablespoons per Ounce
Lactose.....	3
Sucrose (cane).....	2
Dextrin-maltose preparations	
Mead's Dextri-Maltose.....	4
Karo.....	2
Cartose.....	2
Dexin.....	6
Hidex.....	4

Caloric value of each is 120 calories per ounce, except Dexin, 115, and Hidex, 112.

**Example of Formula Calculation.** The following are formulas for an infant three months of age weighing 11 pounds:

1. Total fluid per 24 hours ( $11 \times 2-3$ )	= 28 oz.	Cal.
2. Total whole milk ( $11 \times 1\frac{3}{4}-2$ )	= 21 oz.	420
3. Water	28 - 21 = 7 oz.	
4. Carbohydrate	1 oz.	120
(cal. per oz. - $540 \div 28 = 19+$ )		540
(cal. per lb. - $540 \div 11 = 49+$ )		

1. Total fluid per 24 hours ( $11 \times 2-3$ )	= 28 oz.	
2. Total evaporated milk ( $11 \times 1$ )	= 11 oz.	440
3. Water	(28 - 11) = 17 oz.	
4. Carbohydrate	1 oz.	120
(cal. per oz. = $560 \div 28 = 20$ )		560
(cal. per lb. = $560 \div 11 = 51$ )		

5 bottles of  $5\frac{1}{2}$  oz. each  
These formulas are examples satisfactory for the initial prescription. Subsequent adjustments of milk

and water should be made on the basis of the infant's response as measured by satiety and by the growth curve. It is not necessary to calculate the percentages of the various ingredients of formulas composed on this basis, but for those who may want it, a method of calculation is given below.\*

**Preparation of Formula. Utensils.** Several more bottles than the required number for feedings are needed for water and orange juice. Bottles should be made of heat-resistant glass, be smooth inside, and marked in ounces. A wide-mouthed bottle is preferable because it is more easily cleaned, and those with adequate protection of the nipple are preferable if the baby is to be fed away from home. There should be several more nipples than the number required for feedings. Rubber caps or a plastic such as Pliofilm held in place by cardboard retainers may be used as bottle covers. The graduate should be made of heat-resistant glass and marked in ounces. A saucepan for heating and mixing the formula, a container for nipples, a glass funnel if narrow-mouthed bottles are used, a large kettle or special bottle sterilizer, a measuring spoon, a can opener, a knife, a standard tablespoon and a strainer complete the list of utensils.

**CLEANSING OF UTENSILS.** All utensils required for the mixing and storing of the formula should be sterilized by boiling for five to ten minutes. The rubber nipples and caps should not be boiled more than five minutes. After each feeding the bottle and nipple should be thoroughly flushed and the bottle filled with water until washed with water and a detergent.

**Method.** The hands should be thoroughly scrubbed and the sterilized bottles and utensils arranged on a clean table. If whole milk is used, the bottle is turned so that the contents are mixed, and the top is washed with hot water before the cap is removed. The water for the formula (it is necessary to allow for a slight loss in boiling) is brought to the boiling point in a saucepan; the amount of whole milk ordered is added; and the whole is boiled for five minutes. Constant stirring is necessary. The sugar is added while the milk is still warm.

If evaporated milk is used, the top of the can is washed with soap and hot water, rinsed with hot water, and two holes punctured in it. The water for the formula is boiled for five minutes, and the evaporated milk and sugar are added to it. No further boiling is necessary.

The freshly prepared and sterile formula is poured in appropriate amounts into sterilized nursing bottles. The bottles are capped by aseptic technique and stored in the refrigerator until time for the feedings.

**Terminal Sterilization.** This method has practical advantages and does not require presterilization of bottles or utensils. The formula is poured into clean nursing bottles, and the nipples are applied. The nipples are then loosely covered with glass, metal or paper caps and placed in a container, with a rack on

Number of ounces of milk  $\times$  percentage of  
ingredient in whole or evaporated milk

Total number of ounces in formula

Number of ounces of sugar  $\times$  100  
(percentage of carbohydrate in sugar)

Total number of ounces in formula

\* Percentage of fat, carbohydrate or protein =

Percentage of carbohydrate from added sugar =

the bottom and tall enough to prevent the bottles from touching the lid. The container is filled with water to about the midpoint of the bottles, covered and placed over a moderate flame. The water is allowed to boil gently for twenty-five minutes. The bottles are then removed with tongs and placed in a container of cold water for ten minutes. The caps are then tightened and the bottles stored in a refrigerator.

**Whole milk.** Whole milk or a reconstructed evaporated milk without added carbohydrate may be substituted for the formula when the infant is four to six months of age. Subsequently most infants will take one and a half pints to a quart of milk a day. There is no advantage in the ingestion of more, and there is the possible disadvantage that other essential foods may be displaced. Some of the milk may be incorporated in the cereal and in the preparation of such foods as custards, soups and sauces.

## OTHER FOODS

**Vitamins.** The diets of breast-fed and artificially fed babies should be supplemented from early in the neonatal period by vitamins C and D and possibly by vitamin A.

Orange and other citrus fruit juices are natural sources of vitamin C, but, since many young infants do not seem to tolerate them in amounts large enough to supply an adequate vitamin intake, it is safer not to depend on them initially. Ascorbic acid (25 to 50 mg.) in an ounce or less of boiled water (cooled before adding the acid) or in a concentrated preparation containing vitamins A and D may be used. During the second month of life orange juice diluted with water may be offered; when at least 2 ounces of fresh, frozen or canned orange juice (or equivalent amounts of other sources of vitamin C) are taken daily, the ascorbic acid may be discontinued.

Vitamin D should be started early in the neonatal period with a daily intake of approximately 800 to 1000 I.U. A number of preparations are available which in recommended doses contain this amount of vitamin D, 50 mg. of ascorbic acid and 3000 to 5000 I.U. of vitamin A. Concentrates in water-miscible vehicles are desirable to avoid aspiration of oil. Supplemental vitamin D is needed throughout the period of growth.

**"Solid" Foods.** Which of the so-called solid foods is offered first is largely a matter of individual preference, less often of the individual infant's needs. Cereal is an excellent food to offer the baby who has a large appetite early in life and is not satisfied with the calories provided by his intake of milk.

Fruits, especially bananas and pureed prunes and apricots, are usually well-tolerated and liked and may be offered first, particularly infants whose stools tend to be formed and solid and for whom a mild softening effect is desirable. Egg yolk or strained meats provide a well-tolerated source of iron. There is little evidence that the addition of any of the foods to the normal infant's diet before three or four months of age contributes in any significant way to his well-being.

Any new food should be offered initially once a day in small amounts (1 to 2 teaspoonsful). A demitasse spoon that easily fits the baby's mouth may be used. New foods are generally best accepted if fairly thin or diluted. The food is frequently pushed out rather than back by the tongue, and the fact that it is "spit out" means that the baby does not yet know how to swallow efficiently, rather than that the food does not agree with him or that he does not like it. It is important that the reaction be explained so that it is not misinterpreted by mothers. It is usually wise to offer the same food daily until the baby becomes accustomed to it and not to introduce new foods oftener than every week or two.

The feeding at which these foods are offered is not particularly important. They should be given when the baby is especially hungry and when they logically fit into the daily schedule. Some infants prefer the solid foods before milk; some take them better afterwards. There is no reason for persisting with or forcing a particular food that is definitely disliked. Most infants have the potential to enjoy eating, and a positive attitude toward it should be maintained. The family dislikes and prejudices for particular foods are contagious and should not be evidenced before the infant. The physician should avoid prescribing a definite amount of a given food lest the mother too literally interpret the suggestion. The infant's appetite is the best index of the proper amount, and respect for his wishes will avoid many problems.

**Cereal.** The various precooked cereals on the market provide in a convenient form a variety of grains excellent for infants. Most contain iron and factors of the vitamin complex. They are easily prepared by adding to boiled milk or formula.

**Fruits.** Strained or pureed cooked fruits furnish minerals and some water-soluble vitamins and usually have a mild laxative effect. Raw ripe banana is readily digested and enjoyed by most babies. It should be mashed with a fork. Many infants who are slow in accepting new foods seem to prefer fruits.



**Vegetables.** The various "colored" vegetables are moderately good sources of iron and other minerals and of the vitamins of the B complex. They may be freshly cooked and strained, but the commercially prepared vegetables are preferred by many mothers because of their convenience. "Colored" vegetables are usually added to the diet midway during the infant's first year.

**Meats, eggs and starchy foods.** These foods are usually introduced during the second and sixth months of life, although some physicians offer egg yolk and meat at an earlier age. The yolk of the egg is used initially and preferably hard-cooked and then added to cereal or other food. As with all new foods, a small amount (pea-sized) is offered at first with gradual increases up to a whole yolk daily. Egg white should be introduced with equal caution to minimize the possibility of allergic manifestations.

Meat is an excellent source of protein as well as of iron and vitamins. Ground fresh beef or liver or the strained canned meats may be used initially. They are easily digested by most babies. Meats seem to be more readily accepted when mixed with another food.

The commercial "soups" and meat and vegetable mixtures are relatively high in carbohydrate and are not to be considered optimal sources of iron or protein. Many home-prepared soups are bulky out of proportion to their food value, and much of the vitamin content is frequently lost by overcooking.

Potatoes, rice, spaghetti, bread and similar starchy foods have principally a caloric value. As a rule they are not included in the infant's diet until the more essential foods mentioned above are being taken regularly. Baked potato, mashed with milk and butter, is a favorite. Zwieback, toast or graham crackers may be offered to the infant when he shows an interest in "gumming" on coarser foods (usually about seven or eight months of age). It is with such foods that he learns to chew and to feed himself.

**Desserts.** Puddings, junkets and custards are good foods for older infants, particularly if they temporarily prefer milk in that form. If, however, such foods are given as a bribe or reward or only after other foods have been finished, a poor eating habit will be established. Sweet foods should be offered as casually as the rest of the meal and at any place in the meal that the child desires.

## FIRST-YEAR FEEDING PATTERN AND PROBLEMS

**Recapitulation.** The value and methods of establishing a fairly regular yet flexible feeding schedule have been discussed. The importance of fitting the schedule to the individual infant's requirements and of adjusting it as his needs change has been emphasized. The volume and frequency of milk feedings is best determined by the infant himself. If breast milk is not available, an adequate substitute is found in isocaloric formulas of cow's milk, water and carbohydrate. Attention to the technical details of feeding both at breast and by bottle is necessary to avoid early feeding problems. Both breast-fed and bottle-fed babies need supplements of vitamins A, C and D.

Cereal, strained fruits and vegetables and sometimes egg yolk or meat are added to the diet one at a time and initially in small amounts during the second three months of life. By about six months of age most infants are taking foods by spoon in addition to milk three times a day, with citrus fruit juice at a convenient time in between. Many will also desire milk in the early morning, and some in the late evening. During the second six months babies become less demanding of immediate satisfaction of hunger, and intervals between feedings are lengthened until a pattern of three meals a day is established. Whole egg, meats and starchy foods are added to the diet, and milk is given as whole cow's milk. Variation in the amounts of either solid foods or milk taken at various meals should be expected. Often there are cyclic patterns of exaggerated likes or dislikes for solids, liquids or particular foods. Foods should never be forced; when an infant objects to a particular food, it is well to avoid it for a few weeks. Most foods will be liked, however, if conflicts over them are avoided. Good as well as bad eating habits are established early; eating should be a pleasant experience.

During the second half year of life the infant will show a readiness to chew rather than just to swallow foods. This is an indication for offering him coarser foods such as toast or crackers and to give him less finely strained fruits and vegetables. The canned chopped foods have a limited place in the transition to foods eaten by older members of the family. Vegetables should be mashed and meats ground until the chewing function is well developed. Considerable latitude in the

self-selection of foods should be allowed, but a balanced diet should always be offered.

The physician must interpret for the mother the infant's decreased desire for food during an illness. Her desire not to alter his usual feeding pattern can result in a conflict over food and mark the beginning of poor eating habits.

Frequent changing of formulas because the "milk does not agree with the baby" should be avoided. Gastrointestinal allergy occurs in infants and is frequently relieved by a change to a hypoallergenic milk. Usually a feeding problem is due to underfeeding, technical errors or a physical disturbance in the infant. A formula of average composition will agree with most infants.

*A knowledge of the personality pattern of the parents is most helpful in anticipating and preventing many types of feeding difficulties in the infant.*

**Underfeeding.** Underfeeding is evidenced by restlessness and crying, and by failure to gain weight adequately in spite of complete emptying of the breast or bottle. Underfeeding may also result from the infant's failure to take a sufficient quantity of food even though it is offered. In such instances the frequency of feedings, the mechanics of nursing, the size of the holes in the nipple, the adequacy of eructation of air, as well as the possibility of systemic disease in the baby, should be investigated. The extent and duration of underfeeding determine the clinical manifestations. Constipation, failure to sleep an adequate amount of time, irritability and excessive crying are to be expected. There may simply be an inadequate gain, a failure to gain or an actual loss in weight. In the last instance the skin becomes dry and wrinkled, subcutaneous tissue disappears, and the infant assumes an "old man" appearance. Deficiencies of vitamins A, B, C and D and of iron and protein may be responsible for characteristic clinical manifestations.

*Treatment* consists in increasing the fluid and caloric intake, correcting deficiencies in vitamin and mineral intake, and instructing the mother in the art of infant feeding.

**Overfeeding.** Overfeeding may be quantitative or qualitative. As a rule, infants can be depended upon not to take excessive quantities; but occasionally an infant has postprandial discomfort from eating too much, and he may gain weight excessively. Diets too high in fat delay gastric emptying, cause distention and abdominal discomfort and may cause excessive gain in weight. Diets too high

in carbohydrate are likely to cause undue fermentation in the intestine, resulting in distention and flatulence, and in too rapid gain in weight. Such diets may be deficient in essential protein, vitamins and minerals. Formulas too high in caloric content in the first week or two of life are likely to result in loose or diarrheal stools. Regurgitation and vomiting are frequent symptoms of overfeeding.

**Regurgitation and Vomiting.** The return of small amounts of swallowed food during or shortly after eating is termed "regurgitation" or "spitting up." More complete emptying of the stomach, especially when it occurs some time after feeding, is termed "vomiting." Within limits, regurgitation is a natural occurrence, especially during the first half year or so of life. Regurgitation can be reduced to a negligible extent, however, by adequate eructation of swallowed air during and after eating, by gentle handling, by avoidance of emotional conflicts, and by placing the infant on his right side or abdomen for a nap immediately after eating. One should also ensure that the head is not lower than the rest of the body during the rest period.

Vomiting is one of the most common symptoms in infancy and may be associated with a wide variety of disturbances, both trivial and serious. Its cause should always be investigated (see p. 647).

**Loose or Diarrheal Stools.** Acute infectious diarrhea and chronic diarrheal conditions are discussed elsewhere; here there is consideration only of mild disturbances of a dietary origin.

The stool of the breast-fed infant is naturally softer than that of the infant fed cow's milk. From about the fourth to the sixth day of life the stools go through a transitional stage and are rather loose and greenish-yellow, and contain mucus; but within a few days the typical "milk stool" appears. Subsequently the use of laxatives or the ingestion of certain foods by the mother may temporarily be responsible for an infant's loose stools. Excessive intake of breast milk may also increase the frequency and decrease the consistency of the stool. Actual diarrhea in a breast-fed infant is unusual and should be considered infectious until proved otherwise.

Though the stools of artificially fed infants tend to be firmer than those of breast-fed infants, under certain circumstances loose stools may result from artificial feeding. In the first two weeks or so of life, overfeeding is likely to cause loose, frequent stools. Late



formulas which are too concentrated or whose sugar content is too high, especially in lactose, may be responsible for loose, frequent stools. Many of the temporary diarrheal disturbances in artificially fed infants, however, are the result of contaminations of food such as would not disturb an older child, and not serious enough to cause prolonged disturbance in the infant. The ease with which artificially fed infants acquire diarrheal disturbances and the potential seriousness of them are strong arguments for extreme care in providing a food supply free of pathogenic bacteria.

Mild diarrheal disturbances due to overfeeding respond quickly to temporary decrease or cessation of feeding. The temporary omission of all solid food and of one or several milk feedings, with the substitution of boiled water or 5 per cent glucose solution in water or in a balanced electrolyte solution, is usually all that is required.

**Constipation** (see also p. 652). Constipation is practically unknown in breast-fed infants who receive an adequate amount of milk, and is rare in artificially fed infants receiving an adequate diet. The status of the stool, and not its frequency, is the criterion of constipation. Although most infants have one or more stools daily, an occasional infant will have a stool of normal consistency only at intervals of thirty-six to forty-eight hours. Whenever constipation or obstipation is present from birth or shortly thereafter, a rectal examination should be performed. Tight or spastic anal sphincters occasionally may be responsible for obstipation, and correction usually follows prolonged finger dilatation performed twice or three times a day. Anal fissures or cracks may also cause constipation. If irritation is removed, healing usually occurs quickly. Aganglionic megacolon may be manifest by constipation in early infancy.

Constipation in the artificially fed infant may be due simply to an insufficient amount of food or fluid and is corrected by increasing the intake. In other instances it may result from diets too high in fat or protein or deficient in bulk. Simply increasing the amount of sugar in the formula may be corrective in the first few months of life. After this age better results are obtained by adding or increasing the amounts of cereal, vegetables and fruits. Prune juice ( $\frac{1}{2}$  to 1 ounce) may be given as a temporary measure, but it is better to add foods with some bulk. Enemas and suppositories should never be more than temporary measures. Milk of magnesia may be

given in doses of 1 or 2 teaspoonfuls, but should be reserved for emergencies.

**Colic.** The term "colic" is used to describe a frequent symptom complex of paroxysmal abdominal pain, presumably of intestinal origin, and of severe crying. It usually occurs in infants under three months of age.

The clinical pattern is characteristic. The attack usually begins suddenly; the cry is loud and more or less continuous; so-called paroxysms may persist for several hours; the face is congested and may be somewhat cyanotic, or there may be circumoral pallor; the abdomen is distended and tense; the legs are drawn up on the abdomen, although they may be momentarily extended; the feet are often cold; the hands are clenched. The attack may terminate only when the infant is completely exhausted, but often there is relief with the passage of feces or flatus.

Certain infants seem to be peculiarly susceptible to recurrent attacks of colic. The cause of the recurrent attacks is usually not apparent, although it may be associated with hunger and with swallowed air which has passed into the intestine. Overfeeding may also cause discomfort and distention, but rarely to the degree seen in colic. Certain foods, especially those of high carbohydrate content, may be responsible for excessive fermentation in the intestines, but only rarely does a change in diet prevent further attacks of colic. Crying from intestinal discomfort is seen in infants with intestinal allergy, but colic is not limited to this group. Intestinal obstruction or peritoneal infection may mimic an attack of colic. Recurrent attacks are frequently seen late in the afternoon or evening, and this suggests the possibility of some preceding event in the household routine as a possible cause. Worry, fear, anger or excitement may cause vomiting in an older child, and such emotional disturbances may result in colic in an infant. Certainly no single etiologic factor consistently accounts for colic, nor does any method of treatment consistently provide satisfactory relief.

Holding the baby upright or permitting him to lie prone across the lap or on a hot water bottle or heating pad is occasionally helpful. Passage of flatus or fecal material spontaneously or with expulsion of a suppository or enema sometimes affords relief. Carminatives before feedings are ineffective in preventing the attacks. Sedation is occasionally indicated for a prolonged attack, and sometimes over a period of time for parent and/or

child if other measures fail. The prevention of attacks should include adequate feeding techniques, including burping, the provision of a stable emotional environment, the search for a possible allergenic food in the infant's or nursing mother's diet, and avoidance of underfeeding. The condition rarely persists after three months of age.

## FEEDING DURING THE SECOND YEAR OF LIFE

Most infants naturally adapt themselves to a schedule of three meals a day by about the end of the first year of life. Though considerable latitude in the diet of the individual infant must be permitted to allow for personal idiosyncrasies and family habits, the mother should be given an outline of the daily basic dietary needs. These are as follows:

Milk.....	$\frac{3}{4}$ to 1 quart
Meat (fresh, lean) or fish.....	1 serving (5 to 6 per week)
Liver.....	1 serving or more per week
Eggs.....	1 daily (5 to 6 per week)
Vegetables (1 raw, 1 pigmented).....	2 or more servings
Fruits (1 fresh).....	2 or more servings (one of which should be citrus or tomato juice)
Butter or oleomargarine.....	2 teaspoonfuls or more
Bread and cereals (whole grain).....	Sufficient to meet caloric needs
Vitamin D.....	800 to 1000 I.U.
Salt (iodized).....	For seasoning

**Reduced Caloric Intake.** Toward the end of the first year of life and during the second year, owing to the constantly decelerating rate of growth, there is a gradual reduction in the infant's caloric intake per unit of body weight. In addition, it is not unusual for him to have temporary periods of disinterest in food in general or in certain articles of it. Failure to recognize these features, especially the decreasing caloric needs, results in attempts to force feeding. The natural reaction of the child is rebellion, and feeding problems ensue. Prevention is much more effective than are methods of correction, and the changing pattern of the infant's food habits during the second year of life should be explained to the mother before it makes its appearance.

**Self-Selection of Diet.** Clara Davis demonstrated that infants in institutions, when given the opportunity, will select a balanced diet. Though at intervals the daily intake may be at variance with the usual pattern, and certain foods will be eaten in excessive amounts and others refused, over the longer range the pattern of eating is average and

adequate. In principle, such a policy may be adopted in the home so far as the child is permitted a rather wide latitude in his choice of foods. Though it is not possible to have a wide variety of foods of the same class, such as a variety of meats, at each meal, strong likes or dislikes of children for particular foods should be respected. Spinach is an example of an unessential food which has been unduly emphasized and has been responsible for many feeding difficulties. When the rejected foods include essential items such as milk and eggs, then the child must be slowly "educated" to eat them, provided he is not allergic to them.

Under average circumstances the child should also determine the quantity to be eaten of a given food as well as of the entire meal. Such a plan can and does work under favorable circumstances. At this age the child should be fed separately from the rest of the family. When he eats with them, their eating habits will influence the development of his. Eating habits developed during the first two years of life are usually protracted for years.

**Self-Feeding by Infants.** Before the infant is a year of age he is able and should be permitted to participate in the act of feeding himself. By six months or so he can hold his bottle. Within another two or three months he can hold a cup. The introduction of zwieback, graham crackers and bacon by the time he is seven to eight months of age gives the infant something which he can hold and thus learn one of the principles of self-feeding. He may use a spoon for feeding himself as soon as he can hold it and direct it to his mouth. This may be by ten to twelve months of age. Mothers often inhibit this learning process because of their objection to the messiness incident to the learning of adequate control.

Acquisition of the ability to feed himself is an important step in the infant's development of self-reliance and of a sense of responsibility and has favorable repercussion in the years which follow. By the end of the second year of life the infant should be largely responsible for his feeding.

## FEEDING OF OLDER CHILDREN

In comparison with the supervision commonly maintained over the feeding of infants, the diets of children beyond the age of two years are badly neglected. Though it is desirable that children should not be aware of constant supervision of their dietary habits and that they should be given every opportunity to



form eating habits naturally, the diets of all children should be supervised. Surveys of dietary habits of children in various economic groups reveal a high incidence of inadequate diets and of malnutrition. Although the nutritional requirements per unit of body weight are constantly decreasing with increasing age (110 calories per kilogram in infancy; 50 calories per kilogram at fifteen years), at all times the need for calories as well as for protein, vitamins and minerals is relatively greater than it is in the adult.

**Daily Basic Diet.** Parents should be given a daily basic diet for the child from which the family menu can be prepared. It is essential that the entire family partake of the same diet and that the sense of "being on a diet" be avoided. The quantity of the intake after the basic requirements have been met can in most instances be determined by the healthy growing child; the obese child is an exception. A history of the dietary habits of the child is essential for evaluation of his nutritive intake, but such histories are often unreliable. More dependable information can be secured by providing the mother with a number of dietary history blanks such as the one illustrated in Table 26, on which she can record the daily intake for several representative days. From such information, corrections in the diet may be made more effectively. This table also contains the recommended daily dietary intake.

*Adequate quantities of all the essential classes of foods must be provided in order to avoid specific nutritional deficiencies.* There is no harm in the child's knowing the content of a basic diet and the reason for it. Actually, there is benefit, if it is presented and received in a natural way.

The following is a daily menu which will provide all the essential nutrients:

Breakfast:	Citrus fruit or tomato juice Cereal—whole grain or enriched Egg Whole-wheat toast Butter Milk
Lunch:	Sandwich with whole-wheat bread or Casserole dish—containing meat or meat substitute and starchy vegetable Green vegetable, raw Milk Custard, pudding, cake, ice cream or gelatin dessert
Dinner:	Meat—fish—liver Potatoes, rice or spaghetti Green vegetable

Whole-wheat bread, butter  
Milk  
Fruit  
Vitamin D (throughout childhood)

**Eating Habits.** As stated previously, eating habits formed in the first year or two of life have a distinct effect upon those of subsequent years. Feeding difficulties between the ages of two and five years frequently result from too great parental insistence on eating and too great anxiety when the child does not conform to some arbitrary standard. Negativistic reactions by the child are natural consequences, and correction requires improvement in the parent-child relationship. Other factors which disturb eating are too much confusion at mealtime, insufficient time for eating, either on the part of the adult or of the child, food dislikes of other members of the family, and poorly prepared and unattractively served food. A comfortable chair of proper height with a foot-rest is important for a child's ease at the table.

It is good practice to call the child from play fifteen or twenty minutes before meal-times. This allows time for going to the toilet and washing the hands and face and cooling off from strenuous activity before eating. At this time it is wise to arrange for some diversion such as reading or helping with final preparations for the meal. This is an excellent time especially for younger children to spend with the father, reading or playing quiet games. Mealtimes should be happy. Discussion concerning the food, except for occasional favorable comments, should be avoided, and the conversation should be on subjects of interest to the entire family. The child should feel that he is part of the family group. The child's appetite should be respected; if his desire for food at times is below average, there should be no persuasion to eat more. Adults should realize that eating habits are taught better by example than by formal explanation.

**Lunches between Meals.** During the second year and even for several years thereafter, orange juice or other fruit juice or fruit together with a cracker may be given in either or both of the midmeal periods. For older children midmeal nourishment should be avoided if it reduces the appetite for the following meal. When a snack after school results in greater enthusiasm and energy for play and does not reduce the appetite for the evening meal, it should be encouraged. Fruits are especially recommended for such lunches.

There are differences of opinion concerning midsession lunches in school. Though in

Table 26. Record of Dietary History\*

TYPE OF FOOD	DAILY CONSUMPTION	RECOMMENDED ALLOWANCE FOR GROWING CHILD
I. Milk.....	Total.....	1½ pt.-1 qt.
	With meals..... Between.....	
	With cereal..... In cooking.....	
Milk products.....	Cheese..... Cream.....	
	Others.....	
II. Eggs.....	Total.....	1 daily or 5 a week
	With meals..... In cooking.....	
III. Meats.....	Total.....	1 serving daily or 5 times a week
(a) Lean.....	Beef..... Lamb.....	
	Pork..... Others.....	
(b) Poultry.....	Chicken..... Others.....	2-3 ounces (varies with age)
(c) Fish.....	Salmon..... Others.....	
(d) Sea food.....	Shrimp..... Others.....	
(e) Liver.....	Liver.....	1 serving a week
IV. Vegetables		
(a) Potatoes.....	Total.....	1 serving daily
	Irish..... Sweet.....	
(b) Green, leafy.....	Total.....	1 serving daily
	Lettuce..... Spinach.....	½ cup
	Chard..... Brussel sprouts.....	
	Broccoli..... Cabbage.....	
	Others.....	
(c) Others.....	Total.....	1 serving daily
	Beans..... Peas.....	½ cup
	Asparagus..... Corn.....	
	Beets..... Carrots.....	
	Cauliflower..... Parsnips.....	
	Squash..... Turnips.....	
	Others.....	
V. Fruits		
(a) Citrus and tomato.....	Total.....	1 serving daily
	Orange..... Lemon.....	Whole orange
	Grapefruit..... Tomato.....	½ grapefruit
(b) Others.....	Total.....	1 serving daily
	Peach..... Apricot.....	½ cup
	Pear..... Apple.....	
	Fig..... Prunes.....	
	Plums..... Berries.....	
	Pineapple..... Bananas.....	
	Others.....	
VI. Breadstuffs and cereals.....	Total.....	Varies with caloric needs
(a) Bread.....	Total.....	1 slice or equivalent with each meal
	Whole grain..... Enriched.....	
	Others.....	
(b) Cereals.....	Total.....	1 serving daily of whole grain or e riched cereal
	Cooked:	
	Whole grain..... Enriched.....	
	Macaroni..... Spaghetti.....	
	Soybean..... Others.....	
	Prepared:	
	Whole grain..... Enriched.....	
	Others.....	



Table 26 (Continued)

TYPE OF FOOD	DAILY CONSUMPTION	RECOMMENDED ALLOWANCE FOR GROWING CHILD
VII. Fats		
(a) Butter or oleomargarine with vitamin A.....	Total..... As spread..... In cooking.....	2 tablespoons daily
(b) As source of essential fatty acids.....	Total..... Lard..... Corn oil..... Others.....	Possibly 1 to 2 tablespoons daily
VIII. Vitamin D.....	Total.....	800-1000 I U. daily
IX. Iodized salt.....		As desired (in goiter belt)
X. Desserts, sugars and syrups....	Total..... Custards..... Jello..... Cake..... Cookies..... Ice cream..... Puddings..... Sugar..... Syrup..... Jam, Jelly..... Others.....	As needed for calories

\* Courtesy of Arild E. Hansen.

general they are just as well omitted, when a session is relatively long, fruit juice may be advantageous, especially for the younger child.

JOHN B. BARTRAM

REFERENCES

Aldrich, C. A.: Ancient Processes in Scientific Age; Feeding Aspects. *Am. J. Dis. Child.*, 64:714, 1942.  
Aldrich, C. A., and Aldrich, M. M.: *Feeding Our Old Fashioned Children*. New York, Macmillan Company, 1941.  
Davis, C.: Feeding after the First Year; in Brenne-  
mann, J., ed.: *Practice of Pediatrics*. Hagerstown,  
Md., W. F. Prior Co., Inc., 1957, Vol. 1, Chap. 30.  
György, P.: A Hitherto Unrecognized Biochemical

Difference between Human Milk and Cow's Milk. *Pediatrics*, 12:98, 1953.  
Harris, L. E.: Infant Feeding with and without Added Carbohydrate. *Am. J. Dis. Child.*, 82:677, 1951.  
Hewitt, E. S., and Aldrich, C. A.: Poor Eating Habits of the Runabout Child: The Role of Physiologic Anorexia. *J. Pediat.*, 28:595, 1946.  
Jeans, P. C.: The Feeding of Healthy Infants and Children. *J.A.M.A.*, 120:913, 1942.  
Macy, I. G., and others: Human Milk Studies: XIX to XXVII, incl. *Am. J. Dis. Child.*, 70:135, 1945.  
Powers, G. F.: Infant Feeding: Historical Background and Modern Practice. *J.A.M.A.*, 105:753, 1935.  
Spock, B.: *Baby and Child Care*. New York, Pocket Books, Inc., 1946.  
Stevenson, S. S.: The Adequacy of Artificial Feeding in Infancy. *J. Pediat.*, 31:616, 1947.

HYGIENE

Parents are besieged with and sometimes overwhelmed by a barrage of advice on the bringing up of children. Articles in maga-  
zines, syndicated columns in the daily press, advertising, radio, television and in fact all available forms of communication are being utilized to bring information to this receptive group. Much of the advice is good, but much of it is misinterpreted and confusing. The role of the physician as a health educator is, as a result, that of an interpreter as well as a purveyor.

**Habits.** The infant begins the development of habits at birth. These habits are usually considered good or bad as they reflect the ability to conform comfortably to what is expected. The demands made by the family are frequently out of line with the ability or readiness of the child to learn, and conflicts arise which a physician may help to explain and to resolve. Children acquire habits by repetition of an act, and parents should be reminded that it is much easier to form a habit than to change one. Praise, encourage-

ment and attention, even though of a negative sort, fortify a habit, whereas lack of attention serves to discourage repetition of an act. What parents do rather than what they say is important.

Consistency of action by the parents is essential if a child is to be helped rather than confused. Children seem to do equally well with a strict or a laissez-faire discipline if they are sure of what is expected of them. If parents can appreciate that their responsibility in guiding habit formation is to help the child gain increasing independence at his own optimal rate, much concern over trivia will be avoided. Children want to conform to what is expected of them, and effort as well as actual achievement should be praised. Comparison with others, the setting of too rigid goals, and impatience with lack of early success result in frustration and tensions.

Habit formation is usually thought of in relation to establishment of eating, sleeping, bowel and bladder patterns. Regularity and relatively automatic functioning in these fields are necessary before children are free to progress to more complicated learning.

**Eating.** Eating habits of infants are discussed on page 112, of older children on page 133.

**Sleep.** There is considerable variation in the amount of sleep required by different children. Many children, however, get too little rest, and often the symptoms of irritability, lethargy, anorexia, temper tantrums and perhaps increased susceptibility to infection result. Many behavior problems are precipitated by fatigue.

Most infants sleep sixteen to twenty hours a day during the first half year; by six months of age they will sleep through the night and are awake for periods totaling six to eight hours. By one year of age the child sleeps an hour or two less and by two years of age averages twelve to fourteen hours a day. The need for sleep gradually decreases, but rarely becomes less than ten hours during the pediatric age range. A nap during the day is desirable until school interferes with this routine, and rest periods should have an important place in kindergarten and first and second grade schedules.

Early establishment of regularity of bedtime is most important; nowhere in the field of habit formation is consistency more important. The presleep period should be free of excitement, rushing, scolding and physical activity. Stimulation of children by exciting stories, radio, television, active play or by a

battle of wills should be avoided. A family story, quiet discussion of happy events of the day, a warm bath and reassurance of love and affection are conducive to easy sleep. Children, even when sleepy, normally do not want to stop doing something interesting. The habit of going to bed on schedule and to sleep promptly can be established and maintained by a consistent and understanding approach.

Infants and children should have their own beds and, if possible, their own rooms. The sleeping room should be ventilated, but free of drafts. Bed clothing is frequently too heavy and should be varied with the temperature. Overall sleeping garments for infants who may get uncovered in cold weather are useful. Position during sleep is relatively unimportant. The position of infants, especially of premature ones, should be changed often enough to prevent moulding of the cranium from chronic pressure on one area.

**Disturbances of sleep** (see p. 89).

**Elimination.** Control of the anal and bladder sphincters is naturally acquired by most infants during the second or third year of life. Efforts to "train" a baby before he is ready for voluntary control of his sphincters are usually disastrous and frequently lead to an unhappy parent-child relationship. He is not ready to use the toilet until he is old enough to understand what it is for and to let his mother know of his needs, until his bowel movements come at fairly regular times, and until he is willing to sit on the toilet. A comfortable seat with a rest for the feet and a strap for safety should be provided. Suppositories or soap sticks have no place in the establishment of regular bowel habits, and coercive methods of any sort are contraindicated.

By about eighteen months of age most toddlers have acquired enough bladder control to retain urine for two hours or so. At this age they may be encouraged to sit on the toilet and void. It is best to make initial efforts just after meals or naps and when the child is dry and likely to void readily. Other routines or interesting play should not be interrupted for this purpose. Nocturnal control of urination is not usually developed until the third year of life or later.

**Exercise.** The normal infant or child, in a reasonable environment, will have sufficient muscular activity for good growth and development. The young infant begins to develop his large muscles by kicking, stretching, crying and squirming. He should be allowed to do so several times a day on a safe flat surface unencumbered by clothes. He should be



provided with easily grasped toys to develop hand use. Limits for safety's sake must be provided when he crawls and begins to walk, but his activities at this stage should not be limited to a "play pen." This piece of furniture was designed for adult convenience, not to aid the child's development. Toddlers should be provided with safe areas both indoors and outdoors in which to run, climb and explore. They need large blocks, push and pull toys, materials for imitative play, and the privilege of getting dirty and playing with water. Children's toys should, in general, be washable, not easily broken, free of sharp edges and splinters and of removable parts that can be swallowed or aspirated.

Schools should provide an opportunity for universal participation in organized sports. Intramural teams can offer the less well coordinated boy or girl an opportunity to take part in group sports.

**Sunlight and Fresh Air.** Sunshine and fresh air are essential for the development and maintenance of sound health. Dependence is no longer placed on sunlight for the prevention of rickets, but many other benefits accrue from it. It is unnecessary, however, to make a fetish of exposure of young infants to the sun, particularly in cold weather. Care should always be taken to avoid sunburn. Outdoor play should be encouraged at all ages when the weather permits and clothing is adequate. Fresh air should be provided indoors by adequate ventilation.

**Clothing.** There have been tremendous improvements in the functional design and in the materials of infant's and children's clothing. The diaper is still standard equipment, but tapes, drawstrings, many tiny buttons, frilly dresses and bulky winter clothes have largely been replaced by elastic materials, grippers, zippers, a few large buttons, slip-on shirts and pants and by new materials of lighter weight for cold weather. The principles guiding the choice of good clothing for children are attractiveness and color, simplicity in design, ease of use, softness of texture, lightness of weight, washability, relative looseness of fit and freedom from irritation to the skin. Knitted cotton is usually best next to the body. Children should be dressed appropriately for the environment. There is a universal tendency to overdress children in the winter which frequently results in excessive perspiration. Extra water-repellent garments are easily put on a child to secure the warmth and protection needed for outdoor

activities, and they should be removed as soon as he re-enters the warm house or schoolroom. The legs of both boys and girls should be covered in cold weather.

Layettees are usually too elaborate. Infants need shirts with and without sleeves, nightgowns, diapers, socks or booties, a sweater and an outer garment with a hood for outdoor winter use. Rubber or plastic pants should be loose enough to permit evaporation and should not be used except for relatively short periods to avoid otherwise troublesome situations. Lightweight cotton blankets are generally preferable to heavy woolen ones; a well made sleeping bag is satisfactory for cold weather.

Children's shoes are discussed on page 1253.

**Cleanliness.** Certain aspects of cleanliness such as the bath, washing at mealtimes and at toilet time, the use of a handkerchief and of a napkin, brushing the teeth and some responsibility in caring for clothing are essentials that should be reduced to the level of habitual reactions as early in life as possible. Formation of habits of personal cleanliness is encouraged, like all other habits, by the examples of parents, by praise and recognition of effort, by pleasant rather than unpleasant experiences, by consistency and by gradually decreasing assistance on the parents' part. Many parents need help in achieving a perspective on healthy cleanliness which lies somewhere between asepsis and filth.

A daily bath for infants is a good rule. In warm weather more frequent sponging may be necessary. As soon as the umbilicus has healed, the infant may be immersed in a basin or tub. The room should be comfortably warm; supplies should be ready at hand; a safe flat working surface must be available; care must be taken not to let the infant slip or fall; and the experience should be made a happy, playful one. A regular time for bathing as well as for other routine activities should be established. A nonirritating soap is lathered over the trunk and extremities with care to avoid the eyes and mouth, and the baby is then rinsed with fresh, comfortably warm water. The scalp should be washed as needed. The skin is patted dry, with special attention to the creases.

Oil, powder or lotion is usually not necessary, although their use is sometimes helpful for dry skins and in the diaper area. Caution should be used to avoid inhalation of any powder, and zinc stearate should not be permitted in the nursery (see p. 799).

The face is washed with clear water, except when soap or oil is necessary to remove dried excretions or vomitus.

The external ear may be washed with a soft cloth; dried accretions in the creases may be removed with a cotton-tipped applicator moistened with oil. The ear canal, except at its opening, should not be cleaned by an untrained person.

The eyes usually require no special care. Accumulated secretions in the corner of the eye should be wiped out with a piece of cotton saturated with clear water.

The nose does not need any cleaning unless there are dried secretions at the openings of the external nares. They may be removed with a dry or moistened cotton-tipped applicator. Oil should not be used.

Under no circumstances should attempts be made to clean the mouth, since the mucous membrane is easily damaged and is then especially susceptible to infection.

Brushing of the teeth is not advised until the third year of life. Before this time they may be cleaned occasionally with a cotton-tipped applicator saturated with saline or sodium bicarbonate solution.

Nails need trimming when they protrude beyond the ends of the fingers or toes. Toe

nails should be cut straight across without rounding the corners so that "ingrowing toenails" may be prevented.

The bathing of older children requires no special consideration. In summertime there should be daily baths; in the winter months this is not necessary and, in children with dry skins, should be avoided. In the latter instance, two to four baths a week are adequate depending on the state of cleanliness. Baths should be taken preferably at night to lessen the degree of chafing, which is also reduced if the skin is dried thoroughly. Anointing the skin with oil or skin lotion helps to avoid chafing of dry and sensitive skins.

The genitals should be washed at bath time. In the uncircumcised male infant the foreskin may be retracted as far as possible without trauma. Adhesions will usually be broken as the child grows older, and no strenuous effort need be made to break them. Smegma may be removed from the vulva with a soft cloth or a cotton pledget saturated with oil. Genitals of both sexes should be rinsed with clean water at the end of the bath to prevent irritation from soap, which otherwise might dry on the mucous membranes.

JOHN B. BARTRAM

## PREVENTIVE PEDIATRICS

Prevention of disease, including psychologic as well as organic disorders, ranks with treatment as a goal of pediatric practice, since harmful physical and mental experiences during infancy and childhood may leave permanent handicaps.

In a narrow sense the term "preventive pediatrics" signifies only the avoidance of illness or disability. The broader aspect, however, encompasses more than simply averting illness and accidents; it also includes measures to lessen the progress of chronic disease. Early diagnosis when health can still be restored or preserved is essential and obviously requires widespread application of the health examination during infancy and the preschool, school and adolescent periods.

Measures aimed at preventing the onset of physical or psychogenic illness or disability may be called *primary preventive* procedures, while steps to promote and preserve health by controlling disabilities may be termed *secondary preventive* measures.

### PRIMARY PREVENTION OF DISEASE

#### PERINATAL FACTORS IN NEONATAL DISTURBANCES

Prevention of disease and handicaps among children can begin long before birth. Even during their childhood girls are preparing to bear healthy children by achieving optimal health; immunization against poliomyelitis and having rubella in the premarital years are examples of specific preventive measures.

In the *prenatal* period general practitioners and obstetricians can do much to assure that the infant will be born healthy. Diagnosis and treatment of *maternal infections* such as syphilis and gonorrhea and prevention of other infections in the pregnant woman (human immune serum globulin after exposure to infectious hepatitis at any time in pregnancy and after exposure to rubella in the first trimester) will eliminate some hazards of the neonatal period. Minimal use of radiation



during pregnancy is advisable because of adverse effects on the fetus; if it is used, a record of the amount should be kept in order to prevent uncontrolled exposure of the infant should radiation be required postnatally.

The offspring of healthy women whose *nutrition* has been adequate throughout pregnancy have fewer difficulties during the neonatal period than do infants of mothers whose nutritional status is less good.

Mortality from erythroblastosis fetalis (hemolytic disease of the newborn) can be markedly influenced by determining the blood type of the pregnant woman and her husband prenatally and by obtaining periodic antibody titers to detect iso-immunization when that likelihood exists. Prompt treatment of hemolytic disease depends on prenatal diagnosis of the possibility that iso-immunization may occur. Mortality among infants of diabetic mothers can also be reduced by appropriate management of the maternal disease in the prenatal period and subsequently of the delivery and of the infant.

The most important problem of infancy is premature birth. From 60 to 70 per cent of deaths during the first year of life occur during the first month; of these fatalities, about 60 per cent occur among the 10 per cent of infants who weigh less than 5 pounds 8 ounces at birth. In addition to increased mortality, serious neurologic sequels occur with greater frequency. The majority of factors responsible for premature births can be influenced by prenatal medical care. Advice during pregnancy can often avoid premature labor among women who have a previous history of premature delivery, those with multiple pregnancies, and those who are chronically below par in various respects. Adequate prenatal care can do much to reduce the incidence of toxemias of pregnancy, which contribute significantly to premature birth because of the frequent necessity for interruption of pregnancy before term. The prevention of prematurity offers more hope for preserving life and preventing postnatal handicaps than do measures which can be taken after delivery.

The *natal period* from onset of labor to delivery of the infant is one of great risk, and a number of preventable anesthetic, analgesic and obstetric circumstances contribute to morbidity in the neonatal period and to mortality.

In the *neonatal period* (birth to one month of age) there are many opportunities for preventive measures, which include prompt physical examination of the newborn infant to

detect remediable congenital anomalies and acquired illness, measures to protect the infant from infection and avoidance of the overuse of drugs (for example, unnecessary use of oxygen and vitamin K).

#### PREVENTION OF INFECTION

**Routine Immunizations.** The prevention of infectious diseases by immunization is the most familiar aspect of preventive pediatrics. Today it is routine practice to immunize infants against *diphtheria*, *pertussis*, *tetanus*, *smallpox* and *poliomyelitis* during the first year of life.

**Active immunization against diphtheria, pertussis and tetanus** can be accomplished simultaneously by combined alum-precipitated or aluminum hydroxide-adsorbed diphtheria and tetanus toxoids and pertussis vaccine ("triple toxoid"). It is desirable that the mixture of antigens be such that 0.5 ml. contains adequate amounts of diphtheria and tetanus toxoids for one dose and 4 N.I.H. units of pertussis vaccine. The minimum is three intramuscular injections of combined toxoid-vaccine mixtures given at intervals of four weeks. This interval has the advantage of producing immunity rapidly, but the interval may be extended to three to six months. (See also chapters on Diphtheria, Tetanus and Pertussis.) Immunization of infants is usually started at one or two months of age, although satisfactory results have been reported from immunization begun at birth.

Toxoid and vaccine may be given intramuscularly in the gluteal, the lateral thigh, the deltoid or the triceps muscles. The injections are usually given in the lower extremities during infancy and in the arms of older children. Only one injection of a series should be given into the same muscle mass.

Occasionally there are reactions causing fever, excessive crying and localized swelling, redness and tenderness at the site of injection. In such instances the next dose of combined toxoid-vaccine should be drastically reduced, or the immunization should be completed by using diphtheria and tetanus toxoids and pertussis vaccine separately. When a convulsion occurs as part of the reaction, further immunizing procedures should be postponed for at least a year. Further administration of pertussis vaccine may be hazardous.

Children not immunized during infancy may be given basic immunizations by three injections of "triple toxoid" up to the age of six years; three injections of diphtheria-tetanus toxoid (precipitated or adsorbed) are

advised for those between the ages of six and ten years. Patients ten years of age and older should be tested initially for sensitivity to diphtheria toxoid unless "adult" type of toxoid is used (see footnote of Table 27). The toxoid sensitivity test (modification of the Moloney and Zoeller tests) consists in an intradermal injection of 0.1 ml. of a 1:100 dilution of fluid diphtheria toxoid. The test is read at forty-eight hours; a positive reaction consists of an area of erythema and induration 1 cm. or more in diameter. If the Schick test is positive and the sensitivity test is negative, the individual may be immunized with standard 0.5-ml. doses of diphtheria-tetanus combined toxoids at intervals of four to six weeks. If the Schick and sensitivity tests are both positive, it is not safe to administer diphtheria toxoid, except as the sensitivity test is only moderately positive, when immunization should be carried out cautiously by injecting 0.05 ml. of fluid diphtheria toxoid subcutaneously. If no further untoward reactions occur, this dose may then be doubled at weekly intervals until four injections (0.75 ml.) have been given.

Primary immunization of older children may apparently be safely performed with the "adult" type of diphtheria-tetanus toxoid, which contains less antigen than standard toxoid.

Tetanus toxoid (precipitated or adsorbed) rarely causes local or systemic reactions, so that primary immunization of children over the age of ten may be accomplished by two injections of 0.5 ml. each at an interval of at least one month and not longer than four months. When fluid tetanus toxoid is used, three injections of 0.5 ml. are administered.

Children over the age of six years are usually not immunized against pertussis. If immunization is considered advisable, as when there are small infants in the family for whom pertussis would be dangerous, three intramuscular injections of alum-precipitated or aluminum hydroxide-adsorbed *H. pertussis* vaccine at intervals of at least one month and containing a total dose of at least 12 N.I.H. units should be given. If the saline-suspended vaccine is used for rapid protection, three injections should be made at intervals of one to four weeks, with a total dose of 12 N.I.H. units.

"Booster" or stimulating injections of toxoid and vaccine are given at regular intervals after the initial series of immunizing inoculations to assure maximum immunity. The first "booster" injection should be given one year

after completion of the primary immunization and subsequent "boosters" at intervals of three years. The recall of antibodies is accomplished by extremely small amounts of antigen, so that "booster" doses after the first one may consist of only one fifth to one half of the individual doses of the primary immunization.

The Schick test is seldom used among children under ten years of age who were immunized in infancy. The periodic administration of booster doses of diphtheria toxoid is safer and more effective than relying on the Schick test as a guide for additional immunization. After the age of ten years the need for booster injections should be determined by a Schick test, one at twelve years of age and another at sixteen to eighteen years. Schick tests and diphtheria toxoid sensitivity tests may be avoided among older children by using the "adult" type of diphtheria toxoid containing only 2 Lf. in 0.5 ml.

In general, alum-precipitated or aluminum hydroxide-adsorbed toxoid-vaccine (diphtheria, tetanus and pertussis) is used for recall or booster immunization unless a prompt rise in immunity is required because of exposure to one of the diseases. In such instances fluid toxoids and saline-suspended pertussis vaccine are advised because the more prompt absorption of these substances accelerates antibody formation (see Table 27).

Contraindications to routine immunization of infants and children with toxoid-vaccine are acute illness, obvious cerebral damage or a history of convulsive disorder. In the event of acute illness, immunization should be postponed temporarily. In the other situations immunization should be delayed until after infancy, when it may be started cautiously with small doses of the antigens administered separately, and with the child under close observation. (See above for recommendations when there has been an untoward reaction to a previous immunization.)

A relationship between the localization of paralysis in poliomyelitis and the site of recent toxoid or vaccine injections has been observed. Where poliomyelitis is epidemic, routine intramuscular or subcutaneous injections of toxoids and vaccines should be limited to children under the age of six months. When a child older than six months has been exposed to a disease for which passive or active immunization is advisable, the immunization is justified during a poliomyelitis epidemic. Administration of poliomyelitis vaccine during an epidemic is considered safe, but it offers no immediate protection.



**Vaccination against smallpox** (see p. 501) should be performed during the first year of life, usually after immunization against diphtheria, tetanus, pertussis and poliomyelitis. Revaccination every five years is advisable. When there is any possibility that exposure to smallpox has occurred and there has been an interval of more than one month since the last successful vaccination, revaccination is recommended. Vaccination against smallpox is contraindicated for children with eczema or dermatitis and for household contacts of children with these conditions, to avoid secondary vaccination or generalized vaccinia.

**Vaccination against poliomyelitis** should be performed in infancy at the time of the initial diphtheria-pertussis-tetanus immuniza-

tions (see Table 27) or a month or so after their completion by two injections of poliovirus vaccine one month apart; seven months after the second inoculation a third injection of vaccine should be given. This schedule of administration of poliovirus vaccine is thought to confer effective immunity in most persons for an indefinite number of years. Some observers, however, believe that the probability of significantly greater protection afforded by a fourth injection one year after the third one justifies it as a regular procedure.

**Special Immunizations.** Active immunizations against rabies, mumps, Rocky Mountain spotted fever, virus influenza, typhoid fever and tuberculosis are indicated under certain circumstances. Immunizations against these

Table 27. Recommended Immunization Procedures

<b>I. Primary Immunization</b>	
1-2 Months of age:	0.5 ml. of diphtheria-pertussis-tetanus antigen mixture (D.P.T.*) intramuscularly in the left gluteus maximus
2-3 Months of age:	0.5 ml. of D.P.T.* in the right gluteus maximus; 1.0 ml. of poliomyelitis vaccine at a different site, unless a commercial vaccine containing the 4 antigens should become available
3-4 Months of age:	0.5 ml. of D.P.T.* in the left vastus lateralis or right deltoid; 1.0 ml. of poliomyelitis vaccine as described above
5 Months of age:	Smallpox vaccination over the left deltoid or triceps
6 and 7 Months of age:	Poliomyelitis vaccine, if not given earlier with D.P.T.,* 2 doses of 1.0 ml., respectively; in the deltoid or triceps muscle
<b>II. Routine Recall (Booster Injections)</b> (Give in the deltoid or triceps muscle)	
11-14 Months of age:	Poliomyelitis vaccine, 1.0 ml. (give 7 months after 2 primary injections)
18 Months of age:	0.5 ml. of D.P.T.* (first "booster")
3-4 Years of age, or 2 years after first "booster":	0.5 ml. of D.P.T.*
6-7 Years of age:	0.1 ml. of diphtheria-tetanus toxoid
9-10 Years of age:	0.1 ml. of diphtheria-tetanus toxoid
Every 3 years thereafter:	0.5 ml. of "adult" type of diphtheria-tetanus toxoid† or, if Schick test is known to be negative, 0.1 ml. of tetanus toxoid
<b>III. Exposure Recall (Booster) Injections</b>	
A. Upon intimate exposure to whooping cough or during an epidemic, assuming that the child has not had a routine recall injection in the past 2 months, give saline-suspended <i>H. pertussis</i> vaccine subcutaneously in a dose of 4 N.I.H. units	
B. Exposure to diphtheria: Children under the age of 5 years, 0.5 ml. of diphtheria toxoid; children 5 to 12 years of age, 0.1 ml. of toxoid; those over the age of 12, 0.01 ml. of standard diphtheria toxoid or 0.5 ml. of "adult" type of toxoid.	
C. Exposure to tetanus	
1. For mild to moderately severe scratches, burns, puncture wounds or dog bites, 0.5 ml. of fluid tetanus toxoid subcutaneously, provided not more than 8 years have elapsed since last toxoid injection. When interim is 9 years or more, follow procedure in 2 below.	
2. For extensive contaminated wounds combined active-passive immunization by giving 0.5 ml. of fluid tetanus toxoid intramuscularly and 5000 units of tetanus antitoxin intramuscularly is advisable	
<b>IV. Revaccination against Smallpox</b>	
Every 5 years and during an epidemic ("No reaction" means that the vaccine is not potent, and not that the patient is immune)	

Adapted from Report of the Committee on The Control of Infectious Diseases, American Academy of Pediatrics, Evanston, Illinois, 1957.

\* D.P.T.—alum-precipitated or aluminum hydroxide-adsorbed diphtheria and tetanus toxoid containing at least

4 N.I.H. units of *H. pertussis* organisms.

† 2 Lf of diphtheria toxoid and 5-15 Lf. of tetanus toxoid per 0.5 ml.

Table 28. Special Immunizations for Foreign Travel

<i>Vaccine</i>	<i>Individual Dose*</i>				<i>No. Doses</i>	<i>Interval</i>	<i>Mode of Administration</i>	<i>Booster</i>
	2-36 Mos.	3-6 Yrs.	7-10 Yrs.	>11 Yrs.				
<i>Plague</i>								
1st dose . . .	0.06 ml.	0.12 ml.	0.25 ml.	0.5 ml.	3	Under 11 yrs., 7-10 days Over 11 yrs., 7-28 days	Subcutaneously	Same as first dose, 6 mos. to 4 yrs. after basic series
2nd dose . . .	0.12 ml.	0.25 ml.	0.5 ml.	1.0 ml.				
3rd dose . . .	0.12 ml.	0.25 ml.	0.5 ml.	None				
<i>Cholera</i> . . . . .	Same dosage as for Plague vaccine				3 2 > 11 yrs.			
<i>Epidemic Typhus</i>								
1st dose . . .	0.12 ml.	0.25 ml.	0.5 ml.	1.0 ml.	3 2 > 11 yrs.	1-3 weeks	Subcutaneously	Same as basic immun- izing dose, annually as indicated
2nd dose . . .	0.12 ml.	0.25 ml.	0.5 ml.	1.0 ml.				
3rd dose . . .	0.12 ml.	0.25 ml.	0.5 ml.	None				
<i>Yellow</i>								
<i>Fever</i> . . . . .	0.5 ml.	0.5 ml.	0.5 ml.	0.5 ml.	1	—	Subcutaneously	0.5 ml. every six years or in epidemic
<i>Typhoid-Paratyphoid</i>	<12 mos.		>12 mos.					
1st dose . . . . .	0.2 ml.		0.3 ml.		3-4	1-4 weeks	Subcutaneously	0.1 ml. intradermally every 1-2 years
2nd dose . . . . .	0.2 ml.		0.6 ml.					
3rd dose . . . . .	0.3 ml.		0.6 ml.					
4th dose . . . . .	0.3 ml.		None					

\* All doses are based on subcutaneous administration.

diseases are discussed in the appropriate chapters of this volume.

Increased travel to foreign countries has made it necessary for many infants and children to receive special immunizations not necessary in North America. Information about the required and recommended immunizations in various parts of the world can be obtained from health departments or from publications of The Public Health Service, Washington, D.C. (see also Table 28).

*Passive immunizations* against measles, rubella, infectious hepatitis and poliomyelitis are often carried out by injection of gamma globulin when susceptible persons are known to have been exposed. Passive immunization against diphtheria, pertussis, mumps, tetanus and rabies may also be accomplished by appropriate means. The recommended procedures are described under the sections on the individual diseases.

**Quarantine.** Quarantine has not been effective for the control of contagious diseases. Early periodically stimulated immunization against the preventable diseases, diphtheria, pertussis, poliomyelitis and smallpox, is accepted as a far more positive control measure.

Chickenpox, mumps, rubella and measles are contagious before the disease is usually recognized, and, in addition, quarantine, if it were effective, would not be practical because (1) active immunity cannot be produced artificially, (2) these diseases are milder in childhood than among adults, and (3) complications which cannot be controlled by available therapy are uncommon.

**Rheumatic Fever.** Rheumatic fever is a recurrent disease of childhood, initial and subsequent attacks of which can be prevented by early and effective treatment of beta-hemolytic streptococcal infections with penicillin (see p. 904).

**Dental Caries.** Dental caries is the most widespread health problem during childhood years. Significant primary prevention can be accomplished by restricting the amount of refined sugars in the diet, by periodic topical application of sodium fluoride to the teeth and by fluoridation of community water supplies (p. 626).

#### PREVENTION OF NUTRITIONAL DISORDERS

In childhood there is a need for food to support growth in addition to that for energy and



for repair. The normal, healthy child usually will select an adequate diet for energy, repair and growth if free choice is possible. Owing to parents' lack of knowledge, cultural patterns, economic restrictions or certain behavior problems, many children do not get the right kind of diet. Serious illnesses can be prevented by making sure that children get sufficient calories and adequate protein, vitamins and minerals. The diet may be considered satisfactorily balanced when the calories are derived approximately as follows: 15 per cent from protein, 60 per cent from carbohydrate and 25 per cent from fat.

Nutritional deficiency diseases are preventable. Parent education in simplified dietetics is a necessity. All the dietary essentials can be obtained from natural foods except vitamin D, which must be given as a supplement, either in a separate vehicle or in fortified foods. Occasionally, supplementation of the diet with other vitamins is necessary to prevent the development of specific deficiencies.

In many localities the problem of undernutrition is less common than that of *obesity*. The prevention of overnutrition is properly an objective of preventive medicine because of the high morbidity and mortality attributable to this condition in later years. The causes of obesity may be psychologic, cultural, economic or, rarely, endocrine. The common denominator etiologically is the intake of more calories than are needed. Prevention, which is far easier than cure, is dependent upon early detection of those factors in the child's environment or personality which predispose to obesity. Sometimes instruction about nutrition and counseling about the causes of obesity are sufficient. In some instances psychotherapy is required.

#### THE PREVENTION OF ACCIDENTS

Infectious diseases and nutritional disorders can be controlled by specific measures. Childhood accidents, on the other hand, are a major problem (Fig. 23) and comprise a challenging field for preventive measures. Accidents now are the leading cause of death in all ages of childhood after the first year, and their relative importance steadily increases as other health problems come under control. Though mortality resulting from accidents is decreasing, the decline is slow compared with that of other causes of death and disability. About 12,000 children under the age of twelve die each year from accidents. Mortality statistics are not a valid index of the problem, however, for it is estimated that

each year 50,000 children are crippled and almost 2 million incapacitated for some time by accidents.

Accidents occur in many situations—in the home, in the street, at school, on the playground. The accident rates among infants and preschool children are notably high (Figs. 24, 25). The majority of accidents in each group occur in the home (Fig. 24). Physicians have the opportunity to help parents anticipate and understand the common hazards of early life and thus provide some "immunity" against accidents.

As the child grows older he becomes increasingly able to take personal responsibility for his safety. Accident prevention in childhood must be based on (1) parents' understanding of the typical behavior and interests of children at various stages of their development so that dangerous situations can be avoided, and (2) parents' appreciation of the wisdom of allowing many of their children's activities to take a natural course for the benefit of experience even though a mildly painful result is clearly foreseen. Real danger calls for prompt protection, but there is value in repeated experiences which teach the child to look out for his own safety.

Certain accidents occur more commonly at one age than another. Scalding burns and falls are common in the second year of life, when children are beginning to walk about the house. The curious, active two-year-old

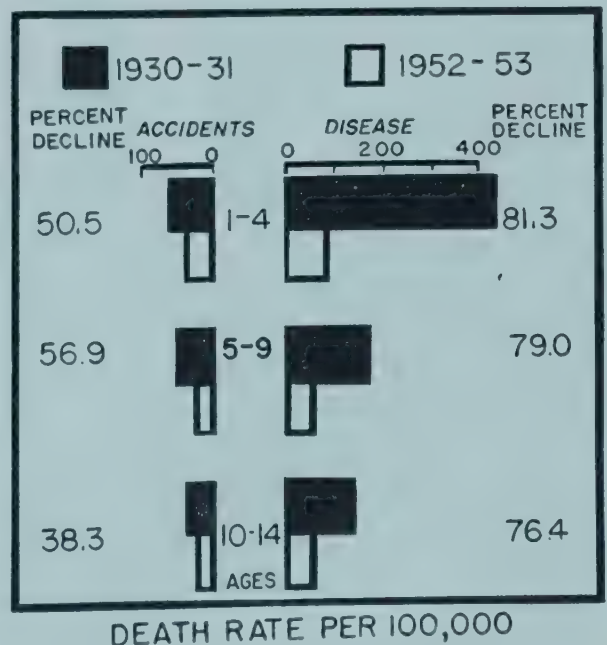


FIG. 23. Decline in accident rates compared to disease. (Used with permission of Wheatley and Kasey, Metropolitan Life Insurance Company, New York, N.Y.)

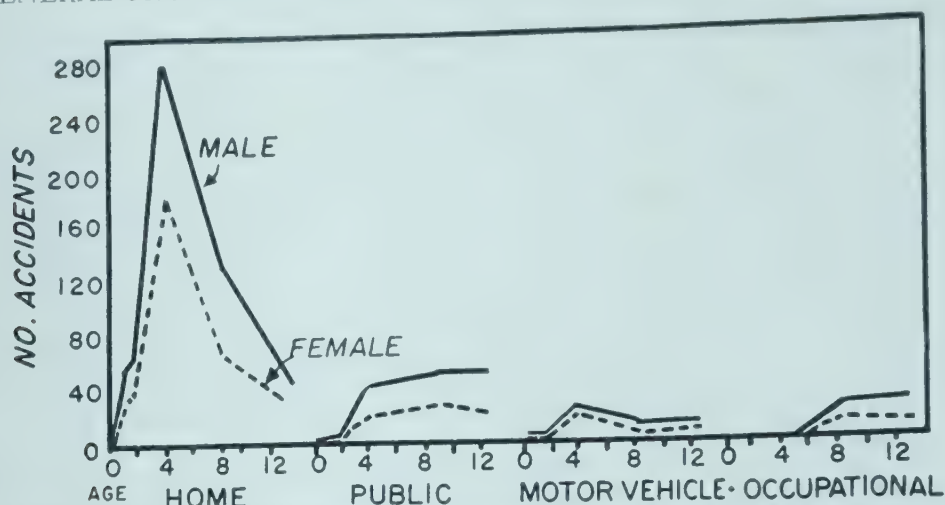


FIG. 24. Incidence of accidents according to locality and age group. (Adapted from A. C. Smid and G. B. Logan. Used with permission of the authors. *Minnesota Medicine*, 39:394, 1956.)

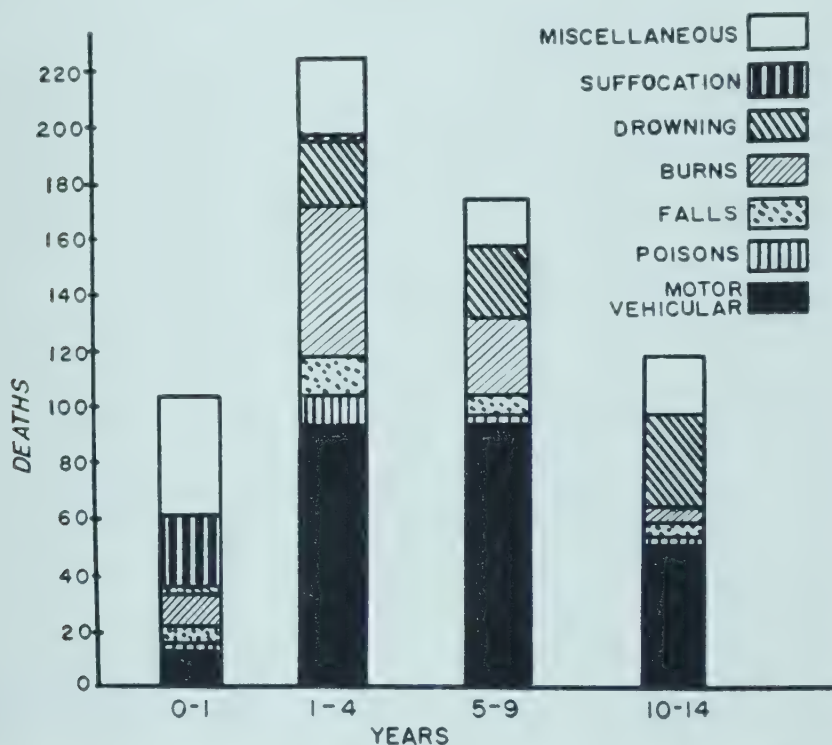


FIG. 25. Causes of accidental death in Ohio, 1955. Suffocation is rarely a cause of death in infancy; there is much evidence that most deaths attributed to it are the result of clinically nonmanifest infections (see p. 351). (From information supplied by Division of Vital Statistics, Ohio Department of Health.)

is particularly liable to find and ingest poisonous substances, to have lacerations and contusions from falls and, if there is unguarded opportunity, to fall in water and drown. The three-year-old who can run, jump and climb is most likely to suffer from falls and burns and to be injured when playing near motor vehicles.

Older children are most likely to have accidents attributable to drowning, bicycles and automobiles. Therefore the physician should urge parents to teach their children to swim,

ride bicycles safely and, at the proper age, to drive automobiles skillfully. Such a role is as significant for physicians as are activities for immunizations and good nutrition.

## SECONDARY PREVENTION OF DISEASE

**Controlling the Progression of Chronic Disabilities.** Children whose optimal growth, development and well-being are retarded by chronic handicaps can benefit from measures aimed at preventing the progression of their



ailments and improving their general condition. This is the realm of secondary prevention of disease.

For satisfactory control of chronic disorders early detection and treatment are imperative. Since many such diseases or handicaps are not recognized in the primary stages by children themselves or by their parents, reliance for early detection cannot safely be based on waiting for the parent to seek medical help. Some recognized disabilities, moreover, have become so accepted that medical attention is not always sought. Despite these obstacles, the chances of early detection have increased steadily with improved programs for the appraisal of children's health. Two distinct but related mediums for routine health supervision are the *child health conferences* ("well-baby clinics," "well-child conferences") and *school health programs*.

## DETECTION OF DISEASE, AND HEALTH EDUCATION

**Child Health Conferences.** The many opportunities for preventive medicine and promotion of optimal growth and development have stimulated the development of routine health supervision of infants and children in physicians' offices or in community clinics. When the patient's economic level and the physician's time permit, individual health conferences are preferable to public clinics, since the same physician can supervise the child in health and in illness. When physicians' services are largely engaged by sick children, it is desirable to have community child health conferences planned and operated jointly by practicing physicians and public health authorities. In either case the objectives are the same: assuring optimal health for the child and helping parents to do the best possible job in carrying out their responsibility for their children's health.

The usual program of health supervision in child health conferences includes (1) medical appraisal of the child's growth and development, physical health and personality development; (2) advice about feeding schedules and practices; (3) immunization against the common contagious diseases (see p. 141); (4) guidance for the parents which should consist in a discussion of the results of the current examination, a description of the type of behavior and growth they can expect in the immediate future and full opportunity for them to ask questions. The physician who carries out the child health conference must

be familiar with the various resources in his community for health and welfare.

Such simple laboratory procedures as routine urinalysis, hemoglobin determination, serologic tests for syphilis and periodic tuberculin testing during early childhood are included in child health supervision.

A desirable schedule of health conferences during infancy and the preschool years is as follows:

Birth to six months . . . . .	every month
Six months to one year . . . . .	every two months
Second year . . . . .	every four months
Two to six years . . . . .	every six months

**School Health.** The term "health program for school-age children" is preferable to "school health." This designation indicates that school health is but a part of the over-all community plan for child health, which should begin in the prenatal period and continue throughout the school years. When the child enters kindergarten or first grade, the school becomes a third party, joining parents and physicians concerned with the health of the child. The need for school personnel to be assured that every pupil has attained his optimal health for learning and for school activities is understandable. Thus teachers should know about any physical handicaps of a particular child so that, if necessary, individualized activities can be planned, as in physical education, recreation and manual arts.

The main purposes of a health program in schools are to maintain the health standards of the school environment, to provide health instruction and to cooperate in maintaining and improving the health of individual children. The school environment includes lighting, heating, ventilation, toilet facilities and playground equipment. Health services such as physical examinations, first-aid procedures and screening tests should also be included in the health program. Health services within the school should not replace the child's relations with his family physician, and there should be special effort to motivate parents to seek medical attention when needed. School physicians and family doctors can, by cooperative planning with school authorities, integrate the school's interest in child health with health services for children elsewhere in the community.

**Screening Tests.** Though prolonged diagnostic health examinations and medical treatment are not feasible in schools, the assemblage of children is ideal for utilizing

screening tests to detect those children presumably in need of medical care. Many important health problems of school-age children are asymptomatic and difficult to detect in the early stages by the classic "look-feel-listen" type of health examination. Discovery of nutritional disorders, growth failure, faulty hearing and visual disturbances, all of which require medical diagnosis and treatment, can be accomplished by simple screening tests in the physician's office or in schools.

Screening tests especially adapted to the health problems of school-age children are tests for visual function, hearing tests, measurements of physical growth, hemoglobin determination, urinalysis for sugar and albumin, appraisal of speech, blood pressure determinations, tuberculin skin test and scalp examination by Wood light.

The *visual acuity* (see also p. 1331) of children should be tested at intervals of not more than two or three years. Usually faulty vision is not known to the child or his parents. *Myopia*, the most common refractory error of older children, can be discovered by using the Snellen E Chart.\* The chart should be illuminated by 10 to 12 foot-candle light, obtainable from a 50-watt bulb in a floor lamp or a 150-watt Mazda spotlight. Charts with built-in illumination are available. The child should be exactly 20 feet from the chart during the test. Children under eight years of age should be expected to have 20/30 vision in both eyes, and children eight years and older, 20/20 vision; poorer vision requires examination by an oculist.

Far-sighted children usually pass the Snellen test, but they can be detected by the "plus-sphere" test. A convex lens of plus 1.50 diopters is held a short distance in front of the child's eyes. A child who has clinically significant *hyperopia* will be able to read the symbols on the chart as well through the lens as without it, since he relaxes his usual over-accommodation to compensate for the convex lens. The vision of a child who is not hyperopic is blurred by the plus sphere because he cannot compensate for it.

Latent ocular muscle imbalance, or *phoria*, often can be detected by the "cover-test," in which the child first fixes his vision on a distant object, and then has one eye covered by a card. When the card is removed quickly, the examiner looks for movement of the eye as it again fixes on the object. Normally,

fusion is not lost when one eye is covered. Noticeable movement of the eye immediately after the card is removed is a sign of *phoria* and merits referral to an oculist.

*Strabismus* is usually detectable by observation and, of course, demands prompt referral to an oculist.

Between 5 and 10 per cent of children have significant *impairment of hearing* (see also p. 766), often unrecognized by them. The pure tone audiometer, which detects loss of hearing at octave levels from 250 to 8000 vibrations, is the only reliable method for testing acuity of hearing. The usual screening test is carried out by setting the intensity at 15 or 20 decibels and testing each ear separately. A child who cannot hear tones of every frequency at an intensity of 20 decibels or misses two tones at an intensity of 15 decibels should have an otologic examination and an audiogram. The audiometric test can be given to children of five years and older. The screening test should be repeated at intervals of two to three years; when this is not feasible in school surveys, priority should be given to children in the third or fourth grade.

*Measurements of physical growth* serve two purposes as screening tests: to detect children whose measurements are extremely distant from the mean and those whose growth progress from one examination to another is not within the expected range. Such children should be singled out for special examination to determine whether a health factor is responsible for their status.

*Urinalysis* to detect glycosuria, albuminuria and abnormal cells and casts should be carried out periodically. By using reagents which do not require heating to test for sugar and albumin, these examinations can be performed away from a clinical laboratory.

*Speech difficulties* (see also p. 91) are common during school years and may have lasting effects on personality development. Early detection of lisping, stuttering, nasality and defective speech associated with cleft lip and cleft palate is important so that the child may have the benefit of prompt study.

The determination of *blood pressure* (see also p. 822) is a screening test which can lead to presumptive detection of some types of congenital heart disease, renal disease and certain endocrine abnormalities. Determination of blood pressure is invalidated unless a cuff of proper width is used; one that is too narrow leads to falsely high readings. Recommended widths for cuffs at various ages are as follows:

\* Obtainable from most optical supply firms and from The National Society for Prevention of Blindness, 1790 Broadway, New York 19, New York.



for children under one year of age, 2.5 cm.; for children one to four years, 5 to 6 cm.; for children four to eight years, 9 cm.; for most children over the age of nine years the cuff designed for adults (12 cm.) may be used.

*Tuberculin skin testing* of children (see also p. 461) by the Vollmer patch test or, preferably, by intradermal injection is recommended to detect those who should have roentgen ray examinations and as an aid in finding open cases of tuberculosis among adults who come in contact with the child.

In areas where *ringworm of the scalp* (see also p. 1292) is endemic or where cases have been recently discovered, children who have not reached puberty should have their scalps examined periodically with a Wood light (ultraviolet light passed through a special nickel-oxide filter).

**Health Education.** Since there are no natural motivations to seek preventive services, health education of the public is essential for the optimal development of preventive medicine. Such education may be carried out by schools and official health agencies or by other community organizations. It may be effected by direct or formal teaching and through experiences. In schools health education is usually a required subject at various levels of the curriculum. The factual content of such courses needs constant revision to keep it abreast of current knowledge.

Physicians and nurses have greater opportunities for meaningful teaching of health than do educators. Sufficient time should be taken during a medical examination or health conference to explain the health procedures and to discuss the results of the examination and the reasons for suggested treatment. Unfavorable attitudes, which may

be lasting, result from hurried, incomplete examinations and inadequate explanations.

THOMAS E. SHAFFER

## REFERENCES

- Batson, R., Christie, A., Mazur, B., and Barrick, J. H.: Response of the Young Infant to Poliomyelitis Vaccine Given Separately and Combined with other Antigens. *Pediatrics*, 21:1, 1958.
- Cooke, R. E., and Odell, G. B.: Perinatal Factors in the Prevention of Handicaps. *Pediat. Clin. North America*, August, 1957, p. 595.
- Health Appraisal of School Children. 2nd ed. Joint Committee on Health Problems in Education of the National Education Association and The American Medical Association. Chicago, Illinois, American Medical Association, 1957.
- Health Supervision of Young Children. New York, American Public Health Association, 1955.
- Immunization Information for International Travel. Department of Health, Education and Welfare, Public Health Service, Washington, D.C., Superintendent of Documents, Government Printing Office.
- McAllister, R. M.: Immunization Procedures. *Pediat. Clin. North America*, 4:611, 1957.
- McClave, C. R., and Shaffer, T. E.: Accidents, Injuries and Children. *Pediat. Clin. North America*, August, 1957, p. 635.
- Report of the Committee on the Control of Infectious Diseases. Evanston, Ill., American Academy of Pediatrics, 1957.
- Report of the Committee on School Health. Evanston, Ill., American Academy of Pediatrics, 1954.
- Salk, J. E.: How Many Injections of Poliomyelitis Vaccine for Effective and Durable Immunity? *J.A.M.A.*, 167:1, 1958.
- Suggested School Health Policies. 3rd ed. National Conference for Cooperation in Health Education. Chicago, American Medical Association, 1956.
- Tuuri, A. L., Johnston, H. L., and Harting, D.: Adapting Immunization Programs to Special Groups. *Pub. Health Rep.*, 72:283, 1957.

# ADOLESCENCE

## PHYSICAL ASPECTS OF ADOLESCENCE

Adolescence, "the process of development from childhood to manhood and womanhood," is considered here the period beginning with the appearance of secondary sex characters and terminating with cessation of somatic growth. Among the laity "puberty" is synonymous with the first menstrual period in the girl. A point developmentally corresponding to this in the boy is the time of

appearance of spermatozoa, which is difficult to determine. It is said to coincide with the development of curly pubic hair. The "pre-puberty" or "pubescent" period refers to that of accelerated growth and the appearance of secondary sex characters which precedes puberty. Separate consideration of adolescence is justified only to the extent that this period differs from the other phases of growth

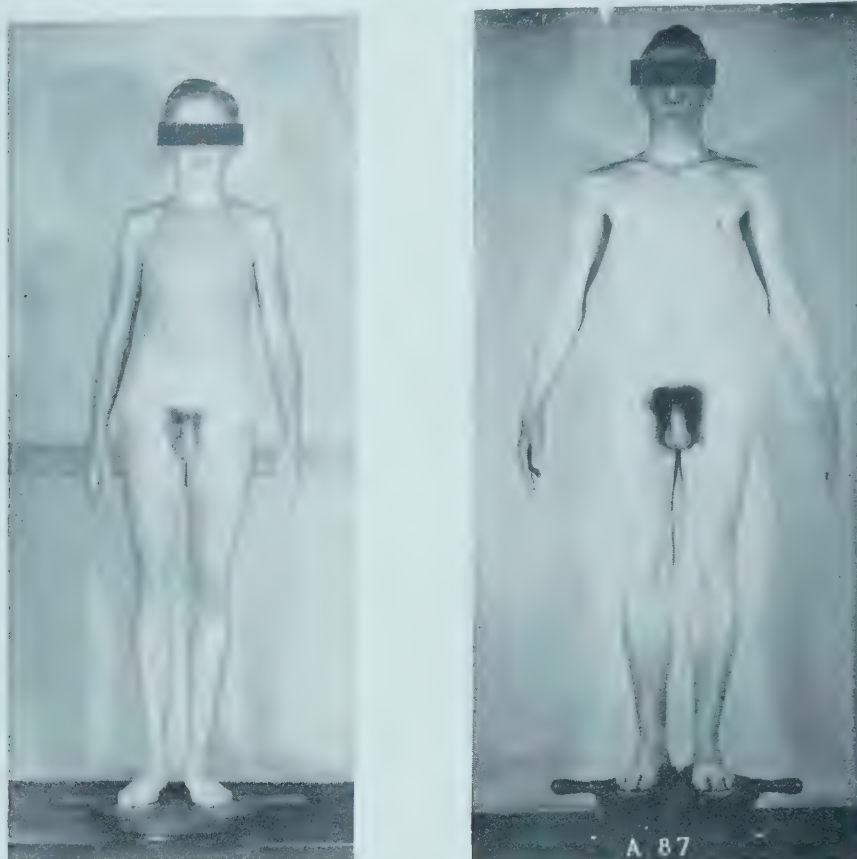


FIG. 26. Illustrating the discordance between chronologic and physiologic ages in the average school. Both boys were given the same diet and offered the same scholastic and extracurricular activities.

Chronologic age .....15-11  
 Height .....61.7  
 Weight .....99  
 Epiphysial age .....13-11

Chronologic age .....15-8  
 Height .....68.7  
 Weight .....145  
 Epiphysial age .....16-9

(Photographs, courtesy of J. Roswell Gallagher, M.D.)

by characteristics which make the approach to its clinical problems unique in pediatrics.

Chronologic age as a point of reference ceases to be useful at this time, if indeed it ever was (Fig. 26). The problems of the thirteen-year-old girl come into focus only when we know whether we are dealing with a prepubescent or pubescent girl, or with one whose menarche may have been one, two or three years previous. The need for assessment in terms of physiologic age was emphasized by Crampton more than forty years ago, but there have been few changes in the handling of school difficulties related to this factor. Adolescence is a period of growth with rapid changes in rate in sharp contrast to the fairly steady rate of the several years that precede it; these changes can be predicted and evaluated only against a scale of physiologic age. The fluctuant metabolism, the food requirements, the scholastic capacity and even morbidity can be discussed only in terms of physi-

ologic achievement. Actually, a school class of thirteen-year-old girls could include examples of eight different physiologic ages (Fig. 28 and Table 29).

The physical, emotional and scholastic problems of the girl and the boy diverge so sharply as to require a totally different set of standards for assessment at this period after a sexless phase when they could be considered in large measure on the same basis. The thirteen-year-old girl who has achieved puberty has progressed at least two years further toward maturity than a boy of the same chronologic age; she feels as if it were five.

So great is the individuality of the pattern of growth and development of the period that attempts at generalization break down in the presence of specific problems.

In private schools where individual curriculums are possible, physical and emotional problems resulting from the discrepancy between physiologic and chronologic age ma-



Table 29. Standing Heights and Menarcheal Ages of Each Group (Fig. 28)

Groups	Averages of Standing Height in Cm.	Averages or Midpoints of Menarcheal Ages	Groups	Averages of Standing Height in Cm.	Averages or Midpoints of Menarcheal Ages
.....	144.52	11.00	E.....	155.16	13.25
.....	151.60	11.75	F.....	154.92	13.75
.....	153.25	12.25	G.....	153.20	14.25
.....	152.33	12.75	H.....	154.87	15.00

From Shuttleworth: Monographs of the Society for Research in Child Development, 2, National Research Council.)

be minimal; this cannot be obtained in the average public high school. Only when growth studies permit an early prediction during the preschool years of the expected growth schedule will it be possible to discard the present rigid plan of starting all children in school at an arbitrary chronologic age and to substitute a plan that will take into account physiologic and mental age. Meanwhile the adolescent will continue to have problems conditioned by the present system. The effect of such frustrations on the psychiatric

problems of adult life is conjectural, but it must be considerable.

Differences in the rates of development of the two sexes are well enough established to take them into account in educational planning. In a "readiness for reading" test the girl is advanced at least a year over the boy. This difference becomes greater as puberty is approached, and scholastic accomplishment is comparable in the two sexes only when both have passed through puberty; the boy accomplishes this about two years later than



FIG. 27. Illustrating somatic changes through male adolescence.

Chronologic age .....14-10  
Height .....61.3  
Weight .....99  
Epiphysial age .....13-6

Chronologic age .....17-5  
Height .....68  
Weight .....133  
Epiphysial age .....15-3

Chronologic age .....22-7  
Height .....69  
Weight .....157

(Photographs, courtesy of J. Roswell Gallagher, M.D.)

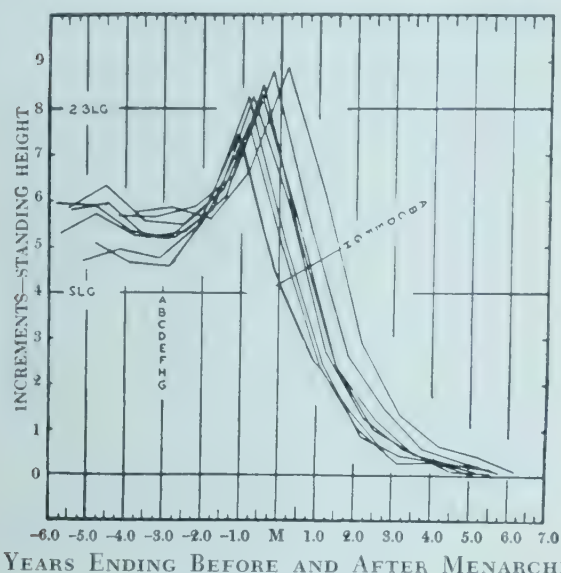


FIG. 28. Shuttleworth's curves of annual height increments to show how strikingly different patterns plotted against chronologic age become reconciled against a physiologic age scale. Annual increments in standing height of 8 groups of girls who attained menarche at different ages (see Table 29). The curves are arranged so that the points corresponding to the menarcheal age are on the same vertical line. The 3 horizontal grid lines indicate, respectively, zero growth per year, one ninth of the average growth from age 8 to 17 (SLG), and two ninths of the average growth from age 8 to 17 (2 SLG).

the girl. To wait until puberty to consider the problems posed by this difference would seem short-sighted.

The individuality of the pattern of growth must also be borne in mind. Figure 27 shows a boy whose time schedule is slower than average. Physically, he is sufficiently different from his chronologic peers to cause concern to parents who may seek advice concerning endocrine therapy to accelerate his development. The need to explain the normal physiologic variations is a constant one in dealing with parents of adolescents, who should be reassured that endocrine therapy is not indicated in such circumstances. The comments of Frank in this regard are especially pertinent.

We cannot expect the individual boy and girl to meet these requirements (the tasks of life and the demands of maturation) effectively if in our various programs and practices in the home, in the school, the clinic and hospital, and in the youth organizations and elsewhere, we persistently deny the basic, ineradicable differences among individuals and impose upon them the tyranny of the norm. Perhaps in no other period except old age is there a greater need for the clinical approach which explicitly recognizes this individuality and mediates both the re-

quirements and the needs of adolescents in accordance with the peculiar make-up and capacities of the individual boy and girl.

**Nature of Growth.** Growth in man does not follow a straight line, but consists in a series of alternating rapid (fetal, infantile, prepuberal) and slow periods, the curves revealing distinct waves roughly likened to three S-shaped curves. The third curve shows a slight lag about three years before sexual maturity, followed by a sharp acceleration, which terminates in—and is apparently conditioned by—the attainment of sexual maturity. This final spurt is followed by a deceleration. Growth during adolescence is a function of physiologic rather than of chronologic age, as demonstrated in the charts of Shuttleworth, by the fact that the growth patterns of girls maturing at ages varying from ten to seventeen years can be superimposed only if chronologic age is ignored and the plotting is done in terms of physiologic age, using years preceding and following puberty as the time scale. This fact is basic to an understanding of many of the normal physiologic variations at this age period which create deep concern in the patient and the parent.

Transition from one growth curve to another, accompanied by changes in metabolism, may be fraught with considerable danger to the growing child. The sharp increase in the incidence of tuberculosis during adolescence and the steadily mounting incidence of rheumatic fever up to puberty, with a decline following it, suggest that reaction to disease is handicapped by the added demands of growth during this period. It is believed that much of the difficulty can be explained in terms of nutrition and that adequate provision for dietary requirements peculiar to this period may be a main factor in the resistance to disease.

In graphs showing the average yearly increments of height and weight (Fig. 8, p. 14) the time of maximum growth of the two sexes is separated by about two years. Weight increments increase steadily from the age of five years, with an acceleration in the prepuberty years. On the average, the girls' weights are overtaken by those of boys and passed in the thirteenth year. Data such as these have the limited usefulness of generalization and need to be individualized against a physiologic achievement scale. For this purpose the Wetzel grid is helpful. There are striking differences in the growth patterns of the two sexes, as evidenced by broadening



of the pelvis in the girl and of the shoulders in the boy in the year of maximum growth.

**Metabolism.** The basal metabolic rate shows a relative decrease from early infancy until the termination of growth. This trend is interrupted by a relative increase during the two years of accelerated growth that precedes puberty. Determinations made at six-day intervals in the prepuberty and postpuberty periods demonstrate this pattern, though the phenomenon may be obscured by averaging the data rather than plotting them and by the use of chronologic rather than physiologic ages. It is probable that this normal physiologic tendency to an elevated metabolic rate in the prepubertal period is related to the increase in hyperthyroidism during this age period. It explains, too, the sharp increase in the requirements for calories and insulin in the diabetic child as he approaches puberty.

**Calcium and Nitrogen Storage.** Studies of the retention of nitrogen and calcium throughout adolescence reflect, as might be expected from the growth patterns, extremely high retentions preceding menarche and frank depressions associated with the decelerating phase of growth following it. With an adequate intake of protein and calcium and in the absence of disease this depression does not reach the point of negative balance; but with an inadequate diet it may readily do so.

The extent of these differences is indicated in data on three normal girls on whom balance studies were obtained for several months preceding and following menarche. With dietary intake constant, nitrogen retention fell from 3.14 to 1.75 gm. a day; calcium, from 495 to 352 mg. a day. Retention of both substances continues to decline with the decrease in the rate of growth.

**Dietary Requirements.** What is an adequate dietary intake during this age period? In the diabetic child, by using satisfaction of appetite and normal growth as criteria, the caloric requirements can be determined by multiplying Wetzel's predicted basals by 1.9. A much better correlation is obtained in relation to physiologic than to chronologic age (Fig. 30). Though in the diabetic child and the institutionalized patient such estimates may serve a useful function, they are not practical in the average home where the dietary intake is governed by appetite and by economic circumstances. In view of the frequency with which one hears the statement from the overcautious mother, "Of course, I don't allow her to have much meat," it would seem that the provision for protein

and calcium requires definite direction. When the diet is adequate in calories, as judged by satisfaction of appetite and normal growth, 15 per cent of the total calories should be derived from protein in order to maintain a consistently positive nitrogen balance. The adolescent child requires 90 to 120 gm. of protein a day, which can be supplied by one quart of milk, one egg and two slices of bacon, one serving of cheese and a liberal serving of meat at the principal meal. The author has found that the child's appetite for protein is a reliable guide to avoid excessive intake. When an attempt was made to explore the upper limits of nitrogen storage, protein intoxication was frequently encountered when the child's refusal was ignored. The converse, however, is not true. The self-selected diet of the adolescent frequently slights protein in favor of carbohydrate and

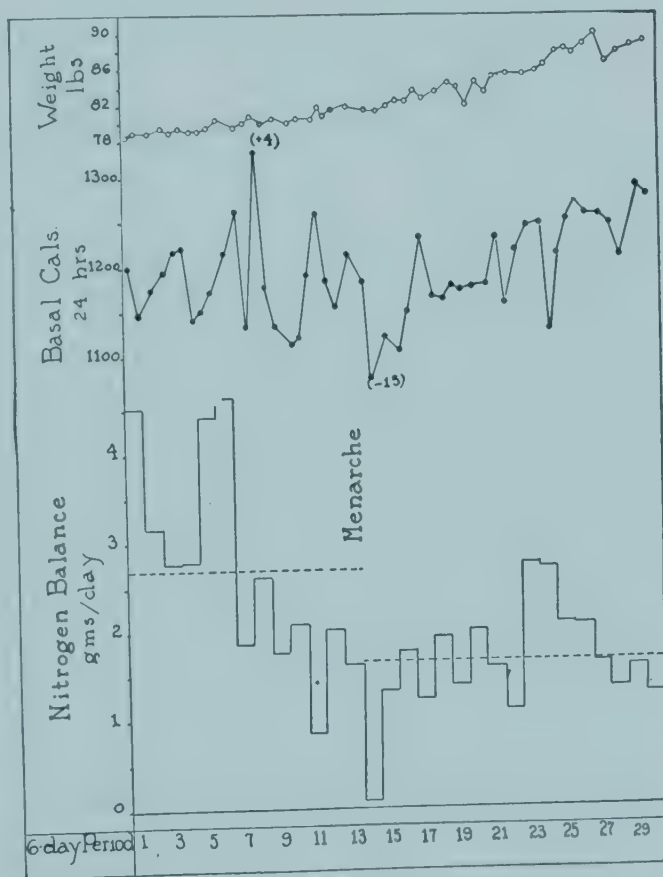


FIG. 29. Metabolism at puberty. The basal metabolic rate is fluctuant in this well trained subject, the range of basal calories being 200. There is a tendency to high rates just preceding and to lower rates following the menarche.

With intake constant, retentions of both calcium and nitrogen were high preceding and depressed following the menarche. This is in keeping with what might be expected from the rates of growth at this time.

## CALORIE INTAKE BY THE DIABETIC

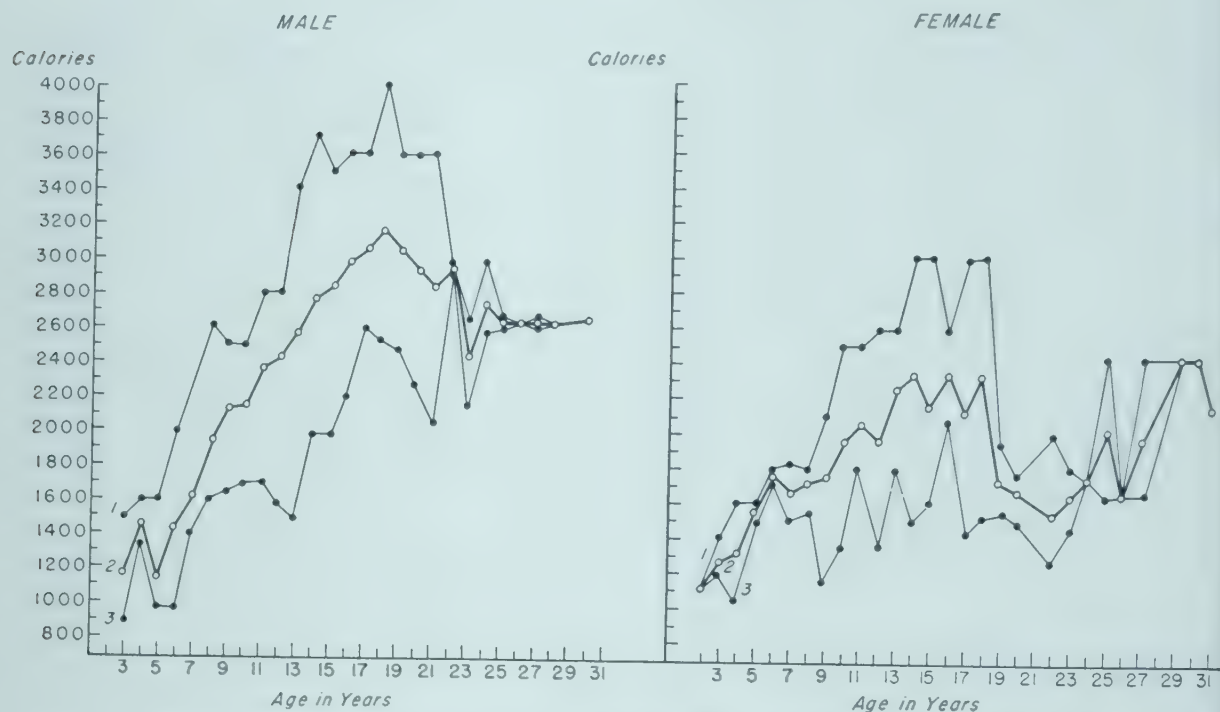


FIG. 30. Caloric intakes of diabetic children by age and sex, illustrating sharp increases with the accelerative phase of growth in the prepubertal and adolescent periods and decreases during the decelerative period of growth.

fat. There is, therefore, indication for defining the protein portion of the dietary intake.

The adolescent's requirement for calcium is approximately 1.3 gm. A quart of milk a day is necessary during the period of accelerated growth, but it is doubted whether this much is required in subsequent years. For the obese child on a reducing diet the proportion of calories derived from protein should be increased to 20 per cent, and, if the intake of milk is less than a quart a day, the calcium deficit should be supplied by a calcium salt. The usual 1-gm. wafer of dicalcium phosphate contains 0.2 gm. of calcium. Vitamin D (about 1000 I. U. per day) is essential for adequate absorption and retention of calcium during the growth spurt of adolescence.

**The diabetic adolescent.** As might be anticipated from the pattern of growth, the caloric intake of the diabetic child increases rapidly during the accelerative phase, declines during the decelerative phase, and stabilizes when growth has terminated. Fig. 30 illustrates these changes in a group followed into adult life.

Vascular complications made their first appearance in this group only after the dia-

betic state had existed for more than eleven years. Examination of the fundus, determination of blood pressure and urinalyses for abnormalities other than glucose should be routine in this age group. In our experience there was good correlation between the development of these complications and the degree of control of the diabetes.

**Tuberculosis.** The sharp increase in mortality from tuberculosis during adolescence and the fact that this increase is manifest in the girl about two years before it is in the boy suggest that something inherent in the metabolism of this period has an undermining influence on a quiescent lesion or on susceptibility to a new infection. In 1000 children with apparently healed primary lesions who were removed over a period of twenty years from homes where there was active tuberculosis to tuberculosis-free foster homes, twenty reinfection lesions appeared after the break in contact. Two thirds of these were in girls, the majority of whom were between eleven and seventeen years of age. The mean menarcheal age was a year earlier than average. Metabolic studies carried out during the course of their infections showed a striking correlation between the healing of disease and the retention of nitrogen and calcium. Unin-



errupted healing was accompanied by strongly positive balances, whereas spread of the lesion was preceded and always accompanied by negative balances (Fig. 31). It would seem that anything which might be a factor in the production of a negative balance (inadequate diet, deviations in basal metabolism, acute or chronic infection or too great an expenditure of energy) may play a role in the flare-up of disease at this time. Supervision of the child with a quiescent tuberculous lesion necessitates provision in this age period for a diet especially adequate in protein, calcium and vitamin D. Thyroid function should also be evaluated. A record of the time spent in school and extracurricular activities will often reveal an expenditure of energy incompatible with the demands for normal growth and development, and, as a corollary, for the integrity of the healed lesion.

**Osseous Development.** In general, epiphyseal closure marking the completion of skeletal growth coincides with the attainment of sexual maturity and correlates better with physiologic than chronologic age. Growth in the extremities ceases before that of the vertebral column. Flory noted the relation of the appearance of the sesamoid bone at the distal end of the first metacarpal to maturity; he observed no girl who menstruated before its appearance. Maresch believes that when fusion of the capitulum of the humerus to the shaft has occurred, the main growth spurt is over, and, in the girl, menarche might be predicted in the following year.

**Osseous disturbances.** The striking changes in growth rates before and after puberty reflect changing rates of speed in osseous growth and probably play a prominent role in the bone disturbances of this age period. Park and others have called attention to definite rachitic changes in this age group.

Perhaps the outstanding osseous disturbance of adolescence is the so-called slipped epiphysis. The etiology of this condition is still a matter of conjecture. The average age in the recorded cases is twelve years for girls and fourteen to fifteen years for boys, ages corresponding to the phase of maximum growth. Characteristically, the patient is tall and heavy, but not the typically fat child. The author has studied the calcium balances of seven children with this condition. Five of them were studied postoperatively, so that their poor retentions might have been the result of the trauma of surgery and of inactivity at bed rest. Nevertheless, in three of

them the administration of vitamin D increased the retention of calcium. Howard observed similar results in children with fractures. Administration of thyroid extract and

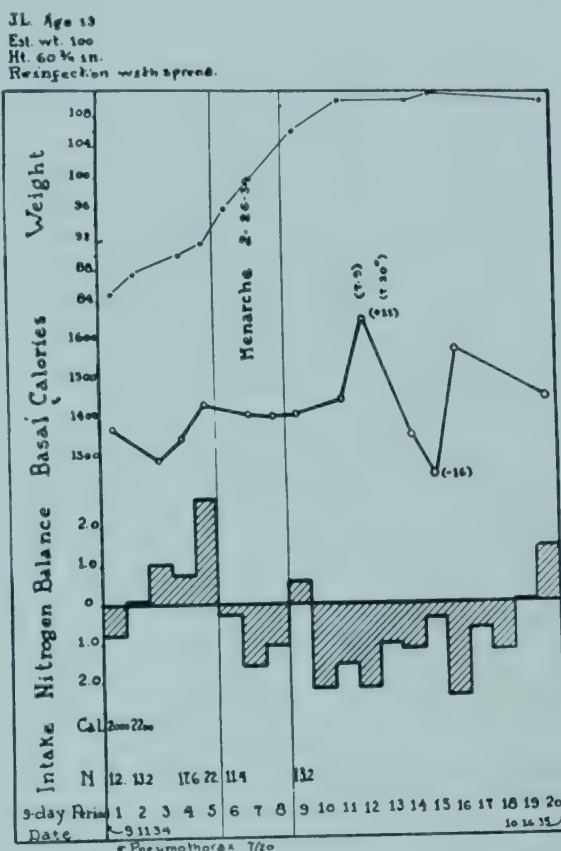


FIG. 31. Metabolism at puberty with spread of a tuberculous lesion of the reinfection type. A girl 13 years of age with an apparently minimal tuberculous lesion of the reinfection type, while being studied to determine nutritional requirements during the adolescent period, gained steadily in weight during the first 45 days, but showed a positive nitrogen balance only with high intakes of nitrogen. The basal metabolic rate was +2 (+5 by Talbot height standard), but it declined gradually. The negative balance at the menarche could be attributed to a diminished intake, but immediately after the menarche the balances were negative on amounts which before the menarche gave positive balances. In the twelfth 9-day period a rise in basal calories occurred from 1409 calories to 1655 (—5 to +11 Boothby; —2 to +18 Talbot), and at this time there was detected a frank spread of the tuberculous lesion which required therapeutic collapse of the lung.

Though cause and effect are difficult to separate, the author's favorable experiences (as measured by gain in weight and by retention of calcium and nitrogen) in the management of children with minimal tuberculous lesions by simply maintaining them at bed rest leads him to conclude that menarche in this girl resulted in an untoward effect on metabolism which favored spread of the tuberculous lesion. Roentgenographic evidence of extension of the lesion was already present when the peak metabolic determination was obtained.

testosterone reduced the retention of calcium. Any method which would effect a normal retention of calcium would seem to offer a contribution to prevention and therapy. It is suggested that this type of child should receive larger than average intakes of calcium (at least 1.5 gm.) and vitamin D (2000 units) during the preadolescent spurt in growth.

Vertebral epiphysitis occurs in the phase of decelerating growth, at the time when leg length has reached its limit, but there is continued growth of the vertebral column.

**Anemia.** There is a significant increase in hemoglobin between the ages of eleven and fifteen years. In the prepuberal period it is the same for both sexes, but, after puberty, the female level is 2 gm. below that of the male level. In the older literature "chlorosis of puberty" was described as a common condition. Though its incidence is now much less, hypochromic anemia occurs sufficiently often in this age period to be considered a cause of fatigue and fainting.

**Thyroid Disturbances.** Most instances of hyperthyroidism among children occur after ten years of age during the prepuberal and early adolescent periods. This relative increase reflects the instability of basal metabolism during these age periods. Mild hyperthyroidism is encountered which, with high caloric diet, elimination of strenuous school schedules and the administration of iodine, seems to terminate with the attainment of sexual maturity. The management of severe disturbance requires more active therapy (p. 1173). Since a fall in the basal metabolic rate is anticipated after menarche, the medical management of hyperthyroidism should be more effective at this age than at other age periods.

In the author's experience, which may be influenced by residence in a goiter belt, hypothyroidism is common in the period just following the onset of sexual maturity. The features which have suggested it have been chiefly (1) delay in growth and development, (2) mental retardation, (3) fatigue, and (4) menstrual disorders. The effect of thyroid at this period is anabolic, and administration of thyroid extract to correct a deficiency will result in gains in height and weight. Hypothyroidism is rarely a factor in the obesity of adolescence, in which basal calories are usually elevated. Hypothyroidism is often suggested because progress in school is unsatisfactory. One of the effects of therapy is an increased span of attention. The menstrual disturbances include scanty or profuse flow

and too short or too prolonged intervals between menses.

There is lack of agreement on the dosage of thyroid extract for hypothyroidism at this age. Administration to "tolerance" would seem to be unjustified, since with such amounts the initially sought anabolic effect on nitrogen and calcium is reversed. It is rarely necessary to use more than 90 mg. of U.S.P. thyroid extract for even the severe cases. When there is an inadequate response to this dose, the intake of protein should be investigated, or, when the initially low blood pressure is not elevated, the adequacy of adrenal function should be determined.

**Obesity.** The subject of obesity is discussed elsewhere (p. 354). The author agrees with Bruch that deficiency of the thyroid is rarely a factor. When the basal metabolic rate of a group of children was determined by Wetzel's standard, the average correction in obese children was 20 per cent. Thus, when a calculation on the conventional surface area method was recorded as -20, the rate by the Wetzel prediction would be normal. The control of weight of greatly obese children by a diet high in protein, calcium and vitamin D, but low in calories, is indicated. In addition, investigation of the behavior problems common in this group is an integral part of the management. Some of these children will have hunger contractions at more frequent intervals than usual, probably as a result of their more rapid utilization of glucose. The high protein-low carbohydrate diet, particularly for the morning meal, is useful in allaying this symptom.

**Secondary Sex Characteristics.** In the order of their appearance these are, in the girl, (1) increase in the transverse diameter of the pelvis, (2) development of the breasts, (3) change from alkaline vaginal secretion to a strongly acid one, (4) appearance of pubic hair and (5) of axillary hair. The first menstrual period tends to occur between the appearance of the last two factors.

In the boy the puberal phenomena make their appearance over a two-year period in the following order: (1) increase in size of the testes and penis, (2) swelling of breasts, (3) appearance of pubic, axillary and facial hair, (4) change in the voice, and (5) production of spermatozoa. This last item is not practicable of demonstration, but is considered to coincide with curliness of the pubic hair.

**Sex Hormones.** That puberal development is subordinated to skeletal growth for a period of years is evidenced by the fact that though



the androgens, or male sex hormones, and the estrogens, or female sex hormones, both show an increase by about seven years of age in both sexes, the great increase does not occur until the prepubertal period.

**Hypogenitalism in the Male.** (See p. 195.)

**Menstruation.** American girls have an average age at onset of menstruation of thirteen years, the range being between eleven and fifteen. Only 3 per cent will begin earlier and 3 per cent later. From growth records the onset can be predicted as likely to occur following the maximum increment of growth in height; except in those who menstruate early, it is likely to occur in the same year. Probably because the cycles are anovulatory, irregularity in interval can be expected in the first year. When irregular intervals or a prolonged or scanty flow persists into the second year after menarche, the factors discussed below should be investigated.

**Menstrual irregularities.** Most complaints of adolescents and their parents that relate to menstruation stem from failure to appreciate one or more of the following: (1) the wide range of age at onset of the menarche; (2) the normality of irregularity in the first year; and (3) the fact that a normal cycle is more closely related to general factors of health than to any specific hormonal defect.

In a study of fifty girls with menstrual disturbances serious enough not to be dismissed as "physiologic variants" the following factors seemed to play some role in etiology:

1. **NUTRITION.** There were five examples of malnutrition and five of obesity. The correction of either state may be all that is necessary to influence favorably the menstrual irregularity, but this may not be simply a matter of diet. One fifteen-year-old girl who had failed to menstruate for six months was profoundly malnourished because of a caloric intake of only 900 calories. Her basal metabolic rate was minus 25. She was attempting school work far beyond her capacity and had become depressed by her inability to keep up with it. As a result she had anorexia of nervous origin; the depressed metabolism was a function of her low intake. Only when her school problems were adjusted did she eat normally, and, with an adequate intake, her menses were resumed.

In obesity of adolescence a low calorie-high protein diet will effect a loss of weight. It is important to inquire why a child is overeating, since few children eat excessively except as a solace for social inadequacy. Correction

of the underlying emotional difficulty constitutes the real solution.

2. **EXERCISE.** The teen-age girl seems to go to extremes on activity; there is either too much in the way of athletics, or, in her concern over her scholastic curriculum, she gets no exercise at all. Each may be expected to influence the menstrual cycle, presumably through fatigue on the one hand, and through the depression of metabolism that results from inactivity on the other. In an industrial plant employing a large number of teen-age girls as office clerks a study was made of absenteeism resulting from dysmenorrhea. One group of girls was placed at complete bed rest during the menstrual period, whereas another group participated in active sport (basketball) followed by hot and cold showers. There was a significant shortening of the duration of the complaint in the latter group. Ewing eliminated the complaint in 50 per cent of 500 girls with a regimen of postural correction and exercises. The Mosher exercise, consisting in contraction and relaxation of the lower abdominal muscles independent of breathing, was used. He also stressed the need for correction of constipation.

3. **PSYCHOGENIC FACTORS.** Such disturbances seemed to play a causative role in 12 per cent of our series. The girl who is "straining her I.Q." in a discouraging attempt to do schoolwork beyond her capacity and the girl whose overambitious parents permit a full school schedule to be supplemented with hours of music practice and social engagements may show evidence of strain by a disorder of the menstrual cycle. A physician at a woman's college reports that during the first semester of the freshman year she expects a majority of the class to have an interruption of the menstrual cycle; this is attributed to two main concerns: attainment of passing grades and acceptance by a sorority.

4. **THYROID DISTURBANCE.** The normal tendency for the basal metabolic rate to be elevated before and depressed after the menarche results in a number of instances in which this physiologic change is extended to abnormal levels. Within the limits of physiologic variation the changes can be ignored, but, when they extend beyond these limits, the disturbed state will be reflected in an abnormal menstrual cycle. We have observed mild degrees of hyperthyroidism, evidenced by nervousness, sweating, elevations in pulse rate and pulse pressure, and increased metabolic rate, which responded to treatment with rest and iodine, which, in turn, was followed

promptly by appearance of the first menstrual period. In the group of fifty girls with menstrual disturbances the metabolic rate was determined in thirty-four. It was elevated in ten and depressed in eighteen. Of the latter, sixteen were benefited by therapy with thyroid extract. A low metabolic rate is not equivalent to the diagnosis of hypothyroidism, and a depressed rate may be observed with an inadequate intake of food.

5. ORGANIC LESIONS. In the study there were five girls who had organic lesions: two with cystic endometritis, two with ovarian cysts and one with an adenomyoma. Though the majority of menstrual disturbances in the first few years following menarche reflect general disturbances capable of being evaluated and treated by the pediatrician, no case should be followed long without gynecologic consultation. To resort to it routinely may result in psychic trauma and may defeat management which otherwise would require only a common-sense direction of activities.

JOSEPH A. JOHNSTON

#### REFERENCES

- Abernethy, E. M.: Correlations in Physical and Mental Growth. *J. Educ. Psychol.*, 16:458, 1925.
- Boas, F.: Studies in Growth. *Human Biol.*, 4:307, 1932.
- Bruch, H. B.: Obesity in Relation to Puberty. *J. Pediat.*, 19:365, 1941.
- Crampton, C. W.: Physiological Age, a Fundamental Principle. *Child Development*, 15:1, 1944.
- Dimock, H. S.: Rediscovering the Adolescent. New York, Association Press, 1937.
- Ewing, R. E.: A Study of Dysmenorrhea at the Home Office of the Metropolitan Life Insurance Company. *J. Indust. Hyg. & Toxicol.*, 13:244, 1931.
- Frank, L. K.: General Considerations; Certain Problems of Puberty and Adolescence. *J. Pediat.*, 19:294, 1941.
- Howard, J. E., and others: Studies on Convalescence IV. Nitrogen and Mineral Balances during Starvation and Graduated Feeding in Healthy Young Males at Bed Rest. *Bull. Johns Hopkins Hosp.* 78:282, 1946.
- Hurxthal, L. M.: Hypogonitalism during the Usual Time of Puberty. *J.A.M.A.*, 136:12, 1948.
- Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in the Growth Period. II. Puberty in the Normal Girl and in the Girl with Minimal Reinfection Type of Tuberculosis. *Am. J. Dis. Child.*, 59:287, 1940.
- Johnston, J. A., Manson, G., and Mitchell, C. E.: Epiphysiolysis. *A.M.A. Am. J. Dis. Child.*, 92:337, 1956.
- Joos, T. H., and Johnston, J. A.: A Long-Term Evaluation of the Juvenile Diabetic. *J. Pediat.*, 50:133, 1957.
- Lewis, R. C., Duval, A. M., and Iliff, A.: Effect of Adolescence on Basal Metabolism of Normal Children. *Am. J. Dis. Child.*, 66:396, 1943.
- Mills, C. A., and Ogle, C.: Physiologic Sterility of Adolescence. *Human Biol.*, 8:607, 1936.
- Shock, N. W.: Effect of Menarche on Basal Physiological Functions in Girls. *Am. J. Physiol.*, 139:288, 1943.
- : Physiological Changes in Adolescence, Forty-third Yearbook. Part I, of the National Society for the Study of Education, 1944, pp. 56-79.
- Shuttleworth, F. K.: Sexual Maturation and Physical Growth of Girls Age Six to Nineteen. Monograph of the Society for Research in Child Development, National Research Council, 1937.
- Simmons, D.: The Brush Foundation Study of Child Growth and Development. II. Physical Growth and Development. Monographs of the Society for Research in Child Development, 1944, Vol. 9, No. 1.
- Stone, C. P., and Barker, R. G.: On the Relationship between Menarcheal Age and Certain Aspects of Personality, Intelligence and Physique in College Women. *J. Genet. Psychol.*, 45:121, 1934.

## PSYCHOLOGIC ASPECTS OF ADOLESCENCE

Adolescence is a long and indeterminate period of growth and development in which the young person experiences profound changes in physical development, in attitudes, in conduct and in the organization of his total personality. He does this without divesting himself of many of the characteristics which have become part of him in his development through childhood. Something of every stage of his emotional growth remains as he approaches maturity. During adolescence adjustments must be made which are not only satisfying to the child, but which must be acceptable to the community. Although he normally reverts on occasion to

earlier and less responsible ways, for the most part he proceeds on new terms with himself and his family. The adolescent may be regarded as striving for self-realization as an adult, being both stimulated and threatened by profound physical changes and consequent thoughts and feelings, and by conflicting demands of a world not certain whether to treat him as a child or a young adult.

A child who has grown to puberty deprived of security through the affection of parents, friends and others is likely to show neurotic patterns during the normal conflicts of adolescence. The child who has been over-restricted is insecure. The adolescent de-



velops best when he has received basic security in the family unit without being enveloped in ties that bind him to dependent relationships. Some attitudes and behavior which resemble symptoms of maladjustment in childhood or adulthood may be said to be normal in adolescence. Any adolescent on occasion finds the demands of his radically changing world too much to deal with; accordingly he fluctuates between extremes of behavior. In adolescence he manifests independence and self-reliance without the judgment and experience which it is to be hoped he will later acquire.

### PROBLEMS OF PHYSICAL HEALTH

Physical and psychic changes may appear suddenly, especially in girls at the onset of menstruation, or more slowly over a period of a few years. A physical awkwardness often develops which must be sympathetically handled, since it is a source of much embarrassment and emotional strain. Adolescence is characterized by changing attitudes toward self, personal relationships and basic social institutions. It is important for the pediatrician to be aware of the growing child's changing attitudes because they are related to physical changes which appear at this time.

Both boys and girls begin at this time to take a careful interest in clothes and personal appearance. The desire to excel in sports is increased; dancing becomes an important part of existence; social clubs, cliques and "gangs" are formed; clubs, fraternities and sororities are joined; and automobiles, cinema stars and far-from-classical music become absorbing interests. The children become noisy and bouncy and introduce themselves unmercifully into the serenity of the adult's life. Although this behavior may superficially appear to be due to emotional and social growth, it is related intimately to physical development. For example, the adolescent's interest in clubs and in his personal appearance hinges on the feelings and attitudes and the beliefs and misconceptions he has about his physical state. In physical health he is in a somewhat precarious position. He has a greater tendency to metabolic disturbances and is more susceptible to some infectious diseases than he was in the preceding period of development. It is possible that growth processes themselves are attended by feelings of anxiety manifested by physical discomfort and even symptoms of illness. Physical illness also may be the result of the child's effort to cope with his emotional prob-

lems. Such symptoms as anorexia, overeating, aches and pains, fatigue, palpitation, breathlessness, and urinary and fecal incontinence may appear.

When physical illness appears, the adolescent may react to it as if it were a threat to his prestige, to his ability to compete with his peers. He experiences deep anxiety about his physical state; frequently he overcompensates for a physical deficiency by attempting to excel in some other direction of physical exercise, trying to develop a robust physique which will overshadow deficiencies. Occasionally when the adolescent feels at a disadvantage physically, he strives to overcompensate by intellectual achievement. Physical difficulties are often concealed, or the child may have complaints about conditions which he imagines are developing. And yet, while he has a tendency to fear illness and to consider himself potentially sick, he also tries to deny the existence of any such incapacity. The surface complaints which bring him to the pediatrician often are physical. They may or may not have emotional beginnings. Many somatic difficulties in adolescence due to psychologic difficulties have their beginnings during infancy and childhood, being precipitated by stresses and strains of the teen-age period.

It is not always easy to see the interrelationship between the physical complaints and emotional disturbances. There is a high correlation between difficulties in social adaptation and excessive interest in the body. This may be true when an organic lesion exists or when the complaint is merely a somatic correlate of an anxiety state. Such complaints often take the form of hypochondriasis.

A frequent complaint is related to the skin. Acne represents a disfiguring condition to the adolescent, who reacts by withdrawing from social relationships, fearing that his whole future is jeopardized. The attitude of exaggerated concern should attract the attention of the pediatrician, and therapy should be aimed at helping the child with his feelings of concern as well as the acne. If attention is focused merely on treatment of the skin, the acne may disappear, but the child's concern will be directed to other cosmetic conditions.

Faulty nutrition, either real or fancied, excessive fatigue, body aches and difficulties of sleeping should also be considered, not only in a narrow physical sense, but also in terms of the total organism. Poor eating habits may lead to either malnutrition or obesity. The reasons for not taking food are often due to

self-imposed limitations, and overeating as an outlet for feelings of tension may be the cause of obesity. Psychologic concomitants of such chronic diseases as diabetes and heart disease should be sought and considered in planning a medical regimen.

Adolescents with physical handicaps are able to make a healthy personal and social adjustment if in their early life they were given a reasonable economic and emotional security by parents who had accepted them fully in spite of their physical incapacities.

Frequently there are disturbed familial and childhood relationships. Often one or both parents are neurotic, and the child has been reared in an environment lacking the security of normal parental affection. Intense hostile and dependent attitudes develop, and the child takes on pregnancy fantasies and defenses against the possibility of growing to maturity. These young people are extremely disturbed, and the problem is primarily one for psychiatric treatment. The obese child is fat because of an excessive appetite. He usually has anxiety and feels incompetent to enter into the activities of adult life. Overeating represents a regressive reaction with further repression of sexual strivings. The obese adolescent seems to revert to an essentially dependent state, expressing this in a retreat to gratification through the mouth such as he exhibited normally in early infancy and childhood. Here again the psychologic condition is complicated and responds best to psychotherapy.

In both sexes there is concern about breast and genital development. In the girl there is interest in body contour and size of breasts. Frequently girls who feel that they are in danger of becoming too large or who believe that their breasts are unusually big, restrict their dietary intake to an extreme degree.

In the male, concern about penis size and descent of testes is a chief complaint in this age group. Sometimes the anxiety has been projected from the parent to the child and represents the parents' own sexual maladjustment, which now expresses itself in overconcern for their child's development, which may be proceeding in a normal fashion.

### SEXUAL PROBLEMS

Sexuality and interest in sex begin before puberty, although there is an increase in sexual impulse at this time. Infants and preschool children show an interest in all parts of the body, the sexual organs exciting no unusual interest. Soon, however, there is

interest in the genitals because of the pleasurable reactions that follow manipulation, whether this be accidental or deliberate. The preschool child is interested in the genitals of his age-mates and begins to recognize the differences of the sexes. There may be experimental play between children as well as exhibitions of prowess and demonstration of body parts at any age period from now on. With puberty there is an increased modesty which began to be evident around five and six years of age, but is now accompanied by an increased curiosity in the function of his own body and that of persons of the same and of the opposite sex.

Sexual problems may arise at any time in the life of the growing child. They stem, in most instances, from a clash between the pressures and demands outside the child (his family and culture) and his inner urges and drives. The anxiety which is a by-product of such a clash may show itself in a number of ways, one being heightened sexual excitability and excessive sexual manipulation. Shame and guilt are frequent accompaniments of masturbation in the adolescent; these feelings may also be felt about menstruation and nocturnal emissions. Such misconceptions may be abetted by a rigid tradition in the home toward sex. An unusual degree of anxiety may also be focused on the homosexual interest which normally comes during puberty and early adolescence.

The adolescent strives to handle the problems inherent in making a sexual adjustment by various methods. These range from defiance of traditional rules of conduct by promiscuity, to the other extreme of ascetic denial of sex impulses. Promiscuity is fairly frequent and arouses much concern in the public because of its extreme and often delinquent quality. Contrariwise, those persons who have unnaturally repressed their sexual impulses receive scant attention because they are more socially acceptable. This group is probably larger than the group of delinquents and also is in need of consideration.

### SEX EDUCATION

Since sexual development is continuous from infancy through adolescence, it should be clear that there is no special sex education of the adolescent. Sexual education is a process which goes on with sexual development. It is true that questions and problems of sex and sex behavior need to be handled differently at various ages, but sexual education should never be considered merely a matter



giving a child the facts of life at a given age. The sexual orientation of the mature adult results from a synthesis and integration of attitudes and values which as a child he experienced with parents who themselves were mature sexually as well as in other respects. The experiences of being loved and cared for in infancy, of being identified with a healthy father and mother, of living with brothers and sisters, and of playing with other boys and girls, result in a broad education which includes sex education. The adolescent with sexual problems may be helped by discussing them with someone acceptable to him, such as a relative, an educator, a nurse or a physician. Simple explanations will help in the re-education of the person who comes for help, but the greatest helpfulness will come from a relationship with an adult to whom the adolescent may entrust his feelings and in whom he may find a sympathetic and understanding listener, who does not condemn or necessarily condone, and who is held in high esteem by the child.

#### SCHOOL PROBLEMS

Many school problems arise because the child has difficulty in learning or keeping up with a pace which is too rapid for him. The adolescent may have difficulty in making an adjustment in high school because the pace is accelerated over that of the grade school or because of problems of his own which inhibit his capacity to study. For some the period of readjustment is short and transient; for others it is long and in an unsympathetic school system may persist. Occasionally, increased pressure from parents will also add to the burdens at this time. Having a larger body, he is now expected to have a greater efficiency and to be able to participate in many more activities. On the contrary, the adolescent may be less able to meet these new demands. Many school problems could be prevented if educators and parents became aware of the differences of the adolescent not only from his age-mates, but also from his previous self. A school system which attempts to deal with the whole child, not only in learning and teaching, but also in physical, emotional and social development, will combine the forces of the educator, school physician and guidance counselor with the parents in planning school activities. Too frequently the child straining for academic achievement is prevented from full development of abilities which are within his reach, owing to the pressures of school and family. The physi-

cally or intellectually handicapped child suffers when his intellectual limitations are not recognized and when his parents and the school do not face the problem realistically.

#### THERAPY

Treatment of the problems of an adolescent entails an understanding which can be achieved only by separate interviews with the child, his parents and educators. The adolescent can be helped only when he is willing; he is resistive when he feels that parents or others are coercing him. Any relationship with an adolescent which he initiates or believes he initiates has the possibility of being of therapeutic value. The adolescent at this phase of development is especially sensitive to the personality and attitudes of the adults with whom he has contact. Teachers and physicians even more than relatives are in a position to help the young person at these times, but only when trust and confidence are felt toward them. Accepting an adolescent as a person approaching adulthood rather than as a child will have a good influence on the insecure adolescent. The parent frequently has difficulty in accepting the adolescent on these terms and hence can serve less objectively, in the therapeutic sense, than professional people. The physician who encourages the adolescent to review his life story and permits a discussion of life situations which are disturbing in terms of his family and personal content without assuming the attitudes of the family members toward him will be able to help in the solution of his problems. An occasional physical examination may also serve as reassurance that there is no disease. The pediatrician can help the adolescent further by working with parents and others who are intimately concerned in his day-to-day welfare. The adolescent's concern and feelings of shame about any of the parental characteristics are normal, and in the more sensitive child are a source of much secret conflict leading to rapid fluctuation between rebellion and sudden gushes of contrite affection. A discussion with parents about the reasons for the rebellion and an explanation of the striving for independence and the craving for dependency often help to clear misunderstandings. No advice or regimen will make adolescence easy, but parents and children often may be helped by a therapeutic relationship with someone outside the family in whom each has confidence. The role of the pediatrician may be enhanced if he has taken care of the adolescent since early

childhood, or it may be hindered if the adolescent resents taking help from "a baby doctor."

One important role of the pediatrician is the safeguarding of the adolescent's physical health and growth. Much has already been said of the heavy physiologic demands in this period of development. Evaluation of every disorder, whether psychologic or physical, should include an appraisal of general health, nutrition, sleep patterns and general activity, keeping in mind the metabolic and infectious disorders prevalent in this age period. *The adolescent must be considered a human being rather than a "case study in pathology."* Since physical complaints are frequently the first manifestations of underlying psychologic disorders, the physician is often the first one called upon for help. Hence he is in a strategic position for recognition of the early stages of severe mental illness by interpreting the psychologic undercurrents of the physical complaints. The adolescent's concern about normality may resemble the hypochondriacal state of adults and should make the physician suspect beginning maladjustment. Help at this time may prevent a more severe breakdown later.

In the event that no physical abnormality is found, the verbal reassurance that nothing is wrong, and hence that parent and child need not worry, is usually ineffective. The concern of the patient often reappears if it has been temporarily removed. It is important that the physician not get caught in the position of simply "telling" the adolescent some-

thing or "giving" him something, but rather should permit him to *talk out* and so gain some awareness of the cause of his difficulties and some insight into their origin. This does not mean that educational and vocational guidance and change of oppressive environmental factors should not be offered. The patient should have an opportunity of returning for interviews, but these should not be forced on him. When adolescents or their parents are not reassured by such psychotherapeutic endeavors, one should suspect psychologic difficulty which warrants psychiatric consultation and treatment.

The pediatrician should view his psychotherapeutic task as twofold: (1) the *relief* of immediate problems, and (2) *prevention* of mental health problems through helping the adolescent to adjust not only to his adolescent period, but also to the responsibilities and stress of adult life and eventual parenthood. *The pediatrician has an opportunity in the field of preventive psychiatry not only during adolescence, but also throughout the lifetime of the infant and child.*

MILTON J. E. SENT

#### REFERENCES

- Frank, L. K., and Frank, M.: *Your Adolescent at Home and in School*. New York, Viking, 1956.  
 Josselyn, I. *The Adolescent and His World*. New York, Family Service Association of America, 1952.  
 Lerrigo, M. O., and Southard, H.: *A Series of Pamphlets on Sex Education*. Chicago, American Medical Association, 1955.



# General Factors in the Care of Sick Children

## CLINICAL APPRAISAL OF INFANTS AND CHILDREN

The pediatrician has the opportunity and the responsibility of developing a balanced, comprehensive approach to evaluation of the subtle psychologic components in disease and to the promotion of emotional as well as physical health in the child and his family. For a variety of reasons hospital-trained physicians often tend to rely too heavily upon laboratory data in their evaluation of the sick child. In so doing they may neglect the manifold clinical impressions and behavioral data available from careful observation of the child and of the interactions between parent and child.

For example, flaring of the alae nasi, shallow respirations with expiratory grunting, restlessness, suprasternal and substernal retractions, and visible disturbances of the peripheral circulation may provide vital clues to an impending state of cardiorespiratory collapse in an infant with serious tracheobronchitis in an early but rapidly advancing stage. Such signs may be present on inspection before physical, roentgenographic and laboratory data reflect the gravity of the situation. Failure to recognize the import of early signs often leads to serious consequences which might have been avoided. Similarly, reliance upon the absence of abnormal physical and roentgenographic findings in a three-year-old child with a history of persistent, nonproductive cough may lead to a strenuous and expensive course of laboratory study or to an unreassuring diagnosis of "no disease." More careful observation of the interaction between mother and child and more painstaking investigation of the history might have revealed that the cough had originated with a mild and transient coryza at the time of the birth of a new sibling and occurred later only when the preoccupied mother picked up the young infant. Data of this kind can lead to demonstration of a psychophysiologic com-

ponent in such a symptom and may permit a more rational approach to management.

Certain basic principles involved in the clinical examination of infants and children from this comprehensive point of view include the following:

1. Health is more than the absence of disease, and a dynamic approach is as essential to its assessment as it is to the investigation of disease.

2. Clinical study is based upon a holistic concept of the functioning of the human organism; physiology and behavior cannot be placed in separate compartments.

3. The etiology of disease involves multiple factors; whether the disorder is predominantly somatic or psychologic, predisposing, contributory, precipitating and perpetuating forces are involved. For the full understanding of any clinical condition the study must include genic, constitutional, physiologic, psychologic and interpersonal factors.

4. The family is the ultimate unit of clinical study and must be considered from the epidemiologic standpoint for both infectious and psychologic disturbances. The child cannot be studied in a vacuum.

Since the parent cannot assess accurately the technical competence of the physician, it is his manner which most effectively permits the development of confidence in him. Such a feeling *may* exist whether medication or other treatment is provided. Some parents unconsciously endow the physician with almost magical attributes, and others have unhealthy patterns of dependence which prohibit them from taking simple and obvious steps without consulting him. Among the negative parental attitudes are fear of criticism, distrust or suspicion, fear of domination or resentment toward authoritative figures. Such parents may be unable to utilize

effectively the services of the physician. Most parents, however, are able with judicious help to establish an effective relationship with the physician who is caring for their child.

The attitudes of children toward the physician are modified by those of their parents and by their own experiences. Most emotionally healthy children are able to overcome their inevitable anxieties and to develop trust in the physician. The child who is acutely ill may regress emotionally, however, and behave like a much younger child even with a physician whom he knows. Fears of pain or of the unknown and fears of going to the hospital and of being separated from the parents play an important part at such times.

The wise and experienced physician who works with children develops a capacity to view the behavior of the parent and the child as data regarding their personalities and their interaction, data which can be added to his clinical findings and may be of importance in the approach to management. In addition to sympathy and understanding, he intuitively has the capacity to put himself in their places and to sense their perspectives. With such an approach he is less likely to interpret a depressed parent's apathetic response as unconcern about the condition of the child or less inclined to label parents "uncooperative," "unreliable" or "rejecting" on the basis of first impressions.

## HISTORY

The leads which arise in securing the history during the initial interview will determine in part the points of emphasis in the physical examination and the selection of laboratory studies. Of equal importance is the opportunity for the physician to begin the establishment of an effective relationship with parent and child. The quality of this relationship will influence both the accuracy of the data obtained and the response to therapeutic measures or to anticipatory guidance. Thus the initial interview helps to establish the psychotherapeutic role of the physician. In later interviews the physician enlarges and at times revises his initial impression. It should be recognized that different physicians will apply the principles of the interview in individual ways. The physician should feel comfortable with *his* interviewing technique rather than attempt to imitate too closely that of someone else.

The following outline of information to be sought in the pediatric history is modified

from the traditional format and is intended only as a guide. Lists of this kind, however necessary, tend to promote in the student a check-list approach in history taking, which may seriously inhibit the parent's spontaneous and more detailed remarks.

The tendency to record the family or social history as "noncontributory" is a pernicious one, arising in part from the check-list practice. The details of the family's living circumstances, their position as members of a particular minority group, the chronic depression of the father over unsatisfying work experiences, the part-time work of a mother coming just at the child's bedtime, and other similar factors may be as relevant to assessment of the child's health status as factors relating directly to a physical illness. In all instances it is important to determine whether there is or has been familial illness which may be relevant to the child's illness. The experienced physician will avoid, however the monotonous listing of all possible illnesses, a feature which frequently confuses parents and may arouse resentment or self-blame in them. Rather he will inquire about symptoms causing illness or death.

In securing details of the child's birth, growth and development, past illnesses and parental child-rearing practices, it must be remembered that the average parent has difficulty in recalling such items with accuracy. Subsequent recollections or other sources of data, such as "baby books," may serve to amplify the initial recollections or to correct them. Complete blocks initially to memory of feeding, toilet-training or other similar experiences may indicate that particular difficulty or conflict was encountered at such times, and subsequently acquired data may establish the nature of it. For these reasons the physician should not place undue reliance on such data secured in the first interview.

Obviously, not all the potential information listed below can be obtained in the initial interview. In recording the history it is important to list pertinent negative items, in order to indicate that all possible aspects of the problem have been considered.

*Identification of Informant:* Initial description of parent or informant (if not parent, state relationship to patient), manner of giving data, and apparent accuracy. Evaluation of emotional state of other factors which might bear on accuracy of data.

*Chief Complaint or Complaints:* In terms of parent or child.

*Present Illness:* Date of onset and initial symptoms.



toms. Careful description of kind, duration and degree of symptoms. Chronologic progress or change in symptomatology, including details of any therapy. Correlation with significant life events. Health prior to onset. Pertinent epidemiologic information (exposure to illness, potential carriers, animal or insect vectors). Effect of illness on behavior or adjustment of patient and family. Pertinent negative data.

#### *Past History:*

#### 1. *Developmental Survey*

*Prenatal:* Health, nutrition, attitudes and emotional state of mother during pregnancy. Illnesses during pregnancy, toxemia, diabetes, cardiac disease, depression. Health and attitudes of father during pregnancy. Living circumstances of family during pregnancy. Fetal activity.

*Birth:* Date; weight; premature or term; birth order. Nature of birth; presentation; use of forceps; cesarean section; length of delivery; degree of difficulty.

*Neonatal Condition:* Spontaneous respiration; difficulty in resuscitation; respiratory distress; degree of activity; jaundice; cyanosis; convulsions; paralysis; hemorrhage; stupor; difficulty in sucking; rash; sniffles; congenital anomalies; intractable crying. Mother's condition; reaction to baby.

#### *Feeding:*

*Infancy:* Breast- or bottle fed; if artificial feeding, when started, type, frequency, amount taken; hunger. Relationship of feeding to stools; infant's response to feeding; paroxysmal fussing; sleep; vomiting; regurgitation; mother's feelings about feeding of infant; attitudes and degree of help by father.

*Supplementary Vitamins:* Age when begun; regularity of administration; amount taken; duration.

*Solid Foods:* Time of starting various items; infant's response; rashes; feeding difficulties if present, nature, time of onset.

*Weaning:* Breast to bottle or breast or bottle to cup; reason weaned; time started; length of time required; infant's response, negative reactions if present; mother's attitudes.

*Childhood:* Child's appetite; food likes or dislikes; feeding difficulties if present, nature, struggles over feeding, parents' attitudes toward food and feeding.

*Discipline:* Parents' methods; child's acceptance; negativism; tantrums; rebelliousness; aggressive or destructive behavior.

*Habitual Reactions:* Age of occurrence, degree, duration of nail-biting, thumb-sucking, rocking, head-banging, pica, rituals, others.

*School Adjustment:* Preschool experience; age of entrance into school; adjustment; attitudes and reactions of child and parents toward separation; child's adjustment (school phobia, withdrawal, aggressive behavior, day-dreaming); child's and parents' attitude toward school program; achievement or intelligence tests; child's progress.

*Social Adjustment:* Early response to separation from mother; child's relationship to peers; degree of independence; adjustment in group situations; degree and nature of participation in scouting and other group activities; difficulties in adjustment (aggressive, withdrawn, oversubmissive) if present; attitudes of child and parents.

#### *Growth and Development:*

*Psychomotor:* Age of control of head; hand-to-mouth coordination; social response; sitting, with support and alone; creeping; differentiation between parents and strangers; standing; walking, with support and alone; speech, babbling, first words, brief sentences, complicated expressions; disturbances in growth patterns, delay, regression; difficulties in coordination; speech disturbance, hesitation, stammering, infantile speech, aphasia.

*Weight and Height:* Approximate weights at one year, two years, five years, ten years; steadiness of gain; growth spurts; disturbances if present, obesity, weight loss, growth lag; reactions of child and parents.

*Sleeping Patterns:* Amount of sleep in relation to age; nightmares; disturbances in sleep rhythm; attitudes of child and parents.

*Toilet Training:* Bowel and bladder; time begun; methods used; age control achieved; difficulties if present; later relapses in control, enuresis or encopresis; parents' attitudes.

*Sexual Development:* Child's questions regarding conception, pregnancy, or differences between boys and girls, information given; preparation for menarche, age of onset, secondary sex characteristics, girl's reaction; preparation of boy for puberty, age of onset, secondary sex characteristics, boy's reaction; parents' attitudes and feelings; attitudes toward nature of relationship with opposite sex; acceptance of male or female role; occurrence of masturbation; difficulties in sexual adjustment if present, attitudes of child and parents.

#### 2. *Medical Survey*

*Prophylaxis:* Immunizations against smallpox, pertussis, diphtheria, tetanus, poliomyelitis, scarlet fever, typhoid fever, Rocky Mountain spotted fever, yellow fever; age at immunization, number of injections, booster shots, untoward reactions; evidence of artificially induced immunity, scar of smallpox vaccination, Dick and Schick reactions, if done; tuberculin and serologic tests for syphilis.

#### *Specific Illnesses:*

*Contagious Diseases:* Measles, rubella, exanthem subitum, pertussis, chickenpox, smallpox, scarlet fever, diphtheria, mumps, poliomyelitis, others; age at illness, degree of severity, complications.

*Other Illnesses:* Listed according to system involved; age, severity, treatment, sequelae; reactions of child and parents to treatment, hospitalization, or to any continuing disability or treatment; reaction to serum, blood or blood derivatives, chemotherapeutic or

antibiotic agents, if administered.

*Allergic Reactions:* Eczema, asthma, hay fever, urticaria, hypersensitivity reactions to inhalants, food, drugs, contact with cloth, soaps, and so on.

*Operations:* Dates, nature, results; complications or sequelae; reactions of child and parents.

*Injuries:* Dates, nature and circumstances of accidents, sequelae; nature of study and treatment; reactions of child and parents.

### Review of Systems

*Head:* Headache, trauma.

*Eyes:* Vision, glasses, strabismus, pain, inflammation, diplopia, other disturbances.

*Ears:* Hearing, pain, discharge, tinnitus.

*Nose:* Discharge, epistaxis, obstruction, disturbances in olfactory sense.

*Teeth:* Extractions, disorders in dentition, abscesses, general condition.

*Mouth:* Mouth-breathing, sore mouth, sore tongue, caries, bleeding gums, taste.

*Throat:* Pain, infections, tonsillitis, difficulty in swallowing, hoarseness.

*Neck:* Masses, pain, stiffness, cervical adenitis, thyroid enlargement.

*Respiratory:* Frequency and nature of colds, cough, sputum, hemoptysis, stridor, foreign bodies, croup, bronchitis, asthma.

*Gastrointestinal:* Appetite, food idiosyncrasies, vomiting, abdominal discomfort or pain, constipation, diarrhea, encopresis, character of stools, jaundice.

*Cardiovascular:* Dyspnea, cyanosis, edema, precordial pain, palpitation, syncope.

*Genitourinary:* Enuresis (diurnal or nocturnal), frequency, urgency, dysuria, circumcision, vaginal discharge, menstrual disturbances.

*Musculoskeletal:* Weakness, joint or muscular pain or swelling, posture, muscular coordination, deformities, fractures.

*Nervous:* Sleep disturbances, tics, tremors, vertigo, twitchings, convulsions, ataxia, paralysis, projectile vomiting, shortened attention span, distractibility.

*Skin:* Eruptions, congenital anomalies, itching, pigmentation, erythema, blushing, bruising, petechiae.

### 3. Family Survey

*Parents:* Age; occupation; state of physical and emotional health of each parent or parent substitutes, currently and at important points in patient's illness; if parents not living, age at death, cause, and nature of symptoms; adequacy of marital relationship; individual attitudes of parents toward patient and toward child-rearing practices; previous pregnancies of mother, outcome, nature of abnormality; brief summary of family circumstances; socio-cultural and ethnic backgrounds from which each parent derived; current state of health of grandparents (if not living, age at death, cause, nature of symptoms, age of patient at time of grandparents' deaths).

*Siblings:* Age; where living; state of health (if not living, age at death, cause, nature of symptoms, age of patient at time of death); general

school and social performance; nature of relationship to patient; attitudes of parents toward patient in relation to siblings.

*Living Circumstances:* Place; nature of dwelling; nature of sleeping arrangements; number of persons living in home in addition to parents and children; nature of relationships of such persons to family members; members of family who work; working hours if unusual; general level of economic independence, support from community agencies if any; neighborhood circumstances; available recreational outlets.

*Familial Illnesses or Anomalies:* Tuberculosis, syphilis, diabetes, cancer, epilepsy, rheumatic fever, allergy, hereditary blood dyscrasias (including Rh status if known), mental illness, mental retardation, dystrophies, congenital anomalies, heredo-degenerative diseases.

*Summary:* A brief recapitulation of the essential features of the present illness or the current state of health if the child is being seen for a health examination; significant correlations between features of past development or illness and significant life events or family circumstances; essentially an organization and synthesis of the historical data into meaningful trends, so far as they can be seen up to this point.

The recorded history of the experienced physician may more closely approximate an expanded summary rather than the basic outline suggested, but for the person in training an outlined plan is essential. With the use of the general approach indicated it is possible to secure psychologic and social data at the same time as somatic factors are explored.

The most valuable aid to the establishment of a positive relationship with the parent and to the attainment of accurate historical data is the manner of the physician, who communicates nonverbally his interest and confidence in the parent through his facial expression, tone of voice, and posture. An unhurried, accepting, respectful and noncritical mien, even if time is limited, is most important, and privacy is essential.

Young children of preschool age are usually seen with the mother. The physician may wisely give the child a toy, appropriate to his age level from a varied supply available in his office, or may offer him a throat stick or other object with which to play. Such an approach indicates to the parent the physician's interest in the child and provides a beginning positive contact with the child. If the parent's concern is the child's behavior, or if the parent talks too freely about the child's personality, the physician may prefer, with the help of a nurse or secretary, to interest the child in some play activity in the waiting room while he talks with the parent.



With older children and young adolescents it is best to see the parent and child together at the first interview, since an anxious or suspicious child may fear that the parent is imparting secret information to the doctor. If it is necessary to see the parent alone for free discussion of emotional problems, this may be done at a later separate interview. Occasionally, if the parent wishes to discuss some urgently disturbing aspect of the child's behavior, the initial interview may be without the knowledge of the child; at this time it can be decided whether the child should be seen alone or with the parent. Whenever both parents can be seen together, with or without the child, valuable impressions may be obtained regarding their relationship, their attitudes as parents and their attitudes toward the child and his illness or adjustment.

If the child is acutely ill, the physician should take only a brief history relative to the current illness before beginning the physical examination. Subsequently the history should be completed.

**Interview with the Parent.** At the outset it is important to permit the parent to talk freely without significant interruption about the problem which concerns her most. Leading questions must be avoided. Even if the physician's time is limited and the parent's initial comments seem confused, too detailed, or irrelevant to the child's obvious condition, the parent should be allowed to talk freely and to set the pace, for at least a brief time. Such a practice permits the parent to talk about the main source of concern and helps to strengthen her impression that the physician values her observations. In addition, the act of talking helps to discharge initial tensions and thus to assist her in overcoming anxiety or fear about the doctor's findings or opinion. Experienced pediatricians have found that a few extra minutes during the initial interview will save time later. With such an approach it may become apparent that the declared reason for a visit or the stated "chief complaint" may not be the source of the parent's concern. For example, the mother of a mildly obese boy of nine, who seeks guidance about his weight, may indicate with some embarrassment in the course of such a relaxed interview that her real concern is the apparent small size of his genitals.

As the interview proceeds the physician may ask pertinent questions about particular details of importance or to round out areas of information left untouched. Rather than rapid-fire questions which permit only a

mechanical "Yes" or "No" answer and preclude any initiative on the parent's part, the physician can use general questions such as, "Can you tell me a little more about his difficulty in breathing?", or, "How about toilet training?" At times he may simply repeat a key word or phrase, indicating by his inflection encouragement for the parent to elaborate. An approach of this kind will permit the parent to bring out many important facts which might otherwise be forgotten or pushed aside as insignificant. In a health examination the parent may thus bring up pertinent data or urgent questions about feeding, weaning, toilet training, the handling of discipline, accident prevention and other vital topics. Some parents may react with oversensitivity or suspicion if the physician focuses too closely on their own behavior or background, at least in the initial contact, before a trustful and secure relationship has developed.

Certain historic data may carry an emotional charge for the parent, and revelations of fact may be painful and difficult. This is particularly true of the history of familial illnesses and emotional disturbances in child or parent. For example, some parents of children with seizures may be unable to disclose during the initial interview the presence of epilepsy in close relatives, because of their fear that they have been personally guilty of transmitting the illness. Parents also recognize that their feelings about the child may be involved in disturbances of his behavior. Thus in following up leads to possible psychologic problems or in asking questions dealing with areas of behavior, it is important not to adopt too frontal an approach, which the anxious parent may misinterpret as a critical attack. Questions such as, "Did you want this child?", "Does your son masturbate?", or "Was she jealous of the new baby?" are all too frequently doomed, in the initial interview, to receive conventional and socially acceptable replies or to be answered with defensive indignation. Such information is important, but must be gathered initially by inference or by the use of less loaded and indirect questions, such as, "Were you able to plan the pregnancy for this child?" or, "How did she seem to take the new baby's arrival?" Later, when a positive relationship has been established with the parent, more detailed and accurate information of this kind may be obtained.

At times parents may become silent or may fail to answer a question, especially if it carries emotionally charged implications. At such points it is wisest for the physician to hesitate

for a moment or two. Much highly significant verbal or behavioral data may emerge under such circumstances, which would only be inhibited by premature shifting of the topic or by too rapid reassurance. The observation of nonverbal behavioral data, such as blushing, nail-biting or neuromuscular tension, may give important clues to be followed later. The practice of expectant waiting is vital even if the mother appears on the verge of tears. The physician can, with practice, curb his natural social impulse to stem the expression of strong emotion, such as an outburst of crying by a tense and troubled mother. The release of such feeling in a sympathetic atmosphere may be of real help to the parent and may strengthen the relationship with the physician. The physician may indicate simply that he understands and avoid any immediate attempts to assuage such seemingly illogical feelings.

In closing the initial interview it is wise to return to the area of the parent's major concern, which may not always be the initial complaint. Such a step provides an opportunity for the physician to ask questions arising from the leads which he has gained up to this point. This technique also gives a kind of closure to the interview which indicates to the parent that the physician has comprehended fully her concern and will endeavor to deal constructively with it during further studies.

**Interview with the Child.** With a preschool child or with a child who is acutely ill the factual information gained from talking with him may be of little value. With older children, however, the data obtained can be of real importance, particularly as to how the child regards his illness, any consequent physical limitation or his state of health in general. Occasionally only the child has the pertinent information, as concerning some toxic substance accidentally or intentionally ingested or the subjective quality and the location of pain or discomfort. While interviewing the parent it is possible to interject questions to the older child, thus making him feel that he is involved in the solution of the problem.

With the preschool child one may learn a good deal in a few moments of casual observation of his play during the interview with the parent, especially if toys are provided. One may obtain impressions of the level of his development from the degree of complexity and organization of his play, the length of his

span of concentration, his drawing, and other factors. His attitude toward the physician, often reflecting parental anxiety, may also be apparent in his drawings, his play with dolls or his general demeanor.

With the older child, interviewed separately or with the parent, verbal data may be much more accurate and voluminous after a positive relationship has been established. In the first contact, school-age children may be inhibited and withdrawn in the face of anxiety without any deep underlying emotional disturbance or limitation in intellectual capacity. The wise physician will avoid premature judgment as to the child's capacity for adjustment. With the child who is old enough to talk freely one can and should gain impressions, even in predominantly somatic illness, of the meaning to him of his symptoms or disability, in terms of its effect upon his adjustment at school, his status with his peer group, and other factors. With frightened or withdrawn children, data of this sort may have to be sought indirectly by asking them for their aspirations, what they wish for most, what they would do if they were well, or even what a hypothetical child might wish for or do in a particular situation.

In early contacts with children, whatever the problem may be, it is wise to avoid questions of anxiety-provoking potential, such as those about sex activity and hostile feelings. The child is not accustomed to discuss such matters comfortably with adults and may become more inhibited or deny any such activity or feelings. Later he may be able to unburden himself to the physician, finding this more neutral but understanding relationship a safe one in which to discuss topics which he may have difficulty in bringing up with his parents.

**Observation of Child and Parent.** The importance of careful inspection of the child and of detailed observation of the parent-child interaction is unfortunately frequently overlooked. Such rich clinical impressions are available to the physician from the moment the parent and child enter his office and indeed may be obtained by him or by an alert nurse or secretary even during glancing observations in the waiting room. For example, pallor, dyspnea, extreme inactivity or listlessness, significant overactivity and short attention span may easily be recognized. Disturbances in gait, limitations in the use of a limb or the degree of exercise tolerance permitted by a congenital cardiac anomaly will



often be much more accurately assessed during casual observation of the small child's play than during the formal examination.

In addition to such clinical data, the physician may obtain important impressions regarding the interaction of child and parent. The school-age child who clings anxiously to the parent and the parent who appears over-protective for the child are readily apparent. Some parents cannot permit the child to answer a question independently, manifesting the need to dominate the child or the situation. Other parents may constantly correct the child or require him to sit impossibly still, indicating unrealistically high standards of conformity. If the father and mother are interviewed together, they may disclose disagreements in child-rearing practices. A few parents pay too little attention to their children, such as the mother who does not stand close to her infant to prevent his falling off the examining table. Occasionally, disturbed parents unconsciously may need to deny the extent or seriousness of the child's obvious illness and to belittle him or to urge him to act "as if he were well." Even balanced and effective parents may exhibit some of these behaviors at times of anxiety. The wise physician will note such impressions and test them against later observations. Such data may later be vitally important in approaching the management of a negativistic diabetic child, for example, or in understanding the sources of overdependent behavior. Observational data of this sort are more readily available to the physician who visits the family's home and enjoys continuity of contact with the parents and child over a long period of time. On a home visit the standards of parental care and the pattern of family living are much more obvious.

## PHYSICAL EXAMINATION OF THE CHILD

In this section certain basic principles involved in the direct study of the child will be presented; no attempt will be made to discuss in detail the techniques of physical examination. Some thought should be given to the appearance and arrangements in the office or the examination room. Most pediatricians recognize that children respond to bright colors. It is further known that white is a cold and strange color to the small child; pastel colors achieve a cheerful and familiar effect. The room should contain some pictures and other colorful items.

**Approach to the Child.** The physician will

have gained certain impressions during the taking of the history of the child's general physical and emotional state, and the nature of any illness, as well as of the interaction between child and parent. With this background he may turn to the child at an appropriate point. He can anticipate active participation in the examination by the child, but he should be prepared for resigned submission, passive resistance or, more rarely, active refusal or violent battle. The degree of rapport established with the child and the parent may determine the diagnostic success of the examination. Subtle changes in cardiac or chest sounds, for example, cannot be detected effectively by auscultation in the loudly crying, squirming child, nor can ocular fundi or deep tendon reflexes be accurately appraised. It is necessary at times to examine acutely ill children during states of crying or resistance; at such times there is no substitute for experience, skill and clinical judgment. In the seriously ill child the physical examination may be combined with the latter portion of the history to save time and to decrease the suspense of the anxious child and the parent.

The child should ordinarily be undressed by the mother or nurse prior to the examination. All clothing should be removed from young children. It is well to remember that refusal by preschool children to remove certain items of clothing may indicate anxiety over being so completely exposed rather than sexual modesty. This initial apprehension should be respected; it is ordinarily soon overcome. Older children may retain their underpants, with temporary dropping for genital examination when the child is at ease.

No matter what the circumstances, the physician must at all costs preserve a relaxed and unhurried approach. A few moments spent initially in conversation with the child about a doll or in admiring an item of clothing, using the child's first name or nickname, may save valuable time and considerable struggle. However, the physician must avoid being overlong in the initial preparation. Tension in both child and parent may build up if the examination is postponed too long, no matter how well-meaning the physician may be in his preparatory efforts. Some explanation of each step, as in examining the throat or darkening the room for ophthalmologic examination, can be given in a quiet and soothing voice, using terms the child can grasp. Although it is important for the physician to be able to relate to the child, he

should not lower himself to the level of the child; he must remain an adult in the child's eyes. It is axiomatic that the child be told the truth at his level of understanding whenever uncomfortable procedures are to be performed; any other course will detract seriously from his later trust or cooperation.

The young child may be permitted to explore certain instruments such as the stethoscope before they are used; attempts at listening to themselves or their dolls may be enjoyed and may overcome tension. "Blowing out" the light of the otoscope is a time-honored pediatric detractor for the toddler.

*Special types of handling are required for infants and children at their different levels of development.*

With the very young infant little difficulty may be encountered if the mother is relaxed and trusting. Pacifiers may be used to diminish crying or restlessness. If feeding time is imminent, much of the examination may be carried out while the mother holds and feeds the infant. An excellent opportunity is thus afforded for the young mother to bring out questions or fears about the infant's body or stage of development.

In the latter part of the first year most infants show some fear of the physician, even if they have seen him regularly for health examinations. This change represents the developing capacity of the infant to distinguish strangers from the mother and his growing awareness of himself as an individual who may be separated from the familiar parent. This phase may persist well into the second year. At this stage it is wise to avoid sudden moves or loud vocal tones in the direction of the infant. The physician may offer the mother a throat stick or similar object to give to the infant while he sits in her lap during the interview, permitting him to appraise the physician from a safe vantage point. If he is crawling or toddling, the infant may later move toward the physician during the history and make overtures himself, thus effecting a more successful relationship than if he is approached.

At this age infants often resist examination on their backs on an examining table, and it is best to examine them on the mother's lap, permitting her to hold his head against her shoulder for examination of the ears and throat. Often the nurse may be able to obtain a more positive initial response from the older infant than the less familiar male physician with a deeper voice. Anxiety or even terror

initially by the infant need not be considered by the physician a sign of failure.

During the latter part of the second and most of the third year the child often exhibits so-called normal negativism, reflecting a healthy drive toward independence and aggressive self-assertion. Asking a child of this age to perform a particular step in the examination, such as opening the mouth, almost invariably results in a firm "No." Patience is of the essence. A stubbornly negativistic child may, if interested in some other activity, later become suddenly able to overcome his previous rebellious stand. Battles almost inevitably result in loss of trust in the physician.

The preschool child can ordinarily be examined on the table. Most children at this stage, however, are frightened when they have to lie down, and they feel less anxious in a sitting position. Each move should be explained briefly, with time permitted for spontaneous questions.

With children of school age, as with older preschool children, much can be learned during the physical examination about the child's attitudes toward his own development, his feelings about himself or herself as a developing boy or girl, and his concern over minor blemishes or abnormalities. If the child feels secure with the physician, he may himself bring up his fears or misconceptions. At times the parent also will bring up similar concerns during an unhurried examination.

With preadolescents and adolescents modesty may become an important feature in the examination. Respect for such feelings should prevail, and children at this stage should be handled in relatively the same way as adults. Adolescent boys may entertain fears about a growth lag bearing upon their ultimate masculinity, or they may have concerns about other deviations from the normal. Adolescent girls may exhibit parallel concerns, particularly around the onset of the menses and the development of secondary sex characteristics. A nurse should be in the room during the examination of girls of this age.

**Approach to the Parent.** Some busy and impatient physicians prefer to exclude anxious mothers from the physical examination, recognizing that the child often submits more passively in her absence. This approach carries with it not only the pain of separation for the young child, particularly acute for the overdependent and frightened child of an overanxious mother, but also the implication for the child of punishment by the physician.



The parent, too, may react with feelings of guilt and at times resentment because of her fear that the physician believes she is a poor parent. It is almost always wisest to permit the parent to remain with the infant or young child.

At times a particularly apprehensive parent will ask to leave during the physical examination and should ordinarily be permitted to do so, preferably before rather than during the examination. Occasionally an extremely difficult situation arises in which the child clings dependently to the mother or father, who is too anxious or too helpless to assist the child in going through with the examination. If patience and preparation of the child fail and he is not acutely ill, the examination can often be held to absolute essentials on the first visit, with postponement of other details and routine laboratory procedures to a later visit. If the child is acutely ill and must be examined thoroughly, it can be suggested to the parent without criticism that the examination may be upsetting to her and that she may prefer to wait outside, the nurse taking her place. Some parents can remain and relax in such situations if the responsibility for gentle but firm restraint of the young child is taken over by the nurse.

If the mother leaves the room, it is wise to tell the child where she will be and when she will return. If restraint is indicated under such circumstances, it should be carried out promptly after a brief explanation of its need.

**Method of Examination.** In examining children it is important that instruments applied to the skin, such as the stethoscope, be warm. It may be of help, with a young or anxious child, to rinse the hands in warm water before beginning the examination, since any coldness to the touch may add to the child's fear or resistance.

The usual order of procedure in the examination of adults is not appropriate for young children. In general, it is wiser to begin with a peripheral and neutral step, leaving the more sensitive head and associated structures until later, in order not to frighten or arouse resistance. This approach may vary with the age of the infant or young child as well as with circumstances surrounding the examination. For the older infant deep tendon reflexes may be a suitable point of departure. Some physicians may find it more effective to use the stethoscope, first playfully on the legs, then abdomen, and finally chest. With the preschool child listening to the chest may be the appropriate opening move. An occa-

sional child is made more anxious by waiting too long for the anticipated and disliked throat examination, and in such instances it may be wiser to perform this earlier. When restraint is required, the need for it should be explained, and then the examination should be made with as much dispatch as is commensurate with gentleness and thoroughness.

Pulse and respiratory rates and blood pressure levels in infants and young children are variable and may be altered by fear or apprehension. Only persistent deviations can thus be relied upon. In young children, in particular, temperature may also be influenced by emotions or activity. Rectal temperatures may be elevated as much as a degree Fahrenheit immediately after active exercise, whereas the oral temperature usually is not. Oral temperatures may be altered immediately after ingestion of hot or cold substances. Rectal temperature recordings are generally considered to be nearly a degree higher than oral ones, but there is a lesser difference if each recording is made appropriately. Rectal temperatures are preferable in infants and small children. Preschool children may resist this approach, although not yet able to retain the thermometer safely by mouth. In such a situation an axillary or groin reading will give an approximate figure, at least a degree lower than an oral reading, which may suffice for the moment.

Examination of the heart and lungs is complicated in infants and young children by the thinness of the chest wall and the consequent relative loudness of breath sounds. Sounds resembling bronchial breathing are frequently heard over the right upper lobe in normal chests. The physician must learn to listen quickly and accurately during periods of freedom from crying or other vocal activity. Many young children cannot cooperate easily on tests for tactile fremitus or vocal resonance. Advantage must be taken of spoken words, the use of a "blowing" game or even periods of crying.

In examining the abdomen of a child considerable time must be spent in putting the child at ease in order to achieve sufficient relaxation of the abdominal musculature. Talking with the child is often helpful in diverting his attention. If the child is old enough to respond to a request to take a deep breath, the pressure of the physician's hand can be increased gently with each inspiration without undue voluntary resistance.

For children beyond early infancy rectal examinations may be disturbing and need not

ordinarily be included as a part of the health examination. Inspection of rectal and genital areas can be done routinely, and a rectal examination carried out if indicated. Caution should be observed in this procedure or in vaginal inspection with preadolescent or adolescent girls, since their apprehension and misconceptions about such manipulations may be extreme.

After the examination the child should be given time to ask questions, if he desires, about procedures or instruments used or about any other phase of the examination. The physician should always terminate the interview with a friendly and personal farewell to the child.

### LABORATORY DIAGNOSTIC STUDIES

The indications for specific laboratory or other diagnostic tests are discussed in the sections on specific diseases. Routine procedures in the course of any clinical examination should include hemoglobin, white blood cell count and differential, urinalysis and a tuberculin test. Routine serologic studies for syphilis have been discontinued in some pediatric clinics.

When additional laboratory studies are contemplated, they should be critically selected on the basis of their relevance to the problem at hand. Many physicians recognize that it is best to disturb the seriously ill patient as little as possible by venipuncture or other tests which involve vigorous moving of the patient or the possibility of the arousal of anxiety. Tests vitally necessary to the diagnosis and determination of the course of treatment should of course be done. Nevertheless patients in cardiac failure, for example, can be detrimentally affected by a battery of tests as a result of the effects of fatigue and anxiety upon the cardiorespiratory system. Possible secondary effects, such as subdural effusion arising from use of the pneumoencephalogram, should also be considered. Internal and external jugular punctures have fortunately been largely abandoned in infants in favor of femoral punctures or other less potentially physically traumatic procedures in securing blood. The need for interpreting carefully the indications for laboratory tests to anxious parents is fundamental in any diagnostic approach.

When painful procedures such as throat cultures, venipunctures, blood cell counts, intradermal tests, as well as more involved procedures, are to be performed, it is essential

that the child be told briefly what will happen in terms he can understand. He can be told that a finger prick or venipuncture is necessary in order to choose the right medicine to "help his throat stop hurting" or some such simple and concrete explanation. The child should be given enough time to ask questions in advance of the procedure. Sufficient explanation should be given to the parent also, even about brief and simple procedures. If restraint is indicated, the child should be told that his arm or other body part will be held in order to help him hold still so that the procedure will be less painful. Many well adjusted parents cannot hold children for painful procedures involving the sight of blood, and the nurse may do this more effectively, the parent remaining in the room if possible. Too long a period of anxious questioning and delay may permit the build-up of excessive anxiety.

After the procedure many younger children and even those of school age cry briefly. The child should not be made to feel that he should not cry or that it is "bad" to do so. If parents express this attitude, as many do, because of fear of criticism by the physician, it is wise to indicate that it is difficult for the child not to cry. In addition, the recognition of the fact that the doctor is not angry or critical is important to the child and the parent. In certain instances the physician may let the child know also that he realizes that the child may be angry momentarily with him for the use of a needle, thus helping the child to avoid the necessity for complete suppression of negative feelings.

Major diagnostic or therapeutic procedures, such as thoracentesis, paracentesis and cardiac catheterization, must of course be carried out in the hospital, and the child should be prepared for admission to the hospital as well as for the procedure itself. Although hospitalization need not be an emotionally traumatic experience, the chances of such an eventuality are great enough that the psychologic aspects of admission and management should not be overlooked. For the child under four years of age, and for some older but dependent or definitely disturbed children, the concomitant separation from the mother, often misinterpreted as punishment, is the most anxiety-provoking aspect of the experience.

With the young preschool child verbal preparation may be of limited value, but should nevertheless be undertaken. Preparation should be discussed by the physician with



the parents, who may have questions, often seemingly irrelevant ones, which may reflect their own apprehensions or a tendency toward self-blame in relation to the child's illness. A period of several days is usually sufficient for the preschool child to bring up questions, misconceptions and potential misinterpretations about the coming experience, which parents can then discuss with the child if they themselves have a reasonably clear grasp of the facts involved. Actual explanation to the young child should be couched in simple terms, related to the need for "getting well" or helping the child's "tummy" to stop hurting. Concrete facets of the experience are best explained, such as the dress of doctors and nurses, the procedures involved in admission, hospital sleeping arrangements, the experience of anesthesia, and the use of bed-pans. A nurse or social worker can be helpful in discussing such factors with the parents prior to elective hospitalization.

The older child can be prepared further in advance in accord with his greater capacities for intellectual understanding and his ability to tolerate, for longer periods of time than the preschool child, the tension involved in the anticipated hospitalization. For preschool and school-age children the opportunity to "play out" feelings of fear or resentment is important, both before and after the hospitalization or painful procedures. Opportunity for the use of dolls, doctor kits, and Plasticine or other play materials should be available to the child for this purpose in the hospital. Occupational therapists or recreational therapy personnel can contribute significantly to such constructive and age-appropriate modes of adaptation.

Frequent parental visiting is valuable in preventing disturbed reactions to hospitalization. Overnight stay in the hospital by the mother may be a most effective support for the young or very anxious child, provided the parent feels comfortable in doing so.

Sedation may be used in preparation of the child for major diagnostic procedures, and general anesthesia with a rapidly effective and short-acting agent may be justified in certain instances. Sedation or anesthesia as aids in the management of a child under such circumstances, however, should not be substituted for psychologic preparation.

Psychologic tests, when indicated for the estimation of intellectual capacity or for the assessment of personality patterns in projective studies, should be performed by a competent psychologist. The physician must

recognize the limitations of a single intelligence quotient, especially with an ill or hospitalized child who has regressed behaviorally and may test below his actual level. Repeated tests and continued study are necessary before a diagnosis of retarded development is accepted in an infant or young child.

The need to take all possible etiologic factors into consideration in arriving at a diagnosis and plan of treatment in a given situation has been emphasized. For example, if a physician is confronted with an initial attack of acute bronchitis, his therapeutic approach is correctly based on the probability of a nonrecurring acute infectious disorder. If the bronchitis recurs several times or continues, however, he must seek further for *predisposing* and *contributory*, as well as for *precipitating*, etiologic factors. After some study it may be found that the child has a *predisposing* allergic diathesis of familial nature. *Contributory* factors may include the presence of chronically diseased adenoids, as well as chronic undernourishment as the result of a feeding problem since early infancy. *Precipitating* influences may derive from incidental upper respiratory tract infections, as well as episodes of exposure to cold weather without sufficient clothing as the result of rebellion by the child against parental overconcern. Chronic sinusitis may be a *perpetuating* factor. In arriving at the conclusion that the foregoing clinical pattern represents the so-called bronch sinusitis syndrome, the physician recognizes the contribution of psychologic or interpersonal factors in the undernourishment and the rebellion against parental overconcern.

In such a comprehensive evaluation concurrent or relevant somatic factors are put into perspective with pertinent psychologic ones. Correlations between significant life events and symptomatic exacerbations, established from the history and observational data, may provide important clues to psychophysiological influences, involving multiple etiologic forces, in many illnesses such as ulcerative colitis, asthma, peptic ulcer, hyperthyroidism. With such an approach the physician will avoid either somatic or psychologic overemphasis.

#### IMPLEMENTATION OF RESULTS OF THE CLINICAL EXAMINATION

Once the physician has achieved a balanced diagnostic appraisal of the child in his family setting, his plan of therapy or his approach

to well-child care must be communicated effectively to patient and parents. He should be confident and at times authoritative in his formulation and recommendations, but humility, patience and understanding remain paramount. In discussing the child's condition with his parents the physician will do well to remember the intense apprehension with which they often await the diagnosis and recommendations. He should repeat in simple language, without recourse to medical terminology, his suggestions for therapeutic plans and write out the detailed or complicated instructions for care. Many parents remain so anxious throughout such a final interview that they may indicate understanding at times when they are too confused to retain details or even to grasp implications. An opportunity for the parents to talk freely

about their reactions will bring out many misconceptions or misunderstandings which must be patiently dealt with if therapeutic or preventive measures are to succeed.

The role of the physician dealing with children and their parents is an exceedingly challenging and uniquely satisfying one. Parents are turning with increasing frequency to the physician for guidance. To bring a comprehensive approach to the clinical examination, the physician must have increased knowledge of human biology in its behavioral as well as its physiologic aspects. With such knowledge he is in the best possible position to foster the detection, treatment and prevention of disease and to assist in the positive promotion of healthy adaptation.

DANE G. PRUGH

## DISTURBANCES OF FLUID AND ELECTROLYTE EQUILIBRIUM

### PHYSIOLOGIC CONSIDERATIONS

Physiochemical conditions in the body are kept within narrow limits of variability by a close integration of various physiologic processes. This tendency to maintain homeostasis is exemplified by the manner in which the electrolyte equilibrium in the blood plasma is maintained in health or disease. Serving as a medium for the transport of metabolic materials within the body, the blood constitutes an internal environment for the tissues; it both affects and is affected by the metabolic activities of all the cells it bathes.

In health the quantity of circulating plasma is remarkably constant, being about 5 per cent of the body weight (slightly more in infants); the interstitial fluids comprise 15 per cent and the intracellular fluids 50 per cent of the body weight (Fig. 32). In abnormal conditions, changes in volume and composition of the blood plasma reflect closely the changes in other body fluids. The total volume of fluids in the body depends primarily on the intake and outgo of water, nutrient materials and metabolic products through the gastrointestinal tract, kidneys, skin and lungs. The water content of the different fluids is closely correlated with their content of salts and, to a less extent, of other osmotically active substances; thus movements of water and salts

into and out of the body and between the various fluid compartments of the body are closely interdependent.

In the gastrointestinal tract a constant turn-

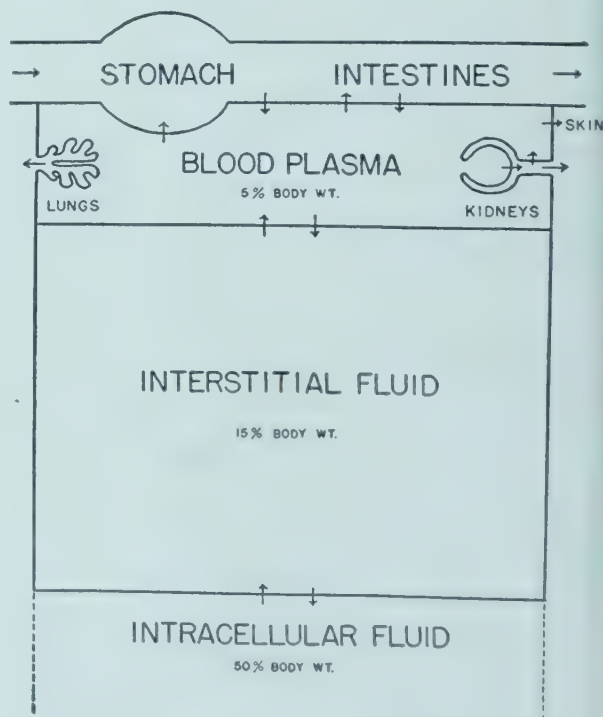


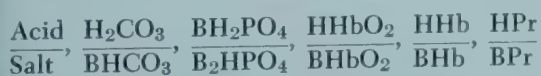
FIG. 32. Distribution of fluids in the body. (J. L. Gamble.)



ver of large quantities of fluid is involved in the secretion and reabsorption of digestive juices, which are practically isotonic with the blood plasma. Failure of reabsorption of these juices, through loss by vomiting or diarrhea, results in depletion of body water and electrolytes. The total osmolarity of the blood plasma tends to be remarkably stable even under conditions involving considerable alterations in its volume and in the concentrations of its constituents. This stability is attained largely through renal mechanisms which serve to control the total concentration of electrolytes in the plasma and to make compensatory adjustments in the concentrations of individual ions when the electrolyte equilibrium is disturbed.

The ionic equilibrium in the electrolyte system is linked with many phenomena of growth, structure and function through the influence of hydrogen ion activity (pH) on enzyme systems and through specific effects of other ions, such as the effects of changing concentrations of calcium and potassium on skeletal and heart muscle, and of carbon dioxide on the respiratory center.

**Acid-Base Relationships.** Normally, blood is kept slightly alkaline, within the narrow range of pH 7.35 to 7.45, by equilibria among a number of buffer systems. Buffers, mixtures of weakly ionized acids and their salts, tend to keep changes of pH minimal when a strongly ionized acid or base is added to their solution. The principal buffer systems of the blood are represented as



(where *B* is "base" or cation equivalents, *Hb* is hemoglobin, and *Pr* is proteins other than hemoglobin).

The ratio between the acid and salt in each buffer system at a given pH depends on the dissociation constant of the respective acid; for the carbonic acid-bicarbonate buffer, the ratio is 1:20 at pH 7.4. Hemoglobin is the most efficient of these buffers, but bicarbonate has special value for defense against increases of anions in the blood, because, when bicarbonate is decomposed by the addition of acid, the lungs liberate and excrete volatile carbon dioxide, thus leaving cations available to neutralize the added acid. Hence bicarbonate has been called the alkali reserve of the body.

Of these buffers, the carbonic acid-bicarbonate system is of most interest to the clinician, because its state is the easiest to determine by simple laboratory methods and

because its correlation with clinical conditions is generally the most apparent. For clinical purposes it is sufficient to say that the pH of the blood depends upon the ratio between the concentrations of carbonic acid and bicarbonate in the blood plasma: i.e., the normal pH value is sustained irrespective of absolute changes in the concentrations of carbonic acid and bicarbonate if the ratio 1:20 between the two concentrations is preserved. Since the concentration of carbonic acid depends upon the rate of formation of carbon dioxide in the body and of its removal from the blood by the lungs, the immediate defense of this ratio is primarily a function of the respiratory mechanism. The concentration of bicarbonate, dependent on the balance between the total cations and the anions other than  $\text{HCO}_3^-$ , is governed by mechanisms of absorption and secretion in the gastrointestinal tract and kidneys that determine the general electrolyte structure of the plasma.

The kidneys control the electrolyte structure of the body fluids by their ability to secrete urine of varying concentration and acidity or alkalinity according to the need for excretion of excess anions or cations. The pH of urine normally is around 6.0, but may vary within the wide range of 4.6 to 8.0. The pH of acid urines is determined mainly by the ratio of acid to alkaline phosphates; the pH of alkaline urines is determined mainly by the ratio of carbonic acid to bicarbonate.

Metabolic activities result in the production of large amounts of acids that require disposal, such as carbonic, lactic, pyruvic, beta-hydroxybutyric, acetoacetic, phosphoric, sulfuric and hydrochloric. In the absence of disease, acid metabolites are transported from their site of formation to their point of disposal with minimal disturbance of the tissues and with minimal alteration in the blood by the buffer systems.

Carbonic acid ( $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3$ ) is the most abundant metabolic product of the body. Though most of the carbon dioxide in the blood is in the form of bicarbonate, that carried by hemoglobin accounts for about 90 per cent of the total turnover of carbon dioxide taken up in the tissues and liberated in the lungs. Rapid release of carbon dioxide in the lungs is mediated by the enzyme carbonic anhydrase in the red blood cells. Phosphoric, sulfuric and hydrochloric anions are excreted mainly in the urine.

Some organic acids, when produced in moderate amounts, may be metabolized by

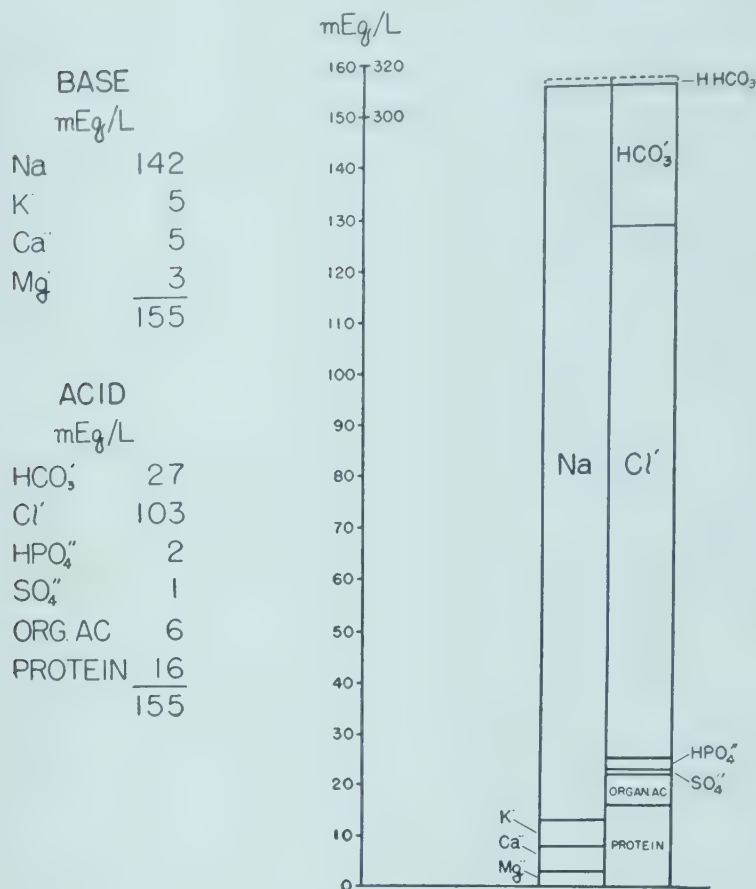


FIG. 33. Acid-base composition of blood plasma. (J. L. Gamble.)

certain tissues, i.e., reutilized to some extent or burned to carbon dioxide and water, but excessive amounts in pathologic conditions must be excreted. The excretion of different anions entails losses of mineral cations from the body according to the kind and amounts of the acids excreted; such losses are kept minimal chiefly by excretion of the anions in the form of ammonium salts and acid phosphates. In extremely acid urines part of the organic acids may be excreted in the free state. On the other hand, in conditions of alkalosis the excretion of bicarbonate by the kidneys serves to conserve mineral anions (as Cl<sup>-</sup>) in the body.

**Cation-Anion Balance.** The "ionogram" in Figure 33 represents the principal components of the plasma electrolyte system in terms of milliequivalents per liter. The expression of the concentrations of the electrolytes in terms of chemical equivalents has great practical value, since the summation of separately determined cations and anions permits ready visualization of the total ionic equilibrium (commonly called acid-base balance) and of adjustments in the electrolyte structure that occur in pathologic conditions.

The electrolyte structure of interstitial fluid is similar to that of plasma except for a low protein content, a slightly lower concentration of total base and a somewhat higher concentration of chloride.

In the soft tissues of the body (intracellular fluid) potassium and magnesium comprise most of the cations, while proteins and organic phosphates comprise most of the anions. Intracellular chemical changes are probably more closely related to functional disturbances than are the better known ones in the extracellular fluids. Changes in the latter provide evidence of factors that affect both the structure and function of the cells by influencing ionic exchanges between them and extracellular fluids.

Two examples serve to emphasize this point: (1) Acidosis has inhibiting effects on several phases of carbohydrate metabolism. Lowered pH of the blood appears to inhibit the action of insulin by interfering with processes of phosphorylation involved in the concomitant cellular uptake (normally stimulated by insulin) of sugar, potassium and phosphorus from the blood plasma. (2) The direction and speed of transfer of potassium



between blood and tissue cells in acidosis and in postacidotic periods of recovery have profound effects on cardiac and skeletal muscle. In acidosis, potassium is liberated from cells, most in the urine if renal function is adequate, or increased in concentration in the blood if renal function is impaired. In the postacidotic period of recovery after acidosis has been corrected, avid uptake of potassium by the cells may result in hypopotassemia. Both hyperpotassemia and hypopotassemia have characteristic effects on the electrocardiogram, and hypopotassemia may result in weakness or paralysis of skeletal muscles.

A relatively few mechanisms are responsible for gross alterations in concentrations of the principal electrolytes in blood plasma. Hyperelectrolytemia and hyperosmolarity of the blood plasma in infants and children may develop under conditions associated with severe water deficit. The concentrations of carbon dioxide and its anion  $\text{HCO}_3^-$  in the blood are governed mainly by respiratory exchange in the lungs. The concentrations of the other electrolytes are governed by their ingress or egress by way of the gastrointestinal tract, kidneys and, to some extent, the skin. Disturbances in the functions of each of these organs may be primary causes of derangements in the electrolyte structure of the body fluids.

## CLINICAL DISTURBANCES\*

### DEHYDRATION

The body suffers from lack of water more quickly than from lack of any other nutrient except oxygen. This is an especially important problem in infancy, in which the requirements for water exchange in proportion to body weight are far greater than in adult life, and fluid balances are more easily disturbed under abnormal conditions. Thus, as Gamble pointed out, the daily intake and output of water is about 700 ml. in an infant weighing 7 kg. whose extracellular fluid is in the range of 1400 ml., in contrast to a daily intake and output of about 2 liters in an adult weighing 70 kg. whose extracellular fluid averages about 14 liters. Normally, fluid balances are maintained despite wide variations in the daily intake and excretion of water and metabolites. These balances are soon disturbed when there is too great a disparity between intake and total expenditure of water or when

abnormal conditions lead to excessive loss or retention of salts.

Depletion of body water in states of dehydration encountered clinically may be initiated by lack of either water or salts or, as is usually the case, of both. Dehydration most often occurs as a consequence of losses in vomiting, diarrhea or diabetic acidosis, but lack of water in itself may be a primary cause of dehydration when there is an inadequate intake of water to cover the obligatory needs for renal excretion, or when there is excessive loss of water vapor from the lungs and skin, as with fever and hyperpnea. Under such conditions impairment of renal function is usually a primary factor or, owing to hemoconcentration, a secondary one.

In severe dehydration, with or without acidosis or alkalosis, oliguria develops; thirst may be present, but is by no means constant. Physical signs are loss of weight, grayish pallor, dryness, inelasticity and diminished turgor of the skin, dryness of the mucous membranes, sunken fontanels in infants, retracted abdomen and collapsed superficial veins. Fever may be due to the dehydration as well as to an attendant infection. Hemoconcentration may be manifest by an elevated volume of red blood cells or by an increased red blood cell count and increased concentration of the serum proteins. These data are not dependable when there is anemia or protein deficiency.

### ACIDOSIS AND ALKALOSIS

**General Considerations.** In clinical usage the term "acidosis" denotes conditions caused by accumulation in the body of an excess of acids (i.e., anions) or by excessive loss of bases (i.e., mineral cations); the term "alkalosis" denotes conditions caused by accumulation in the body of an excess of base or by excessive loss of acid. These conditions are described as *metabolic* when the disturbances arise from faulty intake or output of bases or of acids other than carbonic acid. They are described as *respiratory* when ascribable to disturbances in the respiratory control of the carbon dioxide content of the blood.

In both metabolic and respiratory types of acidosis and alkalosis the terms "compensated" and "uncompensated" are used to denote whether or not the pH of the blood is maintained within normal limits by the buffer systems and physiologic mechanisms that govern the concentrations of different components of the electrolyte system.

When the concentration of blood bicarbon-

\* Parenteral fluid therapy in the treatment of fluid and electrolyte disturbances is detailed in the section beginning on page 183.

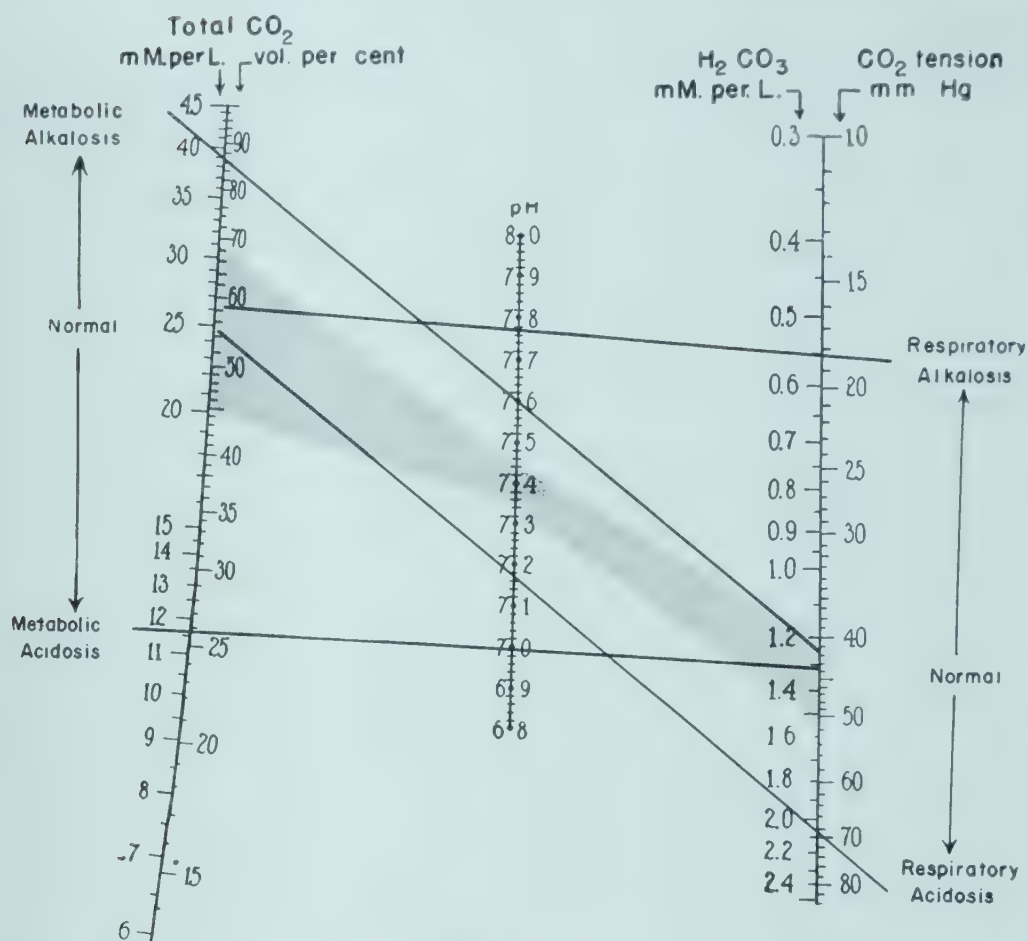


FIG. 34. Nomogram with lines drawn to indicate simultaneously occurring values for bicarbonate, pH and carbon dioxide tension in the blood plasma in normal conditions and in acidosis and alkalosis. A straight line drawn across the chart indicates simultaneously occurring values: thus, if the carbon dioxide content and pH values are known, a line drawn through those 2 values indicates the carbon dioxide tension. (N.B. For  $\text{CO}_2$ , 1 mM. = 1 mEq.) (Adapted from the line chart in Peters and Van Slyke: Quantitative Clinical Chemistry, Vol. 1.)

ate is decreased in metabolic acidosis, central control of the pulmonary mechanism normally leads to an increase in rate and amplitude of respirations (hyperpnea), thereby increasing the removal of carbon dioxide and decreasing its tension in the blood. Conversely, when the blood bicarbonate is increased in metabolic alkalosis, the normal response is a reduction in rate and amplitude of respiration (apnea) until the carbon dioxide tension is increased. In both cases the pulmonary response *tends* to bring the pH value to within normal limits by establishing a ratio approaching 1:20 between the concentrations of carbonic acid and bicarbonate.

In respiratory disturbances, when changes in carbon dioxide tension in the blood are primary, mechanisms responsible for compensative adjustments of other anions in the blood are more obscure, but appear to be governed principally by renal excretion. In respiratory

acidosis, when an excess of carbonic acid accumulates in the blood, chloride leaves the plasma, allowing more bicarbonate ions to be neutralized by sodium; in respiratory alkalosis, when the carbon dioxide tension in the blood is reduced by hyperventilation, the bicarbonate is reduced by a decrease in concentration of sodium and/or an increase of chloride in the plasma.

The fixed relationships among values for bicarbonate, pH and carbonic acid in the blood plasma are expressed in the Henderson-Hasselbalch equation:

$$\text{pH} = 6.1 + \log \frac{\text{BHCO}_3}{\text{HHCO}_3}$$

Figure 34 represents these relationships in a nomogram based on that equation. Data in Table 30 similarly illustrate the relationships among values for bicarbonate, pH and carbon dioxide tension of the plasma characterizing



each of the four categories of acidosis and alkalosis in uncompensated states, and the adjustments in these values postulated as occurring with compensation in each state. Complete compensation, within the meaning of the term here indicated, is rarely attained except in mild disturbances; in pathologic conditions the pH of the blood usually is changed in the same direction from normal as the bicarbonate changes in metabolic acidosis and alkalosis, and in the reverse direction from those of the bicarbonate in respiratory acidosis and alkalosis. Metabolic disorders affecting the blood electrolytes may occur concomitantly with conditions of disease leading to respiratory acidosis or alkalosis. Secondary disturbances in respiratory control of the carbon dioxide tension in the blood may complicate the pictures of metabolic acidosis and alkalosis, leading to changes of pH and carbon dioxide of the blood in directions opposite to those of the primary disturbance.

#### METABOLIC ACIDOSIS

The type of acidosis most frequently encountered is metabolic acidosis. It occurs in severe diarrheal states, especially in infants,

and in diabetes, nephritis, starvation, dehydration and practically all moribund states. It may result from increased production of acid metabolites in the body, from ingestion of acids or acid-producing salts (e.g., ammonium chloride) or from failure of the kidneys to excrete anions as rapidly as they accumulate in the blood. It may also result from excessive losses of mineral cations and bicarbonate in diarrhea. In conditions such as these, dehydration and acidosis are closely interdependent, each aggravating the other. Acidosis leads to increased excretion of mineral cations (sodium and potassium), partly because the excretion of excessive amounts of acids in the urine necessitates increased excretion of cations beyond the power of the kidneys to form ammonia for the economy of mineral cations, and partly because acidosis increases cellular catabolism, liberating potassium. Such losses of mineral cations from the body are additive factors in the development of dehydration and, when the mineral cations are excreted as buffer salts (e.g., phosphates), are an added cause of acidosis. Darrow suggests that with infantile diarrhea, in patients suffering from deficits of potassium, water,

Table 30.  $\text{H}_2\text{CO}_3\text{—BHCO}_3$  Buffering of Blood Plasma in Different States of Acidosis and Alkalosis

	Carbon Dioxide in Plasma				pH
	BHCO <sub>3</sub>		H <sub>2</sub> CO <sub>3</sub>	CO <sub>2</sub> Tension	
	mEq./L.	Vol./100 Cc.	mEq./L.	Mm. Hg	
Normal range . . . . .	22-30	50-65	1.1-1.5	35-50	7.35-7.45
1. Metabolic acidosis					
(a) Uncompensated . . . . .	15	33	1.35	45	7.14
(b) Compensated . . . . .	15	33	0.75	25	7.4
2. Metabolic alkalosis					
(a) Uncompensated . . . . .	45	100	1.35	45	7.6
(b) Compensated . . . . .	45	100	2.28	76	7.4
3. Respiratory acidosis					
(a) Uncompensated carbon dioxide excess . . . . .	27	60	2.28	76	7.16
(b) Compensated carbon dioxide excess . . . . .	45	100	2.28	76	7.4
4. Respiratory alkalosis					
(a) Uncompensated carbon dioxide deficit . . . . .	27	60	0.75	25	7.65
(b) Compensated carbon dioxide deficit . . . . .	15	33	0.75	25	7.4

Adjustments postulated as occurring with compensation in the various states of acidosis and alkalosis: (1) *metabolic acidosis* (a) with normal carbon dioxide tension, bicarbonate deficit and lowered pH, and (b) the decreased carbon dioxide tension required to bring the pH to normal with the bicarbonate deficit unchanged; (2) *metabolic alkalosis* (a) with normal carbon dioxide tension, bicarbonate excess and elevated pH, and (b) the increased carbon dioxide tension required to bring the pH to normal with the bicarbonate excess unchanged; (3) *respiratory acidosis* (a) with normal carbon dioxide tension, bicarbonate deficit and lowered pH, and (b) the increase of bicarbonate required to bring the pH to normal with the increased carbon dioxide tension unchanged; (4) *respiratory alkalosis* (a) with normal carbon dioxide tension, bicarbonate excess and elevated pH, and (b) the decrease of bicarbonate required to bring the pH to normal with the decreased carbon dioxide tension unchanged.

sodium and chloride, shifts of sodium from extracellular to intracellular fluids may lead to states of acidosis with low levels of sodium in the plasma in relation to those of chloride. With dehydration, decreased volume and increased viscosity of the blood result in inadequate circulation and lead to increased production of metabolic acids, owing to poor oxygen exchange in the tissues and to retention of metabolites following diminished renal output.

Ketonuria may occur with or without a state of acidosis. Ketonuria frequently accompanies severe vomiting, especially in infants and children. Accumulation of ketone acids in the blood in conditions associated with severe vomiting may balance the losses of chloride and prevent what would otherwise be a state of alkalosis with hypochloremia (e.g., in intestinal obstruction).

**Symptoms.** The symptoms of metabolic acidosis vary. Hyperpnea may be evident when the bicarbonate is reduced to half of normal, but becomes progressively greater when the acidosis increases beyond this point. There may be increasing restlessness, headache, nausea, drowsiness, meningismus and hyperpnea until coma supervenes. In nephritic acidosis, convulsions may occur. Patients with chronic nephritis tend to adjust to a state of mild uncompensated acidosis, with lowered pH and bicarbonate of the blood, and remain relatively free from unfavorable symptoms for long periods of time. They may get along better in this state than if correction is attempted by administration of alkali.

#### METABOLIC ALKALOSIS

Metabolic alkalosis is most often associated with severe and persistent vomiting when hydrochloric acid of gastric juice is lost. It may also be caused by administration of excessive amounts of alkaline salts such as sodium bicarbonate, particularly in the presence of renal impairment.

Darrow and others have shown that metabolic alkalosis with hypochloremia may be associated with decreases of intracellular potassium and increases of intracellular sodium (probably mainly in muscle tissue) in infants with diarrheal disease and in rats rendered potassium-deficient by low potassium diets and injections of desoxycorticosterone. Such alkalosis may occur as a result of renal excretion of chloride without sodium (Berliner et al.) or of shifts of cations (hydrogen, sodium, potassium) between muscle and extracellular fluid (Darrow et al.) apart from

renal mechanisms. The repair of such alkalosis following the administration of potassium is associated with a reversed shift of potassium and sodium between muscle and extracellular fluids.

**Symptoms.** Numbness, tingling sensations, headache, stupor, tetany and convulsions may be related to the state of alkalosis. Hypocalcemic tetany is usually not accompanied by alkalosis, but alkalosis developing in a susceptible infant may precipitate tetany. Alkalosis caused by persistent vomiting is associated with dehydration, whereas alkalosis caused by excessive ingestion of alkalinizing salts often may be associated with edema.

#### RESPIRATORY ACIDOSIS

Increased carbon dioxide tension in the blood may result from conditions leading to an increase of carbon dioxide in the alveolar air, as with generalized obstructive emphysema, with pulmonary edema, with asphyxia from smothering or tracheal obstruction, with rebreathing of air in a small closed space, and in asthma. It increases somewhat more slowly after suppression of the respiratory center by drugs (e.g., morphine) or infections (e.g., poliomyelitis).

The slowing of respirations by central depression leading to respiratory acidosis must be differentiated from apnea, which may occur with metabolic alkalosis; the dyspnea of cardiac and respiratory disorders must be differentiated from the hyperpnea of metabolic acidosis. The appearance of cyanosis may serve to differentiate the dyspnea of pulmonary congestion from hyperpnea of metabolic acidosis, and respiratory paralysis from the apnea of metabolic alkalosis. The plasma bicarbonate is progressively increased in respiratory acidosis by the departure of chloride from the plasma, and the resultant hypochloremia may be confused with the hypochloremia of metabolic alkalosis brought about by vomiting. Laboratory data in such conditions must be interpreted with careful consideration of the clinical history and physical examination. Compensating adjustment (Table 30) of blood electrolytes in respiratory acidosis may lead to values for bicarbonate and carbon dioxide tension similar to values in compensated metabolic alkalosis with hypochloremia.

**Treatment.** Artificial respiration must be used in asphyxia and in respiratory paralysis and respiratory stimulants must be used to counteract the effects of overdosage with depressant drugs. Cardiac stimulants and oxy-



en may be given for congestive cardiac failure.

RESPIRATORY ALKALOSIS

transient decrease of carbon dioxide tension in the blood may result from overbreathing, either voluntary or with crying or undue excitement in infants and children, or with hysteria in older persons. Hyperventilation of longer duration, as may be induced by injections (e.g., encephalitis) or drugs (e.g., salicylates, lobeline) affecting the respiratory center, is followed by a decrease of plasma bicarbonate and an elevation of the pH value.

In the diagnosis of respiratory alkalosis the hyperventilation induced by central stimulation must be differentiated from the hypernea accompanying metabolic acidosis. Compensating adjustments of the blood electrolytes in respiratory alkalosis lead to values for bicarbonate and carbon dioxide tension in the plasma similar to those in compensated metabolic acidosis (Table 30). For the differential diagnosis of such states the determination of

the pH of the plasma may be the most valuable laboratory test, since this determination permits calculation of the carbon dioxide tension.

ELECTROLYTE STRUCTURE OF THE BLOOD  
PLASMA IN VARIOUS DISTURBANCES

The data in Table 31 have been assembled to provide a perspective of the general patterns of derangements of electrolytes in various clinical disturbances. The comments which follow here may assist in securing this perspective.

A fairly satisfactory estimate of the state of the electrolytes of the blood plasma in most pathologic conditions can be obtained from three measurements: total base, bicarbonate, and chloride (Table 31).

The undetermined anions, or the remainder obtained by subtracting from the total base the sum of the bicarbonate and chloride values, are comprised of proteins, phosphates, sulfates and organic acids. A value lower than normal suggests that the

Table 31. Examples of Concentrations of Total Base and the Principal Anions in the Blood Plasma in Various Conditions of Acidosis and Alkalosis\*  
(Values in Milliequivalents per Liter)

Conditions	Total Base	HCO <sub>3</sub>	Cl	Ketone Acids	Undetermined Anions
1. Normal.....	155	27	103		25
Metabolic acidosis					
2. Fasting, with ketosis.....	155	15	100	12	28
3. Diabetic acidosis.....	141	5	80	22	34
4. Diarrhea.....	146	10	98		38
5. Nephritis, with retention.....	148	6	88		54
6. Nephrosis.....	150	18	115		17
7. Chloride acidosis.....	155	15	115		25
Metabolic alkalosis					
8. Mild vomiting.....	155	34	95		26
9. Pyloric stenosis, severe vomiting.....	145	45	60		40
10. Duodenal obstruction, with vomiting and ketosis.....	150	30	60	20	40
11. Overdosage of NaHCO <sub>3</sub> .....	165	45	90		30
Respiratory acidosis					
2. Pulmonary edema; generalized obstructive emphysema.....	156	40	80		36
3. Pulmonary fibrosis (with pancreatic fibrosis).....	150	35	70		45
Respiratory alkalosis					
4. Encephalitis.....	150	10	115		25
5. Salicylate intoxication.....	155	20	110		25
6. Salicylate intoxication.....	142	10	110		22
Hyperelectrolytemia					
7. Gastroenteritis.....	177	7.1	145		25
8. Hyperventilation.....	182	6.3	119		56

\* The data illustrate the trend of the deviations observed in the various pathologic states, but do not indicate the range of values that may be observed in varying degrees of severity of the clinical disturbances.

concentration of proteins is low, as in nephrosis (item 6). Values above normal signify failure of renal excretion and accumulation of acid metabolites. Thus the decrease of bicarbonate in nephritic acidosis is caused mainly by an increase of the metabolic anions, although a decrease in total base may be contributory (item 5); also in dehydration from any cause diminished renal output is responsible for retention of acid metabolites and consequently a decrease in bicarbonate.

A more accurate estimate of the undetermined anion fraction can be made if the concentration of the plasma proteins is known; determination by the falling drop method or by the copper sulfate method is adequate. The anion equivalence of the proteins is calculated as milliequivalents per liter by multiplying the grams of protein per 100 ml. by 2.43. Subtraction of the value for protein equivalence from the anions listed in Table 30 as undetermined anions would then give a closer accounting of the anions that increase with renal disability.

In *metabolic acidosis and alkalosis* the ketosis of fasting (item 2) offers an example of reduction of plasma bicarbonate by an increase of organic anions, with little other change in the electrolyte structure. In diabetic acidosis (item 3) the reduction of plasma bicarbonate is caused both by a large accumulation of the ketone acids and by a decrease in concentration of total base that results from urinary excretion of sodium and potassium. With increasing dehydration there is an increase of acid metabolites other than ketone acids, ascribable to failing renal excretion. With intestinal obstruction and vomiting the accumulation of ketone acids in the blood (from fasting) may mask what would otherwise be a state of alkalosis induced by losses of chloride (item 10).

In gastrointestinal disturbances, losses of electrolytes by vomiting and diarrhea lead to dehydration. If there is diarrhea without vomiting, acidosis develops with a lowered concentration of total base and little reduction of chloride (item 4); if there is vomiting and little diarrhea, hypochloremia and alkalosis are likely to develop (items 8, 9). If sodium and chloride are lost equally, neither acidosis nor alkalosis may develop until dehydration leads to renal retention with an increase of acid metabolites and acidosis.

Chloride acidosis (item 7) is an example of reduction of plasma bicarbonate by accumulation of mineral anions in the blood. It may be caused by ingestion of ammonium chloride or calcium chloride. In infants with diarrhea, chloride acidosis may be caused or

aggravated by administration of sodium chloride solution for the treatment of dehydration, when the administered sodium is lost with continuing diarrhea and the chloride ions accumulate in the body.

Alkalosis from ingestion of large doses of sodium bicarbonate (item 11) is especially liable to develop when renal function is impaired or if insufficient water is available for renal excretion of the excess sodium bicarbonate. Such retention of bicarbonate may result in edema. If cardiac decompensation with pulmonary edema is superimposed, there is retention of carbon dioxide with an increase in concentration of bicarbonate in the plasma and a corresponding decrease in the chloride level. If these changes are sufficient, the electrolyte disturbance may shift to a respiratory acidosis (item 12). Such conditions can be differentiated only by determination of the pH and carbon dioxide tension of the plasma.

*Respiratory acidosis* occurs most commonly in association with pulmonary edema and with generalized obstructive emphysema (items 12, 13). An increase of carbon dioxide tension in the blood is followed by a decrease in concentration of chloride in the plasma, leaving cations to neutralize the accumulating carbonic acid.

The examples of *respiratory alkalosis* (items 14, 15, 16) illustrate changes occurring with prolonged hyperventilation caused by encephalitis and by salicylism. The resulting carbon dioxide deficit is followed by a decrease of bicarbonate, which is accounted for by a decrease of sodium or an increase of chloride in the plasma, or both.

States of hyperelectrolytemia and hypoelectrolytemia (items 17, 18) may result from water deprivation (especially with fever and high environmental temperature) or from excessive losses of water vapor from the body as with hyperventilation. The magnitude of ventilatory losses of water vapor is demonstrable by measurements of insensible weight loss. This rate, normally around 1 gm. per hour per kilogram of body weight in infants, may rise threefold or fourfold with severe hyperventilation.

GEORGE M. GUNDEL

#### REFERENCES

- Berliner, R. W., Kennedy, T. J., Jr., and Orloff, R.: Relationship between Acidification of the Urine and Potassium Metabolism: Effect of Carbonic Anhydrase Inhibition on Potassium Excretion. *Am. J. Med.*, 11:274, 1951.
- Darrow, D. C.: *Body-Fluid Physiology: The Relationship of Tissue Composition to Problems of Water and*



- Electrolyte Balance. *New England J. Med.*, 233: 91, 1945.
- : Physiological Basis of Potassium Therapy. *J.A.M.A.*, 162:1310, 1956.
- Darrow, D. C., and Yannet, H.: The Changes in the Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte. *J. Clin. Investigation*, 14:266, 1935.
- Fenn, W. O., and others: A Symposium on Potassium Metabolism. *Journal-Lancet*, May, 1953, pp. 159–256.
- Gamble, J. L.: Dehydration. *New England J. Med.*, 201:909, 1929.
- : Chemical Anatomy, Physiology and Pathology of Extracellular Fluid; A Lecture Syllabus. Cambridge, Harvard Medical School, 1942.
- Guest, G. M., Mackler, B., and Knowles, H. C., Jr.: Effects of Acidosis on Insulin Action and Carbohydrate and Mineral Metabolism. *Diabetes*, 1:276, 1952.
- Kerpel-Fronius, E., and Uonoczk, J.: Significance of Changes in the Tonicity of Body Fluids in Infantile Diarrheal Dehydration. *Ann. paediat. Fenniae*, 3:403, 1957.
- McQuarrie, I.: Significance of Water Metabolism in Health and Disease. *J. Pediat.*, 3:539, 1933.
- Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, Williams & Wilkins Company, 1932, Vol. 1.
- Rapoport, S.: Hyperosmolarity and Hyperelectrolytemia in Pathologic Conditions of Childhood. *Am. J. Dis. Child.*, 74:682, 1947.
- Van Slyke, D. D.: The Carbon Dioxide Carriers of the Blood. *Physiol. Rev.*, 1:141, 1921.

## SHOCK

The term "shock" is applied to a syndrome of circulatory collapse and attendant disturbances that may result from physical injury (especially with hemorrhage, crushing injuries of the trunk and extremities, surgical operations, and burns) and from disease. In infants and small children shock, except as associated with birth, is more frequently encountered in severe illnesses, such as diarrheal disorders, than in injuries.

**Causes.** The most important factor in the development of shock appears to be a reduction in effective blood flow through the tissues, resulting in tissue anoxia and impaired removal of cellular metabolic products. A reduction in circulating blood volume may result from functional failure of the cardiovascular system and/or from losses of blood from the circulation. A decreased volume of blood in the circulation may result from hemorrhage, either external or internal, from loss of plasma, such as occurs after burns, or from general dehydration of the body as with severe vomiting and diarrhea or with diabetic acidosis. In infections and after burns the development of shock may be aggravated by toxic effects on the nervous system, the adrenal glands, the heart and other organs. Anuria resulting from circulatory failure and/or dehydration may be a serious complication of a prolonged state of shock.

Pre-existing nutritional deficiencies (malnutrition, anemia, hypoproteinemia or dehydration) favor the development of shock. Since infants normally have a more labile and unstable fluid balance than adults and more

commonly suffer nutritional deficiencies, it is especially important that preventive measures be taken early in the treatment of any condition in which shock may develop.

**Clinical Varieties.** Shock is characterized by extreme weakness, cold clammy skin, grayish pallor, cyanosis, rapid pulse, low blood pressure, thirst and eventual loss of consciousness; if prolonged, it results in death.

**Syncope.** So-called neurogenic shock with temporary loss of consciousness may develop from reflex vasodilatation and slowing of the heart after physical injury, pain, fright or other emotional stress (see also p. 1127). With crushing injuries or with burns transient primary shock may be followed by secondary shock induced by such factors as loss of blood or extravasation of plasma.

**Shock due to loss of blood or plasma.** Reduction of blood volume by 30 to 40 per cent leads to a profound state of shock that will end fatally unless restorative procedures follow quickly. For a short time after the blood volume has been reduced to a dangerously low point, intravenous infusion of whole blood or of a blood substitute (e.g., plasma; saline and glucose solutions; dextran or gelatin) in sufficient amount to restore the circulating blood volume may prevent death, but such treatment is ineffective if delayed.

The severity of shock due to hemorrhage depends upon the rate of bleeding and the amount of blood loss. If the rate is sufficiently slow, vasoconstriction and the passage of tissue fluids into the blood serve to compensate the loss of blood and may afford an

adequate volume of circulating fluid for a considerable time. Prior to circulatory collapse, the blood pressure is not a reliable index of impending shock. With the entrance of tissue fluid into the circulation the percentile volume of plasma increases; this change is designated "hemodilution."

After burns and crushing injuries of soft tissues the escape of blood plasma into and from the surfaces of injured tissues leads to a reduction of blood volume with an increased percentile volume of cells in the blood; this change is designated "hemoconcentration." The increased viscosity of the blood slows the circulation through the capillary beds and thus increases anoxia of the tissues.

**Shock due to infections, dehydration and other systemic disturbances.** In a variety of diseases many concomitant factors may contribute to circulatory collapse. In diabetic acidosis the increased excretion of electrolytes (sodium and potassium) in the urine results in progressively greater dehydration, with decreased blood volume and hemoconcentration. Loss of electrolytes in vomitus and stools in infants leads to a similar state of severe dehydration with hemoconcentration, and the concomitant development of acidosis increases the loss of electrolytes. With acute peritonitis a state of shock may develop, owing to the loss of plasma into the peritoneal exudate and to losses of fluid and electrolytes by vomiting or by accumulation of fluids within partly obstructed loops of bowel. With some infections, especially toxemia causing myocardial damage, circulatory failure may be responsible for a decreased rate of effective blood flow without a decrease in the total volume of blood.

**Treatment.** The immediate treatment of shock, as well as its prevention, should be directed primarily to the maintenance of normal blood circulation and to the correction of pathologic changes in the blood. In case of injuries, hemorrhage must be arrested, pain should be relieved by appropriate sedatives, and the patient should be kept quiet in "shock position," i.e., with head low and feet slightly elevated. The type and amount of fluids required for restoration of a depleted blood volume will depend on the conditions leading to the shock state. Thus, after hemor-

rhage or skeletal injuries, with hemodilution transfusion of whole blood is needed; whereas, after burns or crushing injuries of soft tissues, with hemoconcentration, plasma is needed rather than whole blood. In either case, saline and glucose solutions may be used in addition to, but not in place of, blood or plasma. In shock associated with dehydration solutions of sodium chloride and of sodium bicarbonate or sodium lactate to restore electrolytes and to correct acidosis should be given according to need. Potassium-containing solutions are contraindicated until renal function is adequately established.

Laboratory tests are necessary to guide such therapy properly, but, in the absence of laboratory facilities, closely observed objective signs must be depended upon in emergencies. The state of collapse of superficial veins is a dependable sign of low venous pressure and diminished circulating blood volume. Determinations of hemoglobin, the hematocrit value, the red blood cell count and plasma protein afford indices of hemodilution or hemoconcentration; in infants and young children these indices are less dependable than in older persons, since such values may have been abnormally low, owing to pre-existing nutritional deficiencies.

For the treatment of severe dehydration and acidosis associated with infections, gastroenteritis and diabetic acidosis see page 18.

The application of heat or cold to the patient in shock may be harmful. In experimental animals the survival rate from comparable states of shock has been higher at environmental temperatures of 70° to 72° (room temperatures) than at temperatures significantly above or below this level. Reasons for the higher fatality rate at lower temperatures are not clear; at higher temperatures it may be ascribed to vasodilatation, and at temperatures as high as 95° F. to increase in the insensible water loss. Elevation of body temperature also increases the basal metabolic rate, resulting in a demand for increased oxygen consumption. It would appear that merely covering the patient with a light blanket or sheet would be adequate provision for thermal regulation.

GEORGE M. GUN



# PARENTERAL FLUID THERAPY

The preceding sections have outlined the chemical anatomy of the body and the physiologic mechanisms regulating body composition. This section presents a practical application of such principles to specific problems of fluid therapy.

Fluid therapy should be viewed from four aspects: (1) *deficit therapy*, which is concerned with the normalization of the volume of body fluids (water) and of the concentration of solutes (usually electrolytes) in them. Such therapy supplies water and electrolytes to replace deficiencies resulting from inadequate intake in the presence of usual losses as in thirsting and fasting or from excessive losses in the presence of usual intake as in diarrhea or diabetic acidosis; (2) *maintenance therapy*, which is concerned with administration of water and solutes in quantities approximating those lost from the body under usual circumstances; (3) *the concomitant replacement of abnormal losses*, which applies water and electrolytes to meet losses occurring in the particular disease states under treatment. These losses may be from the body as a whole (external abnormal losses, such as gastric drainage) or may represent sequestration of water or solutes, or both, in certain regions of the body (internal abnormal losses, such as pleural effusion). The replacement of abnormal losses represents a special phase of maintenance therapy, but must be separately quantitated. (4) *Supplemental therapy*, which is concerned with the supply of water and solutes over and above the usual requirements for maintenance and for replacement of abnormal losses, to facilitate a specific physiologic function, such as alkalization of the urine or induction of diuresis.

## DEFICIT THERAPY

**General Considerations.** Disturbances in body composition may result from reduced intake in the presence of usual losses or from excessive losses with or without the usual intake. The severity of the disturbance depends on the relation between intake and output and the magnitude of the body reservoirs. Infants frequently exhibit decreased appetite with disease and have limited capacities to reduce the usual loss of water in the urine. On the other hand, the volume

of water and the quantity of available sodium and chloride per unit of body weight are greater in the infant than in the adult. Deficit therapy must be based, therefore, on an appraisal of the relative changes in body composition. Such an appraisal must rest largely on clinical evaluation of the patient by means of an accurate history and precise physical examination. Table 32 lists the historical data which should be elicited in every problem involving fluid therapy.

Of particular importance in judging the magnitude of deficits in infants is change in weight. Losses in excess of 1 per cent of the body weight per day represent loss of body water. The precise composition of the infant's feeding mixtures also permits some assessment of the water and electrolyte balance. Home-made electrolyte mixtures for the oral treatment of diarrhea are often responsible for severe hyperosmolarity, owing to failure of the mother to follow precisely the directions of the physician. The time and frequency of recent urinations, whether excessive or suppressed, may provide some appreciation of the severity of dehydration. Frequent and excessive urination is suggestive of diabetes mellitus. Usual output in association with physical signs of dehydration suggests a loss in capacity of the kidney to conserve water.

The physical signs of disturbances in body composition are of even greater value than the historical data in the planning of fluid therapy (Tables 33, 34). Some of the signs listed in Table 33 are not specific for dehydration, but are characteristic of shock, which frequently accompanies dehydration. In the well nourished older infant and child,

Table 32. Historical Data Required in Planning Deficit Therapy

Intake
Quantity
Kind: water, electrolyte, protein, drugs
Output
Quantity
Kind: urine, vomiting, diarrhea, sweat, drainage
Balance
Weight change
General Medical
Age
Cardiovascular, respiratory, renal or central nervous system disease

Table 33. Physical Signs of Dehydration

	<i>Iso-osmolarity</i> (Loss of Water and Salt) <i>Isotonic Dehydration</i>	<i>Hyperosmolarity</i> (Loss of Water in Excess of Salt) <i>Hypertonic Dehydration</i>	<i>Hypo-osmolarity</i> (Loss of Salt in Excess of Water) <i>Hypotonic Dehydration</i>
Skin			
Color*	Gray	Gray	Gray
Temperature	Cold	Cold or hot	Cold
Turgor	Poor	Fair	Very poor
Feel	Dry	Thickened	Clammy
Mucous membrane	Dry	Parched	Slightly moist
Eyeball	Sunken and soft	Sunken	Sunken and soft
Fontanel	Sunken	Sunken	Sunken
Psyche	Lethargic	Hyperirritable	Coma
Pulse*	Rapid	Moderately rapid	Rapid
B.P.*	Low	Moderately low	Very low

\* Signs of shock rather than of dehydration per se.

skin turgor may remain fairly normal in the presence of dehydration. The clinical determination of isotonic, hypertonic or hypotonic dehydration is usually not as definitive as may be suggested by Table 33. When findings are marked, differentiation may be possible, but borderline findings, such as somewhat dry mucous membranes and somewhat poor skin turgor, cannot be interpreted as confirming the presence of disturbances in osmolarity.

The physical findings which characterize variations in the concentration of specific substances in the blood (Table 34) require some explanation. The characteristic signs of acidosis are increased depth and rate of respiration, which, however, may be depressed markedly in the presence of severe circulatory insufficiency. The compensatory diminution in breathing that is associated

with alkalosis is usually absent in adults, marked in infants with pyloric stenosis. deficiencies of other electrolytes, such as potassium, may exist without obvious physical findings. Hypokalemia may not always be present even when cells are depleted of potassium. Such deficits are recognized by history alone.

Certain laboratory data (Table 35) are helpful in the initial planning of therapy. None is so essential that adequate therapy cannot be initiated without it. Of great importance is the use of the laboratory in assessing the results of deficit therapy in guiding subsequent maintenance therapy. The carbon dioxide content usually indicates the degree of acidosis or alkalosis, except in respiratory disturbances. It is rarely necessary to know the pH of the blood to determine whether the disturbance is metabolic or respiratory in origin. The sum of carbon dioxide content and chloride concentration plus 15 approximates the sodium concentration, except in the presence

Table 34. Physical Signs of Variations in Concentration of Specific Ions

<i>Acidosis</i>	Respiration: increased depth and rate
<i>Alkalosis</i>	Respiration: decreased depth and rate
<i>Hypokalemia</i>	Heart: fast or slow; poor quality Skeletal muscle: weakness or paralysis; diminished reflexes Smooth muscle: abdominal distention; ileus
<i>Hyperkalemia</i>	Heart: slow or fast; poor quality Skeletal muscle: fibrillation; paralysis
<i>Hypocalcemia</i>	Latent tetany (see p. 1112) Manifest tetany (see p. 1112)
<i>Hypercalcemia</i>	Gastrointestinal: fecal masses
<i>Hypotonia</i>	

Table 35. Laboratory Data Useful in Planning Therapy

<i>Serum or Plasma</i>	Carbon dioxide content and chloride concentration Sodium and potassium concentration Protein concentration
<i>Whole Blood</i>	pH (especially in salicylism) Hematocrit BUN or NPN
<i>Urine</i>	Volume and specific gravity Albumin, sugar, acetone Sediment
<i>Electrocardiogram</i>	



etosis. The sodium concentration can, however, be determined directly in most hospitals by means of the flame photometer. The serum sodium level is of particular importance in determining the loss of water in relation to that of electrolytes. Hypernatremia indicates excessive loss of water in relation to electrolytes; hyponatremia indicates excessive loss of electrolytes in relation to water. The serum potassium concentration at the beginning of therapy is not particularly helpful, since it may be elevated, owing to hypoxia, diminished renal function or acidosis even in the presence of significant cellular deficits. Measurement of the blood urea nitrogen or nonprotein nitrogen is helpful in following the progress of therapy, a rising blood urea nitrogen indicating either intrinsic renal injury or continuing circulatory insufficiency. The level of plasma protein and the hematocrit value have limited usefulness at the beginning of therapy, but the initial determinations are of considerable help in assessing the effects of therapy. When correlated with physical findings, they may be useful in planning therapy. For example, when there is a low or even normal hematocrit value with signs of dehydration, anemia must be present which should be corrected during deficit therapy. Serial determinations of the hematocrit value and the plasma protein concentration of capillary blood using a refractometer are essential in following the course of patients with burns. Measurements of urinary output, specific gravity, albuminuria, glycosuria and ketonuria are valuable in assessing the degree of renal compensation which may be expected during therapy, as well as in guiding therapy in diabetic acidosis.

Serial electrocardiograms may provide clues of disturbances in concentration of such electrolytes as potassium and calcium. Leads 2 and aV<sub>5</sub> are particularly useful for this purpose (see p. 830).

The quantities of water and electrolytes which may be lost in various conditions (Table 36) have been obtained by a variety of techniques, such as recovery balance studies, isotope dilution methods, tissue and whole body analyses and animal experiments. They represent *only an order of magnitude* and serve as a partially quantitative guide rather than as a precise determinant of therapy. It can be seen from Table 33 that there is a decided similarity in the magnitude of the deficits, despite the fact that the precipitating conditions vary widely. This situation is not surprising, since the deficits

are related to readjustments as well as to the direct losses. Loss of chloride in the vomitus in pyloric stenosis, for example, leads to an increase in excretion of sodium and potassium in the urine. Thus deficits of these cations will result even though the original losses of them in the vomitus were relatively small. Similar compensatory losses are seen in diarrhea and other conditions. This fact justifies a similar therapeutic approach, with only minor modifications, to a variety of conditions.

In planning deficit therapy the physician must be aware that circulatory insufficiency and renal dysfunction are of primary importance in the morbidity and mortality of dehydration. Consequently the initial step is aimed at improving circulatory dynamics and renal function. Restoration of these functions depends on rapid expansion of extracellular volume with a fluid such as Ringer's lactate, which resembles the extracellular fluid and remains completely in this compartment. Such solutions are preferentially administered intravenously, although some improvement may result from subcutaneous injection. However, solutions of glucose in water or in dilute saline solutions must not be administered subcutaneously. Shock can be precipitated by the rapid migration of salt and water into the subcutaneous pool as glucose slowly diffuses into the vascular compartment. Circulatory insufficiency due to dehydration should not be treated by the immediate administration of blood, owing to the possibility of thrombosis and renal tubular injury from minor degrees of blood incompatibility. Blood should be given for shock associated with dehydration

Table 36. Probable Deficits of Water and Electrolytes in Infants with Moderately Severe Dehydration

Condition	H <sub>2</sub> O ml. Per Kg. of Body Weight	Na mEq.	K* mEq.	Cl mEq.
Fasting and thirsting.	100-120	5-7	1-2	4-6
Diarrhea				
Isotonic.....	100-120	8-10	8-10	8-10
Hypertonic.....	100-120	2-4	0-4	-2- -6†
Hypotonic.....	100-120	10-12	8-10	10-12
Pyloric stenosis.....	100-120	8-10	10-12	10-12
Diabetic acidosis....	100-120	8-10	5-7	6-8

\* Converted for breakdown of tissue cells: - 1 gm. N = 3 mEq. of K.  
† Negative balance of chloride indicates excess at beginning of therapy.

Table 37. Deficit Therapy of Infants with Moderately Severe Dehydration and Electrolyte Disturbance

Clinical Condition	Solution	Ml./Kg.	Time Schedule in Hours from Onset of Therapy
Fasting and thirsting.....	Ringer's lactate	20	0-1
	5% or 10% invert sugar or glucose in H <sub>2</sub> O	60	1-8
	Darrow's K lactate*	20	
Diarrhea			
	Isotonic dehydration.....		
	Ringer's lactate	20	0-1
	Blood†	10	1-2
Hypotonic dehydration.....	5% or 10% invert sugar or glucose in H <sub>2</sub> O	40	2-8
	Darrow's K lactate*	60	
	Ringer's lactate	20	0-1
	Blood†	10	1-2
Hypertonic dehydration.....	5% invert sugar or glucose in Ringer's lactate	40	2-8
	Darrow's K lactate*	60	
	Ringer's lactate	20	0-1
	Blood†	10	1-2
Pyloric stenosis.....	5% or 10% invert sugar or glucose in H <sub>2</sub> O	60	2-10
	M/6 Na lactate	20	
	K glutamate concentrate‡	1	
	or	or	
	K acetate concentrate§	0.5	
	Calcium gluconate		
Diabetic acidosis.....	Isotonic NaCl	20	0-1
	Blood†	10	1-2
	5% or 10% invert sugar or glucose in H <sub>2</sub> O	40	2-8
	Isotonic NaCl*	40	
	Isotonic KCl*	20	
Diabetic acidosis.....	Ringer's lactate	20	0-1
	Blood†	10	1-2
	5% or 10% invert sugar or glucose in H <sub>2</sub> O	50	2-8
	KPO <sub>4</sub> concentrate‡	0.5	
	Darrow's K lactate*	50	2-8

All of above to be followed by maintenance therapy.  
\* May be given separately subcutaneously.  
† For shock not responding to Ringer's lactate.  
‡ K glutamate and phosphate concentrates contain 2 mEq. of K per ml.  
§ K acetate concentrate (Cutter) contains 4 mEq. of K per ml.  
|| Total dose, 10 ml. of 10% solution slowly IV.

only after the extracellular volume has been rapidly expanded. The intracellular deficits of water and electrolytes must be replaced slowly and only after improvements in circulation and renal functions have been effected.

DEFICIT THERAPY IN SPECIFIC CONDITIONS

**Fasting and Thirsting.** One of the commonest problems requiring fluid therapy is the initial treatment of the infant or child who has taken little or no water and food for periods of one to five days. Inspection of Table 36 indicates that such infants are deficient not only in water, which has evaporated from the lungs and skin, but also in electrolytes, particularly in sodium and chloride, which have been excreted in the urine. The administration of electrolyte-free

solutions under such circumstances leads to an increase in urine volume with possible increased losses of electrolytes and may actually increase the dehydration. If fasting and thirsting continue beyond four or five days, urinary output will fall to such a level that there will be no significant continued loss of electrolytes, and severe deficiency of water alone will result.

Therapy (Table 37) is begun with administration of Ringer's lactate solution to produce rapid and safe expansion of extracellular volume and improvement in renal function. A large part of the remaining deficiency of water and electrolytes may be made up by a solution containing calcium lactate, sodium chloride, some potassium and potential bicarbonate, such as lactate.



or acetate. Children and adults should be given approximately one fourth to one third less water and sodium per kilogram of body weight than infants for a given degree of clinical dehydration, owing to the relatively smaller extracellular reservoirs with increasing age. Potassium deficits are relatively the same in infants, children and adults, since there is approximately the same quantity of potassium per kilogram of body weight in such patients. When deficit therapy is planned, correction of the body weight toward ideal weight should also be made in the presence of obesity. Water, carbohydrate and electrolytes may be administered to the mildly ill patient by mouth. Infants, however, often vomit when they are dehydrated, and for this reason initial therapy is usually given parenterally. After completion of the deficit therapy the patient should be sustained on a maintenance basis as outlined on page 192.

**Acute Diarrhea.** Despite improved infant care, diarrhea continues to be a serious problem in many areas of the world. The physical signs which result are principally those outlined in Tables 33 and 34. As indicated in Table 36, diarrhea results in large losses of water and electrolytes in varying proportions. In approximately 70 per cent of instances there is isotonic dehydration in which the losses of water and electrolytes are equivalent, so that total solute concentration in body fluids remains fairly normal even though there may be severe acidosis.

**Isotonic dehydration.** The therapy outlined in Table 37 is based upon the principle that extracellular volume must be restored first in order to improve circulation and renal function. Administration of an approximately isotonic fluid, such as Ringer's lactate solution, for a short time expands extracellular volume effectively and leads to improvement in solute concentration, whether the sodium concentration is elevated or low. The balance of the deficit of extracellular water and electrolytes and the beginning of correction of the intracellular deficit of potassium and water are carried out slowly over a subsequent six- to eight-hour period. After this deficit therapy, usual maintenance therapy is begun, and in addition enough water, sodium, chloride and potassium is administered to approximate the continuing abnormal losses in the stool. It can be seen that the deficit therapy outlined for diarrhea does not differ greatly from that for fasting and thirsting, nor from that for diabetic ketosis,

and differs only in a minor way from the therapy for pyloric stenosis. This plan does not represent the only approach to the treatment of diarrhea, but serves as a framework upon which modifications may be made.

**Hypertonic dehydration.** Although this condition is less common (approximately 20 per cent of cases of diarrhea) than isotonic dehydration, it occurs frequently in young infants in whom conservation of water by the kidney is limited and particularly when the renal solute load is high, as when boiled skimmed milk is fed to infants with diarrhea. Hypertonic dehydration may also result from administration of solutions of high electrolyte concentration, such as home-made or commercial salt and water mixtures. High environmental temperatures and hyperventilation also significantly increase evaporative losses of water. Obviously attempts should be made to avoid all these circumstances in infants with diarrhea.

Physical signs of hypertonic dehydration are listed in Tables 30 and 31. Of particular importance are the cerebral changes which result from severe hyperosmolarity. The exact cause of these changes is unknown, but there is usually an elevated protein level in the cerebrospinal fluid. Hypocalcemia has occasionally complicated hyperosmolarity (Finberg and Harrison). It can be prevented in experimental animals by administration of potassium. Marked hypocalcemia has not been observed in the author's clinic, in which administration of potassium is part of the routine therapy of diarrhea. The cerebral symptoms have been attributed to too rapid reduction of the serum sodium concentration even though the sodium level may still be above normal. However, seizures have been observed in children recovering from hypertonic dehydration when no significant change in extracellular osmolarity had been effected by treatment. It is possible that the convulsions represent a response to damage from the hyperosmolarity and from hyperthermia. The cerebral changes may be permanent and be one of the causes of acquired cerebral palsy.

Balance studies reveal a slight deficiency of sodium, but an excess of chloride and a relatively minor deficit of potassium. Serum potassium, however, frequently falls to low levels during therapy unless potassium is administered. Characteristically, whether treatment consists of large amounts of water with or without salt, there is expansion of extracellular volume with the development

of significant edema and at times of cardiac failure before there is any notable excretion of chloride and correction of the acidosis.

The therapy for hypertonic dehydration (Table 37) represents some deviation from the usual therapy of diarrhea. The principles are essentially the same, however: namely, rapid expansion with extracellular fluid to improve circulation followed by *slow* replacement of intracellular water and electrolytes. The intake of chloride is minimized. Changes in concentration should be effected slowly, whereas changes in volume may be effected more rapidly. In this scheme of therapy, water is administered rather slowly after the initial improvement of circulation and renal function. Intravenous administration of calcium may occasionally be required. Digitalization is indicated when there is hepatomegaly or rales as evidence of pulmonary congestion. Administration of phenobarbital may minimize the occurrence of seizures. If seizures occur which do not respond to usual anticonvulsant therapy and are not the result of hyperpyrexia, 3 per cent sodium chloride (3 to 5 ml. per kilogram) may be given intravenously. The cause of some seizures has been attributed to relative water intoxication even though the serum sodium has been reduced only 5 to 10 mEq. per liter and is still considerably above normal. Such an assumption has not been proved.

**Hypotonic dehydration.** At times, and particularly in bacillary dysentery in children, large amounts of electrolytes may be lost in the stool. Consequently hypotonic dehydration (10 per cent of all cases of diarrhea) may result and be accentuated if only electrolyte-free fluids are taken by mouth. The serum sodium concentration may be lowered to less than 130 mEq. per liter. Under these circumstances the basic plan of therapy is modified by administering relatively less glucose in water and relatively more glucose in electrolyte-containing solutions (Table 37) so that gradual correction of concentration is accomplished as volume is expanded. No attempt is made to elevate abruptly the sodium concentration by administration of hypertonic saline solution unless symptoms of water intoxication, such as convulsions, are present. Delay in administration of potassium is necessary, owing to the frequency of hyperpotassemia in association with hypotremia.

**General considerations in treatment of diarrhea.** In addition to replacement of the deficits of water and electrolytes in the treat-

ment of diarrhea, efforts must be made to obtain an etiologic diagnosis so that specific chemotherapy may be given if indicated (see p. 655). There are no aspects of chemotherapy that affect fluid therapy except during the administration of sulfonamides; adequate amounts of fluid for urine formation must be provided.

The maintenance of fluid balance in a patient with diarrhea (see p. 187) requires an excess of water and electrolytes for stool formation. The extent of the losses range from 40 to 400 ml. per day in infants and 100 to 1000 ml. in children. These losses may be replaced by equal parts of 5 per cent glucose in water and Darrow's K lactate or similar commercially available solutions.

Drugs which inhibit peristaltic activity such as methylcellulose derivatives which absorb intestinal contents and produce a more bulky stool have relatively little effect on the course of infantile diarrhea.

Although the net absorption of carbohydrate, fats and proteins may be increased by feeding large amounts of milk during diarrhea, there is unquestionably an increase in the volume of stool which makes the replacement of water and electrolytes exceedingly complicated and extends the need for parenteral fluids over several days.

With complete starvation of the patient with moderately severe diarrhea, frequency and volume of stools will usually subside rapidly within forty-eight hours. When this occurs, and in the absence of gastric distention and vomiting, glucose, carbohydrate and electrolyte mixtures may be started by mouth. Mixtures of carbohydrate and electrolyte, such as Lytren, are available commercially, or a home-made mixture\* may be prescribed. Every effort should be made to guarantee that the mother does not make up mixtures more concentrated than recommended, since hypotonicity may result. When the infant tolerates the carbohydrate and electrolyte mixture by mouth without exacerbation of diarrhea, the caloric intake may be increased gradually by the substitution of mixtures which also contain fat and protein until the usual dietary intake is achieved in six to eight days. Premature administration of a large

\* Example of a sugar and electrolyte mixture for oral administration:

	Final Concentration
Sucrose . . . . . 50.0 gm.	Sucrose . . . . . 5 gm./%
NaCl . . . . . 1.7 gm.	NaCl . . . . . 30 mM./%
KHCO <sub>3</sub> . . . . . 2.0 gm.	KHCO <sub>3</sub> . . . . . 20 mM./%
Dissolve in 1 quart H <sub>2</sub> O	



number of calories in the form of milk may induce exacerbation of the diarrhea. In the young infant with a family history of allergy the use of a hypoallergenic feeding mixture, such as Nutramigen or a soy bean mixture, is recommended for the recovery phase from diarrhea, since permeability of the gastrointestinal tract to whole protein may be increased during this time. During the period of reduced caloric intake (30 to 80 C. per kilogram) the feeding mixture may be made up in an electrolyte-containing solution, such as Lytren, instead of in distilled water, to ensure adequate electrolyte intake to balance possible abnormal losses.

**Therapy of mild diarrhea.** Many infants and children with diarrhea do not require parenteral fluid therapy. The decision for the use of oral rather than parenteral therapy rests on clinical appraisal of the patient. If there are signs of circulatory insufficiency, lethargy, vomiting or gastric distention, intravenous therapy must be given. In the absence of these findings and in the presence of only mild signs of dehydration, mixtures of sugar and electrolytes as described above may be fed. Parenteral therapy is indicated for infants when amounts in excess of 1.5 liters per day are required to meet continued stool losses. Infants with mild diarrhea have been observed who have taken 2 to 3 liters of electrolyte mixtures orally per day with resultant increase in the volume of stools; cessation of oral intake resulted in prompt cessation of the diarrhea. Such instances are rare and do not detract from the value of oral carbohydrate and electrolyte mixtures in the prevention of severe disturbances when given early.

**Chronic Diarrhea.** When diarrhea is severe and prolonged, administration of amino acids, plasma and alcohol parenterally, in addition to carbohydrate and electrolytes, is required to sustain body reserves. Occasionally, full oral feedings are required during chronic diarrhea in addition to parenteral electrolyte therapy. In such instances allergy to milk protein should be suspected and hypoallergenic feeding mixtures administered. The use of diiodohydroxyquinoline has not been evaluated in other than mild nonspecific chronic diarrhea.

**Congenital Alkalosis of Gastrointestinal Origin.** Rarely, chronic diarrhea may be due to a congenital defect in the transport of water and electrolytes across the intestinal wall. In contrast to usual diarrhea the watery stools of such patients have a high content of potassium and chloride, and alkalosis results. The deficit therapy is analogous to that of

pyloric stenosis, but must be on a continuing basis and planned in conjunction with an adequate dietary intake of potassium and chloride.

**Pyloric Stenosis.** This condition is used as an example of the correction of deficits associated with alkalosis. The therapy (Table 37) differs little from that of diarrhea, except for the substitution of solutions which contain relatively more chloride in relation to sodium and potassium (NaCl and KCl), thereby permitting replacement of the relatively larger deficit of chloride with some correction of the alkalosis as volume is expanded. Correction of the hypochloremia by administration of ammonium chloride without correction of the deficit of potassium leads to continued alteration in function of renal tubular cells as well as other cells. Although deficits may be replaced and serum levels returned to normal within twelve hours, operation should not be performed for at least thirty-six to forty-eight hours to permit optimal readjustment of body functions, except in very mildly ill infants with no signs of dehydration. Adequate fluid therapy prevents deterioration during this period of preparation, and the stomach may be decompressed by gentle suction. (See page 195 for preoperative, paraoperative and postoperative therapy.)

**Diabetic Acidosis** (see also p. 1209). The deficit therapy of diabetic acidosis (Table 37) approximates that of diarrhea. Extracellular volume is expanded rapidly with Ringer's lactate solution. The balance of the deficit of extracellular water and electrolytes and the beginning of correction of the intracellular deficit of water, potassium and phosphate are carried out slowly over a six- to eight-hour period. A portion of the fluid (Darrow's K lactate) probably should be given subcutaneously to permit separate regulation of the intake of carbohydrate and water which is administered intravenously. In the appraisal of deficits in patients with diabetic ketosis, laboratory studies may be misinterpreted. Hypo-osmolality may be assumed erroneously on the basis of measurement of the serum sodium concentration. Extracellular osmolality may be normal or high even in the presence of a low serum sodium concentration if there is a high concentration of glucose. Blood sugar levels of 1800 mg. per 100 ml. are the equivalent of an additional 50 mEq. per liter of sodium. In addition, elevations of serum lipid and protein concentrations in diabetic acidosis may reduce the water content of the serum so that sodium concentrations per liter of serum are low

while sodium concentrations per liter of extracellular water are normal or high.

Administration of potassium fairly early in therapy of these patients is essential. A rapid fall in potassium concentration occurs shortly after administration of insulin or fructose. Such changes may produce alterations in the functioning of the heart, liver, brain and kidneys, may contribute to gastric distention and may even lead to respiratory paralysis. Changes in serum inorganic phosphate concentration during therapy are likewise striking and parallel those in potassium concentration. This fall is due primarily to cellular uptake of phosphorus as glycogen is formed. Although the significance of such changes has not been established clinically, it is the author's opinion that serum inorganic phosphorus levels should be sustained at low normal levels. For this reason a portion of the potassium is administered as the phosphate salt. No specific attempts are made initially or routinely to elevate the low carbon dioxide content and pH except by expanding extracellular volume with fluids resembling an ultrafiltrate of normal plasma (Ringer's lactate) (see p. 185). Such therapy frequently effects a significant reduction in acidosis with symptomatic improvement. If extreme respiratory distress persists, the administration of sodium bicarbonate or lactate may be indicated. The dose required may be calculated from the formula on page 191. However, there is a large reservoir of potential bicarbonate in the form of ketone acids which are metabolized with improvement in carbohydrate utilization after administration of insulin, so that bicarbonate concentration of the serum should not be elevated abruptly to more than 12 to 15 mEq. per liter.

The amount of insulin which can be given during this time varies considerably from one patient to another. Enough insulin to effect clearing of the ketosis by accelerating the utilization of carbohydrate should be given with adequate carbohydrate to prevent development of hypoglycemia. An initial dose of approximately 2 units per kilogram of body weight for severe diabetic ketosis and then subsequent doses at one- to three-hour intervals of  $\frac{1}{2}$  to 1 unit per kilogram are usually appropriate. Half of the initial dose of insulin should be given intravenously. Approximately 1 to 2 gm. of carbohydrate per unit of insulin may be necessary to prevent hypoglycemia. The aim of therapy should be the elimination of ketonemia and ketonuria, since persistence of acetoacetic acid and beta-hydroxybutyric

acid indicates diminished operation of Krebs cycle. Collection of urine at hourly intervals, preferably without resort to catheterization, is essential for modifying the dosage of insulin and carbohydrate as therapy progresses. Ordinarily in children will ketones be absent from the urine, when present in the serum in significant amounts; qualitative tests on serum are helpful in such instances. Reduction of the blood sugar to levels which avoid glycosuria (3+ to 4+ qualitative Benedict's or glucose oxidase) prevents excessive loss of water in the urine. However, reduction of the blood sugar to excessively low levels by administration of insulin without adequate carbohydrate rapidly leads to a return or exacerbation of ketosis. In children glycosuria frequently disappears before ketonuria, and hypoglycemic shock must be avoided.

Fructose is phosphorylated rapidly in the absence of insulin and can be converted to glycogen in the diabetic more rapidly than glucose. Fructose, therefore, may be given relatively early in therapy without significantly increasing total blood and urinary sugar. Rapid administration of fructose, however, produces a profound acidosis by the transfer of organic acid to extracellular fluids. In addition, fructose is probably not metabolized by the cerebral cortex, and symptoms due to hypoglycemia induced by excessive doses of insulin would probably not be relieved by fructose until it was converted to liver glycogen and thence to glucose. For these reasons the use of invert sugar is recommended to provide fructose for rapid increase in glycogen stores, and glucose for the prevention of hypoglycemia.

The parenteral administration of vitamins of the B complex is advised because of pre-existing malnutrition. Gastric aspiration early in therapy is helpful in relieving massive distention which can occur; pulmonary aspiration of vomitus is also avoided thereby. Administration of large doses of appropriate antibiotics if bacterial infection is present may rapidly improve the response of the patient to insulin therapy.

Oral feedings usually can be started cautiously within twelve to fourteen hours, and parenteral therapy may be discontinued in favor of oral carbohydrate and electrolyte mixtures or other more adequate liquid diets. It is particularly important at this time to avoid the frequent error of omitting necessary small doses of insulin, which must be given at intervals of six hours during the ensuing twelve to twenty-four hours.



## THERAPY OF DISTURBANCES IN CONCENTRATIONS OF ELECTROLYTES

**Acidosis.** The preceding discussion has been devoted to therapy of clinical conditions in which the volume of body fluids is reduced with or without associated alterations in concentrations of electrolytes. In some instances acidosis may persist, particularly in infants recovering from diarrhea and in patients with renal insufficiency. The dosage of sodium lactate, acetate or bicarbonate necessary for the correction of this acidosis can be calculated from the following formula:

$$(C_d - C_a) \times f_a \times \text{body weight in kg.} = \text{mEq. required}$$

Here  $C_d$  and  $C_a$  represent respectively the concentration desired and the one actually present;  $f_a$  represents that fraction of the total body weight in which the administered material is apparently (not actually) distributed. This factor, of course, varies with the substance administered.

The apparent distribution factor for bicarbonate or potential bicarbonate is empirically determined and approximates one half to six tenths of the body weight. In terms of such a calculation, 4.2 ml. of sixth-molar sodium lactate solution or 0.058 gm. of sodium bicarbonate per kilogram of body weight would raise the serum bicarbonate concentration approximately 1 mEq. per liter. However, wide variations in individual response to administered bicarbonate occur, since administered sodium may be sequestered in bone or muscle or lost in urine. In glomerular insufficiency caution must be exercised in correcting acidosis; hyperphosphatemia should be corrected by diet and administration of aluminum hydroxide before the pH of the blood is elevated.

**Hypochloremic Alkalosis.** Rarely respiration may be so depressed in infants with severe hypochloremic alkalosis that oxygenation of the blood is diminished. Severe alkalotic tetany may also occur. In such instances the administration of ammonium chloride may effect symptomatic improvement. The dose of ammonium chloride may be calculated from the preceding formula; the probable  $f_a$  is 0.2 to 0.3. Such therapy is for relief of symptoms only and must not be used in place of administration of potassium chloride for repair of intracellular deficits.

**Hyponatremia.** Sodium chloride is the main solute of extracellular fluid. Hyponatremia, therefore, always indicates hypo-osmolarity except in the presence of hyperglycemia and hyperlipemia as in diabetic acidosis (p. 189).

A lowered concentration of sodium in the serum may result from a decrease in the amount of sodium in the extracellular space or from an increase in the volume of extracellular water (Table 38).

Of particular pediatric interest are the disturbances in sodium concentration related to diseases of the central nervous system. They seem to be of three types:

1. Patients with diverse lesions such as encephalitis, bulbar poliomyelitis, cerebrovascular accidents, tumors of the fourth ventricle and subdural hematoma may lose large amounts of sodium in the urine. These so-called cerebral salt wasters show signs of sodium depletion such as dehydration, hypotension and azotemia unless large amounts of salt are administered and the intake of water is somewhat limited.

Table 38. Clinical States Complicated by Hyponatremia

I. Expansion of extracellular space
A. Excessive intake
1. Parenteral fluid therapy—glucose in water
2. Oral (with diminished output)
B. Diminished output (usual intake)
1. Renal
a. Intrinsic: nephritis, nephrosis, tubular necrosis, prematurity
b. Extrinsic
(1) Excess of antidiuretic hormone—acute central nervous system disease, Pitressin therapy, surgery
(2) Circulatory—heart failure, cardiovascular surgery, malnutrition
2. Skin—premature in high humidity
II. Deficiency of extracellular sodium
A. Inadequate intake
1. Low salt diet
2. Parenteral therapy with glucose in water
B. Excessive losses
1. Gastrointestinal—vomiting, salivary, gastric, biliary, pancreatic drainage, diarrhea, resin therapy, enemas (especially megacolon)
2. Genitourinary
a. Intrinsic renal disease—chronic nephritis, acute tubular necrosis (recovery phase), nephrosis (diuresis)
b. Extrinsic influences—mercurial diuretics, Diamox, hypoadrenalism, central nervous system disease, pulmonary disease, expanded volume (Pitressin, excessive water therapy)
c. Arachnoid—ureterostomy
3. Skin
a. Normal sweat
b. Abnormal sweat—cystic fibrosis, adrenal insufficiency
4. Parenteral—thoracentesis, paracentesis, burns
C. Redistribution
1. Potassium deficiency
2. Trauma

2. Patients with tuberculous meningitis who are severely ill and comatose are frequently hyponatremic, but exhibit no symptoms which can be attributed to hyponatremia. This situation may be analogous to the asymptomatic hyponatremia of severe malnutrition or pulmonary disease. Relatively large amounts of salt may be lost in the urine when attempts are made to correct the hyponatremia by salt loading. It has been postulated that there may be a deficit of intracellular solute which leads to a homeostatic lowering of osmolarity. Careful clinical and laboratory observations are essential to ensure that salt depletion and water intoxication do not occur. Potassium should be administered in amounts at least 50 per cent greater than usual maintenance therapy (see p. 194).

3. Patients with acute infections of the central nervous system occasionally have symptoms of acute water intoxication as a manifestation of rapid fall in serum sodium concentration. These patients retain an excessive amount of water and have excessive thirst. Convulsions are severe and resistant to anticonvulsant therapy, but respond rapidly to the intravenous administration of hypertonic saline solution. The dose may be calculated according to the formula on page 191. Since there is osmotic equilibrium between cells and extracellular water, changes in osmolarity are distributed over total body water, and the value of 0.6 to 0.7 may be used for  $f_a$ .

Elevation of the sodium concentration should be effected in small increments (5 to 10 mEq. per liter) over one to four hours. A dose of 12 ml. per kilogram of body weight of 3 per cent (M/2) saline solution should raise the concentration of sodium approximately 10 mEq. per liter.\*

If no symptoms are present, correction of hyponatremia may be accomplished by restriction of water, administration of alcohol to produce a water diuresis or brief substitution of isotonic electrolyte solution for the usual water intake. In the therapy of disturbances in concentration, accurate chemical analyses are essential for confirmation of clinical findings. However, therapy must be directed at correction of symptoms and not at laboratory findings. Central nervous system diseases in which *hypernatremia* predominates must be differentiated; in these situations further limi-

tation of the intake of water would be disastrous.

**Hypopotassemia or Hypokalemia.** Disturbances in concentration of potassium in the absence of disturbances of volume of body fluids have been described in primary hypoadosteronism and in a poorly defined condition termed congenital alkalosis of renal origin. In these disturbances large amounts of potassium are lost in the urine, resulting in low serum potassium and high serum bicarbonate concentrations. The administration of large amounts of potassium (10 mEq. per kilogram per day) and severe restriction of the intake of sodium effect some clinical as well as biochemical improvement. Congenital alkalosis of gastrointestinal origin represents another anomaly of metabolism in which large amounts of potassium and chloride are lost in the stools (p. 189).

**Hypocalcemia and Hypercalcemia** are discussed on pages 1175 and 1177.

## MAINTENANCE THERAPY

This phase of fluid therapy is concerned with supplying the usual requirements of water, electrolytes, protein and calories. Such therapy, either by oral or parenteral routes, directly follows deficit therapy and is continued until the usual dietary intake is re-established. As noted previously, deficit therapy is calculated on the basis of body weight. Maintenance requirements, on the other hand, depend upon the rate of metabolic turnover and hence are calculated on the basis of 100 calories metabolized (Darrow and Pratt). The use of such a unit rather than surface area has a sound theoretic basis and does not unduly complicate practical therapy, since the pediatrician commonly thinks in terms of caloric requirements in infant feeding (see Table 37).

Use of ideal weight as obtained from the fiftieth percentile for age and height from the table on page 50 is necessary for obese infants and children. Calculation of the total number of calories metabolized is readily made by the additions or subtractions listed below in Table 39. Such corrections must be made to assure optimal intake rather than to depend upon estimations determined from a fixed surface area. Corrections for activity may be approximated by observation of the patient. No increments for activity are needed for patients in coma or under anesthesia. Usual bed activity does not exceed an increment

\*  $(10) \times 0.6 \times 1 = 6$  mEq. per kg. required.

1 ml. 3% NaCl = 0.5 mEq.

Therefore, 12 ml. per kg. required.



Table 39. Standard Basal Calories

Weight Kg.	Calories/24 Hours Male and Female	
3.....	140	
5.....	270	
7.....	400	
9.....	500	
11.....	600	
13.....	650	
15.....	710	
17.....	780	
19.....	830	
21.....	880	
25.....	1020	960
29.....	1120	1040
33.....	1210	1120
37.....	1300	1190
41.....	1350	1260
45.....	1410	1320
49.....	1470	1380
53.....	1530	1440
57.....	1590	1500
61.....	1640	1560

(Modified from Talbot.)

Increments or Decrements.

- 1. Add or subtract 12% of above for each degree C. 8% for each degree F.) above or below rectal temperature of 37.8° C. (100° F.)
- 2. 0 to 30% increments for activity.

20 to 30 per cent. In the first three to five days of life, activity is low and total caloric expenditure does not usually exceed 50 calories per kilogram of body weight. Increments for growth may be ignored, as may those for specific dynamic action, unless large amounts of amino acids or alcohol are administered.

The range as well as the usual losses of water and electrolytes from the lungs and skin, in the stool and in the urine is charted in Table 40 per 100 calories metabolized. The amount of water necessary for urine formation is directly related to the concentrating or diluting activities of the kidney and

Table 40. Water and Electrolyte Losses per 100 Calories Metabolized

	H <sub>2</sub> O ml.	Range		Usual	
		Na mEq.	K mEq.	H <sub>2</sub> O ml.	Na K mEq.
Evaporative*					
Lungs...10-60		0	0	15	
Skin...20-100		0.1- 3.0	0.2- 1.5	40	
Total...30-160		0.1- 3.0	0.2- 1.5	55	0.1 0.2
Stool*..... 0-50		0.1- 4.0	0.2- 3.0	5	0.1 0.2
Urine*..... 0-400		0.2-30.0	0.4-30.0	65	3.0 2.0

\* High values may also be considered to represent abnormal losses.

to the renal solute load, which is largely a function of the diet (Fig. 35). The approximate solute excretion for patients receiving no electrolyte and adequate carbohydrate to minimize tissue breakdown is 10 to 15 milliosmols per 100 calories metabolized. Usual electrolyte allowances would increase this value to 20 to 25 milliosmols per 100 calories. The amount of exogenous water needed to meet maintenance needs is approximately 10 to 15 ml. per 100 calories less than total requirements because of the release of that volume of water during oxidation of endogenous and exogenous carbohydrate, fat and protein. Thus the maintenance supply of water for the average patient ranges from 110 to 120 ml. per 100 calories metabolized. Such an allowance permits excretion of solutes without maximal dilution or concentration of the urine. This volume of fluid is less than that prescribed in usual oral infant feeding (140 ml. per 100 calories of food) because the intake of excretable solute is considerably greater on a milk or other protein-containing diet.

With alterations in body functions, adjustments in water allowances for maintenance must be made. In anuria or extreme oliguria (less than 10 ml. per 100 calories metabolized) only about 45 ml. of exogenous

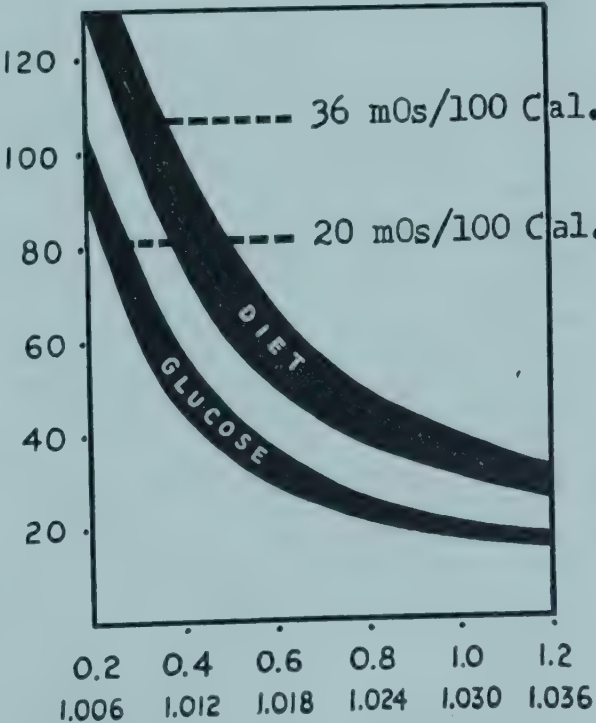


FIG. 35. Relationship of water requirement for urine formation to urinary concentration and dietary renal solute load. (Modified slightly from Darrow and Pratt, J.A.M.A., Vol. 143.)

water per 100 calories are required, since only evaporative and stool losses occur. Careful calculation of water of oxidation is particularly important in this condition, and water allowances should be adjusted accordingly. In the presence of excessive release of antidiuretic hormone as in some acute infections, particularly of the central nervous system, the intake should not exceed 80 to 90 ml. per 100 calories. When urinary specific gravity is fixed as in chronic renal disease, water requirements rise to 140 ml. per 100 calories, and in diabetes insipidus of nephrogenic or hypothalamic origin to as high as 400 ml. per 100 calories. In such instances the thirst of the patient and an awareness of the urinary output are usually more reliable than the physician's estimates, and oral feedings should be used if possible; urinary losses of water must not be replaced on a volume-for-volume basis. The author has observed adult patients who put out daily volumes of urine up to 8 and 10 liters in order to excrete loads of water administered "to balance" urinary losses incident to an initial diuresis of fluid retained during an oliguric phase. In hyperventilation and in heat stress evaporative losses of water may increase as much as 90 and 120 ml. per 100 calories, respectively, and increments in fluid intake should be made accordingly. High humidity environments, such as in incubators, may reduce evaporative losses of water by 20 to 50 per cent, and appropriate decrements in intake should be made.

Although there is great variability in excretion of electrolytes (Table 40), the sodium and potassium requirements for the average patient receiving parenteral fluids are 2 to 4 and 2 to 3 mEq., respectively, per 100 calories metabolized. A solution of 5 or 10 per cent invert sugar containing 30 mEq. per liter of sodium and chloride and 20 mEq. per liter of potassium as the lactate, acetate or glutamate salt represents an adequate maintenance solution\* which meets the usual requirements when given in amounts of 110 to 120 ml. per 100 calories metabolized. Such a solution should be given *only* intravenously at a fairly constant rate throughout

* 5 or 10% invert sugar or glucose in	
H <sub>2</sub> O .....	800 ml.
Isotonic saline .....	200 ml.
Potassium glutamate concentrate (Abbott) .....	10 ml.
or	
Potassium acetate concentrate (Cutter) .....	5 ml.

the day. If maintenance therapy must be conducted by subcutaneous administration of fluid, owing to technical difficulties, equal parts of 5 per cent glucose or 5 per cent invert sugar in water and Darrow's K lactate may be administered. Glucose in water or a very dilute electrolyte solution should not be given, since diffusion of sodium chloride and water into such an extravascular pool may acutely reduce plasma volume and precipitate shock.

Just as intake of water must be adjusted to meet specific alterations in body functions, so must intakes of electrolytes be individualized. For example, in anuria or oliguria no electrolyte should be administered for maintenance. In congestive heart failure limitation of sodium intake is as important in parenteral as in oral therapy. Reduction of sodium intake during fluid therapy of a patient with cardiac failure also demands some limitation of water since renal solute load is decreased and retention of water may occur.

In parenteral maintenance therapy for extended periods of time, and particularly in malnourished patients, carbohydrate, alcohol and amino acids may be necessary to attain caloric and nitrogen balance. A solution containing 10 per cent fructose, 2.5 per cent alcohol and 2.5 per cent Amigen,† plus necessary electrolytes for maintenance, has been used successfully by the author for complete parenteral alimentation. Albumin may be given as a source of preformed protein intravenously in doses of 3 gm. per 100 calories metabolized, particularly when severe malnutrition is present. The addition of a multivitamin preparation such as Berocca is indicated whenever previous nutrition was poor and maintenance therapy is prolonged.

Regardless of the accuracy of planning, periodic analyses of the serum and frequent physical examinations of the patient must be carried out in order to assess alterations in concentration and volume of body fluids as therapy progresses. Measurements of the non-protein nitrogen or blood urea nitrogen and the serum sodium, chloride and potassium levels are essential at intervals of twenty-four to seventy-two hours, depending on the clinical status of the patient. Such analyses may now be performed in many laboratories of capillary blood.

† Supplied by Mead Johnson & Co. Now available commercially as 5% Amigen, 12.5% Levogen and 2.5% alcohol.



MAINTENANCE THERAPY IN PREOPERATIVE, PARAOPERATIVE AND POSTOPERATIVE CARE

Preoperative preparation of a patient who has no pre-existing deficit or in whom the deficit has been repaired consists mainly in the supply of carbohydrate to ensure adequate storage of glycogen in the liver. The requirements of water and electrolytes for maintenance are similar to those for the average patient. As for small infants who are not vomiting, carbohydrate and sodium chloride mixtures should be given by mouth until three hours before operation. Such fluids are readily absorbed from the gastrointestinal tract and will not produce aspiration pneumonitis if vomited. During operation and for the first twenty-four hours postoperatively, limitation of water and electrolytes is indicated. Owing to the dangers of anoxia and shock, no potassium should be administered during these periods. The water intake should not exceed 35 ml. per 100 calories metabolized because of antidiuresis resulting from trauma or circulatory readjustment unless renal insufficiency and limited concentrating capacity are present. If the intake of water is not limited, whether given parenterally or by mouth, water intoxication may result. Sodium intake should also be low, owing to the low caloric expenditure during anesthesia and postoperatively. During operation, fluid, such as blood or plasma, must be given to meet large losses into traumatized tissue. The magnitude of such internal abnormal losses is judged best by the experienced surgeon as he operates. Postoperatively, limitation of intake should be maintained for twenty-four hours. Thereafter, usual maintenance therapy is gradually resumed.

ABNORMAL LOSSES OF WATER AND ELECTROLYTES

The principles underlying the concomitant replacement of external abnormal losses require little explanation. Such losses depend on the specific clinical disturbance (see Table 41) and must be replaced as they occur in order to prevent the development of further deficits. Considerable variation in composition exists from patient to patient and from time to time in the same patient. Although only an approximation can be made, these losses must be replaced, as nearly as possible, volume for volume as they occur in order to prevent physiologic readjustments which may further deplete the body of water

and electrolyte. Gastric or intestinal drainage can be replaced satisfactorily by solutions which are isotonic or somewhat hypotonic and contain some excess of chloride over sodium for gastric replacement and sodium over chloride for intestinal replacement. Ten to 20 mEq. of potassium should also be included. Losses of sodium chloride in sweat are of little significance except in adrenal insufficiency and cystic fibrosis of the pancreas. Heat stress should be avoided in such patients.

**Burns.** Internal abnormal losses of fluids are difficult to quantitate. This phase of fluid therapy is exemplified by the treatment of burns. Unless unusual delay has occurred before a burned child is brought to the hospital, pre-existing deficits are minimal and significant deficits result solely from inadequate or delayed fluid therapy after admission. Maintenance requirements for water are diminished when the large surface area is covered by wet dressings which limit evaporation from the skin; evaporation from the lungs is normal or increased. Urinary output of water is probably limited by some antidiuresis which results from massive stimulation of nerve receptors. Thus the fluid therapy of burns is concerned principally with the replacement of abnormal losses. Some of these losses are external, such as plasma oozing from the burned surface. In addition, a significant number of erythrocytes are destroyed or damaged by exposure to heat, and their survival time is shortened. The largest part of the abnormal loss is internal in the form of plasma and plasma ultrafiltrate sequestered around the burn site. The magnitude of this sequestration has been approximated by measurements of the extracellular space in patients with severe burns. Such measurements are partially invalidated, however, by the fact that

Table 41. Composition of External Abnormal Losses

Fluid	Na	K	Cl	Protein
	mEq./L.			Gm. %
Gastric.....	20-80	5-20	100-150	—
Pancreatic.....	120-140	5-15	90-120	—
Small intestine.....	100-140	5-15	90-130	—
Bile.....	120-140	5-15	80-120	—
Ileostomy.....	45-135	3-15	20-115	—
Diarrheal.....	10-90	10-80	10-110	—
Sweat.....				
Normal.....	10-30	3-10	10-35	—
Cystic fibrosis....	50-130	5-25	50-110	—
Burns.....	140	5	110	3-5

large amounts of saline solution were administered therapeutically, and true obligatory losses can only be approximated.

Losses of fluids are proportional not to the weight or metabolism of the patient, but to the surface area of the second- or third-degree burn. This area can be approximated by the "rule of nine"\* or from appropriate charts of the body surface.

The composition of an ideal replacement solution cannot be fixed. A mixture of 3 parts of plasma, 1 part of blood and 3 parts of a balanced saline solution† represents a reasonable replacement fluid which may be given at the rate of 10 liters per square meter of second- or third-degree burned surface area per forty-eight hours. A third is administered in the first six hours, a third in the next twelve hours and a third in the next thirty hours. Such a program can only approximate the actual needs. The progress of therapy must be monitored at one- to two-hour intervals by the determination of hematocrits of capillary blood and of plasma protein levels and by careful measurements of the volume and concentration of urine obtained by an indwelling catheter. Urine volume should remain at 30 to 50 ml. per 100 calories metabolized. A rising hematocrit value and falling urine volume, for example, indicate an inadequate rate of replacement of fluids. After forty-eight hours fluid therapy should be sharply limited. The sequestered fluid may return at this time to the vascular compartment and produce acute pulmonary edema, particularly if there has been thermal injury to the lungs. Digitalis and mercurial diuretics, if there has been no renal injury, may be helpful at this time.

**Abnormal Urinary Losses.** There are certain conditions in which occult abnormal losses occur into the urine. Sodium-losing disorders such as pulmonary, cerebral or adrenal "salt wasting" or potassium-losing disorders such as primary hyperaldosteronism or congenital alkalosis of renal origin may be suspected when there are alterations in con-

centrations of serum electrolytes in the absence of obvious losses. "Wasting" a particular electrolyte is established when excessive quantities of it are demonstrated in the urine in the presence of restricted intake and a low serum concentration in association with normal or reduced volume of body fluid. "Spot tests" which indicate only the concentration of electrolytes in the urine are inadequate for diagnostic purposes.

## SUPPLEMENTAL THERAPY

It is occasionally necessary in fluid therapy to supply an excess of certain substances to effect a particular change in physiological function or to facilitate excretion of a particular substance. Such therapy in the form of water and electrolytes is given in the absence of specific deficits and above the usual needs.

**Salicylate Poisoning.** Supplemental therapy is of particular importance in the treatment of salicylate poisoning. The initial effect of a high concentration of salicylate is to sensitize the respiratory center to carbon dioxide. The resultant hyperventilation leads to increased evaporative losses of water and to respiratory alkalosis. The renal compensation for respiratory alkalosis consists in the excretion of large amounts of sodium and potassium bicarbonate. In addition, to levels of salicylate may reduce hepatic glycogen. Ketonemia and ketonuria usually result, and occasionally there is hypoglycemia. The loss of sodium and potassium in excess of chloride and the accumulation of acetoacetic and beta-hydroxybutyric acids eventually lead to severe metabolic acidosis. Transition from respiratory alkalosis to metabolic acidosis may be relatively rapid. Therapy must be followed by periodic evaluation of the serum carbon dioxide content and the pH of blood and urine. Early in therapy adequate amounts of water, carbohydrate and electrolytes must be supplied to meet the increased evaporative losses and to permit maximal renal compensation. Approximately 160 to 180 ml. of water, 15 gm. of invert sugar or glucose, 6 to 8 mEq. of sodium and 3 to 6 mEq. of potassium per 100 calories metabolized should be given.

As the phase of metabolic acidosis begins, administration of sodium bicarbonate or potassium acetate or glutamate to maintain alkaline urine (pH >7.5) will facilitate excretion of salicylate. The dose of bicarbonate necessary to alkalinize the urine is

\* Head, arm, one quarter of trunk, one half of leg: each equals 9 per cent of the body surface. The sum of the percentages times total surface area as given by nomogram on page 209 equals the area used in calculating requirements. Infants and small children, owing to relatively larger heads and trunks and smaller extremities, fit more exactly to a "rule of sixes." Arm, one half of head or leg and one eighth of trunk: each equals 6 per cent of the body surface.

† Two parts isotonic saline, 1 part sixth-molar sodium lactate.



Table 42. Composition of Commonly Used Oral and Parenteral Solutions

Oral									
	CHO	Prot.*	Calories	Na	K	Cl	HCO <sub>3</sub> †	Ca	P‡
	Gm./100 ml.		per L.	mEq./L.					
Milk (whole).....	4.9	3.5	670	22	36	28	30	60	54
Orange ale.....	9.0		360	3.5	0.1		3.6		
Pepsi-Cola.....	10.9		435	0.4	13		13.4		
Fruiti-Cola.....	12.0		480	6.5	0.8		7.3		
Orange juice (sweetened).....	14.0		540	0.2	49		50		
Grape juice.....	18.0		670	0.4	31		32		
Tomato juice (canned and salted).....	4.3		210	100	59	150	10	3	9
Pyren.....	7.0		280	50	20	30	34	4	10
L.H. mixture.....	5.0		200	30	20	30	20		
Parenteral									
H <sub>2</sub> O§ in H <sub>2</sub> O.....	5-10		200-400						
Isotonic saline.....	0-5		0-200	154		154			
½ Isotonic saline.....	2.5-5		100-200	77		77			
¼ Isotonic saline.....	5		200	50		50			
½ (M/2) saline.....				500		500			
¾ Saline.....				850		850			
¾ Ammonium chlorate.....						400			
1/6 Sodium lactate.....				167			167		
75% Sodium bicarbonate.....				446			446		
Ringer's.....	0-10		0-400	147	4	155.5		4.5	
Ringer's lactate.....	0-10		0-400	130	4	109	28	3	
Marrow's KNL.....				122	35	104	53		
Butler's.....	5-10		200-400	55	23	45	26		12
Modified Butler's 1.....	5-10		200-400	25	20	22	23		3
Modified Butler's 2.....	5-10		200-400	60	25	53	25		12
Calbot's.....	5-10		200-400	40	35	40	20		15
Hardway's.....	3.5-10		140-400	26	27	53			
Gastric replacement.....	0-10		0-400	63	17	150			
Intestinal replacement.....	5-10		200-400	80	36	63	60	4.6	
Pyrimigen.....	5-10	5	345-515	30	15	22		5	30
Pyrimigen, dextrose and Ringer's lactate.....	3.3	3.3	230	65	10	51	10	5	20
Pyrimigen, dextrose and alcohol.....	5-12	5	670-800	30	15	22		5	30
Dextran 6%.....	0-5		0-200						
Dextran 6% in saline.....				154		154			
Plasma  .....		5		146	5	75	60		3
Blood ¶.....		3		95	4	50	40		2
Additives									
Glucose 50%.....			0.5 gm. per ml.						
Sodium chloride.....			2.5 mEq. per ml.						
Sodium lactate.....			2.5 mEq. per ml.						
Potassium chloride.....			1.0 or 2.0 mEq. per ml.						
Potassium phosphate.....			2.0 mEq. per ml.						
Potassium glutamate.....			1.0 mEq. per ml.						
Potassium acetate.....			4.0 mEq. per ml.						
Ammonium chloride.....			5.0 mEq. per ml.						

\* Protein or amino acid equivalent.  
† Actual or potential bicarbonate, such as acetate, lactate, citrate.  
‡ Calculated according to valence of 1.8.  
§ Glucose (dextrose), fructose or invert sugar.  
|| Freshly separated with A.C.D. solution.  
¶ Red cell contents not included in calculations.

proximately 5 mEq. per kilogram of body weight, which can be given over twelve hours in divided doses. Approximately 2 of the 5 mEq. of cation should be given as potassium to prevent alkalosis and to avoid renal tubular potassium depletion with paradoxical aciduria. Exchange transfusion or dialysis by means of the artificial kidney may also be used to remove salicylate loosely bound to plasma proteins in severely ill patients with high blood levels of salicylate.

**Potassium Intoxication.** The excretion of potassium may be increased acutely by loading with hypertonic sodium bicarbonate (2 mEq. per kilogram in one hour as M/2 sodium bicarbonate). Such supplemental therapy may be lifesaving in acute hyperkalemia, since elevation of serum sodium concentration and pH reduces serum potassium concentration even in the nephrectomized animal. A small amount of invert sugar and 0.2 unit of insulin per kilogram may accelerate the shift of potassium from the extracellular to the intracellular space.

Although water loading may be considered a form of supplemental therapy, excretion of solute, such as urea in glomerular insufficiency, is not increased by such a procedure unless pre-existing dehydration is present. Water retention, edema or water intoxication may result.

## PARENTERAL SOLUTIONS

Table 42 lists various solutions commercially available for use in deficit, maintenance, abnormal loss replacement and supplemental therapy. The large number of carbohydrate and electrolyte mixtures available permits great flexibility and individualization of therapy.

ROBERT E. COOKE

## REFERENCES

Bonham-Carter, R. E., Dent, C. E., Fowler, D. I., and Harper, C. M.: Calcium Metabolism in Idiopathic Hypercalcemia of Infancy with Failure to Thrive. *Arch. Dis. Childhood*, 30:399, 1955.  
Calcagno, P. L., Rubin, M. I., and Singh, N. S. A.: The Influence of Surgery on Renal Function in Infancy: The Effect of Surgery in the Postopera-

tive Renal Excretion of Water—The Influence of Dehydration. *Pediatrics*, 16:619, 1955.  
Chung, A. W.: The Effect of Oral Feeding at Different Levels on the Absorption of Foodstuffs in Infantile Diarrhea. *J. Pediat.*, 33:1, 1948.  
Cooke, R. E.: The Role of Potassium in Fluid Therapy. *Postgrad. Med.*, 4:257, 1953.  
Cooke, R. E.: Contributions of the Laboratory to Practical Management of Disorders of Body Water and Electrolyte. *Pediatrics*, 16:555, 1955.  
Cooke, R. E., and Crowley, L. G.: Replacement of Gastric and Intestinal Fluid Losses in Surgery. *New England J. Med.*, 246:637, 1952.  
Danowski, T. S., Greenman, L., Weigand, F. A., and Mateer, F. M.: Acidosis and Coma in Juvenile Diabetics. *Am. J. Dis. Child.*, 93:341, 1957.  
Darrow, D. C.: Congenital Alkalosis with Diarrhea. *J. Pediat.*, 25:519, 1945.  
Darrow, D. C., and Pratt, E. L.: Fluid Therapy: Relation to Tissue Composition and Expenditure of Water and Electrolyte. *J.A.M.A.*, 143:365, 1950.  
Darrow, D. C., Pratt, E. L., Flett, J., Jr., Gamble, H., and Wiese, H. F.: Disturbances in Water and Electrolyte in Infantile Diarrhea. *Pediatrics*, 44:129, 1949.  
Finberg, L.: Experimental Studies of the Mechanisms Producing Hypocalcemia in Hypernatremia. *J. Clin. Investigation*, 36:434, 1957.  
Gruskay, F. L., and Cooke, R. E.: The Gastrointestinal Absorption of Unaltered Protein in Normal Infants and in Infants Recovering from Diarrhea. *Pediatrics*, 16:763, 1955.  
Harned, H. S., Jr., and Cooke, R. E.: Symptomatic Hyponatremia in Infants and Children Undergoing Surgery. *Surg., Gynec. & Obst.*, 104:519, 1957.  
Holliday, M. A., and Segar, W. E.: The Maintenance Need for Water in Parenteral Fluid Therapy. *Pediatrics*, 19:823, 1957.  
Nyhan, W. L., and Cooke, R. E.: Symptomatic Hyponatremia in Acute Infections of the Central Nervous System. *Pediatrics*, 18:604, 1956.  
Rapoport, S.: Hyperelectrolytemia and Hyperosmolality in Pathologic Conditions of Childhood. *Am. J. Dis. Child.*, 74:682, 1947.  
Schlesinger, B. E., Butler, N. R., and Black, J.: A Severe Type of Infantile Hypercalcemia. *B.M.J.*, 1:127, 1956.  
Skinner, A. L., and Moll, F. C.: Hypernatremia Accompanying Infant Diarrhea. *Am. J. Dis. Child.*, 92:562, 1956.  
Talbot, N. B., Crawford, J. D., and Butler, A. N.: Medical Progress: Homeostatic Limits to Severe Parenteral Fluid Therapy. *New England J. Med.*, 248:1100, 1953.  
Weil, W. B., and Wallace, W. M.: Hypertonic Dehydration in Infancy. *Pediatrics*, 17:171, 1956.

## ADMINISTRATION OF PARENTERAL FLUIDS

Parenteral fluid therapy is dependent not only upon the correct choice of fluids, but also upon the ability of the physician to administer these fluids adequately. This requires the development of technical skill, particu-

larly in intravenous administrations, since this is the preferred route for most solutions and the required one for some.

Other routes for the parenteral administration of fluids are the subcutaneous, periton-



and intraosseous ones. The subcutaneous route has limitations which are also applicable to intraperitoneal administrations. The peritoneal and intraosseous routes are dangerous because of the possibility of infection; their use is not recommended except in extraordinary circumstances. In patients in profound shock, the prompt use of the intraosseous space for blood transfusion may occasionally be lifesaving.

### INTRAVENOUS INFUSIONS

**Long-Term Intravenous Infusion.** Success in intravenous therapy which extends for a day or more depends upon proper restraint of the patient, adequate and well prepared equipment and skill in cannulating the vein.

In infants and young children the veins about the wrists and feet offer the best sites for intravenous administrations. The lower arm and hand or the lower leg and foot are more easily immobilized than the upper portions of the extremities, and the veins will generally receive 22- or 23-gauge needles without difficulty. Larger needles can often be used, and, in general, the largest needle which will fit the vein will be the easiest to use. Immobilization is best obtained by fastening the hand and lower arm or foot and lower leg with wide adhesive ( $\frac{3}{4}$  inch) to a well packed sandbag of appropriate shape and of sufficient weight to maintain the extremity in a satisfactory position. In older children the veins in the antecubital area may be used, but adequate restraint is difficult to obtain except in a cooperative child.

Veins of the scalp are sometimes easy to cannulate in infants, but it is difficult to immobilize the head, so that these veins do not lend themselves to continuous infusions unless the need for restraint is lessened, as it may be through the use of the Gardner and Murphy needle. This consists of a needle shaft without a hub, to which is attached 6 to 8 inches of polyethylene tubing, thus permitting the bulky stopcock and syringe to be placed at a position not immediately adjacent to the head.

In exceptional circumstances when an assured route of fluid administration is urgently needed, as during surgical procedures, it is expedient to "cut down" on the saphenous vein at the ankle and cannulate the vein with a nonwetttable plastic tubing which will not be so easily dislodged from the vein as a needle.

**Venipuncture.** A satisfactory system for the administration of intravenous fluids con-

sists of a closed fluid container,\* disposable plastic tubing with a drip chamber and with blood or plasma filters when needed, terminating in a three-way stopcock to which the needle and a 10- or 20-ml. syringe are attached. The needle should be the largest which can be used for the vein chosen; a flat bevel about twice as long as the thickness of the needle is satisfactory. The needle should be carefully examined for irregularities of the cutting edge and for patency. A few milliliters of saline solution are then drawn into the syringe, and any air present is evacuated.

With the extremity carefully immobilized, the skin over the vein is prepared with alcohol or Zephiran solution and the vein distended by pressure over its proximal portion. The needle is inserted through the skin directly above the vein and, with the bevel up, is advanced through the tissues parallel to and above the vein in such a way that the bevelled edge carries it into the vein. The point at which this occurs can often be seen. If penetration of the vein is not seen but suspected, it may be confirmed by the appearance of blood in the syringe or by the fact that saline solution may be easily pushed into the vein without the formation of a nodule of extravasation about the point of the needle.

When the needle enters the vein, it may be expedient to advance it cautiously while saline solution is injected to keep the vein dilated before the advancing edge of the needle. The needle is then taped securely to the skin and the stopcock turned to permit flow of fluid through the drip chamber at the desired rate. If it is intended to give the fluid requirement for twenty-four hours, the rate of flow will vary from about 0.5 to 1 ml. per minute, depending upon the size of the patient and the clinical problem.

**Cannulation of a vein.** The internal malleolar vein is usually chosen for insertion of plastic tubing or a cannula. Initially the vein is located just above the internal malleolus by application of a tourniquet, and the area is prepared by sterilization of the skin and establishment of local anesthesia. An incision is then made transversely through the skin over the vein, and the vein is brought into view by blunt dissection. A suture is passed behind the vein and tied as far distally as possible. A small transverse incision is then

\* Commercial preparations of standard solutions, available in sealed bottles, are provided with sterile packets of dispensable plastic tubing and with air filters. The use of such equipment eliminates some of the factors which contribute to contamination.

made in the vein, and a polyethylene or other suitable plastic catheter of proper size is inserted for a distance of a few centimeters. A second suture is tied over the tubing proximal to its point of entry into the vein. The incision in the skin may then be closed with a suture or two. Catheters so placed may be used for several days. The catheter may be kept open when no fluid is actually going through by filling it with saline solution containing a little heparin to retard or prevent clotting at the end of the tubing. If signs of infection or phlebitis occur, the tubing should be promptly removed.

**Short-Term Intravenous Infusion.** When intravenous therapy is limited to a small amount of fluid for a relatively short time, as for an elective blood transfusion, operative cannulation of veins is not recommended unless absolutely necessary, since the vein will not subsequently be available for intravenous therapy and since disfiguring scars sometimes result. The technique for infusion by venipuncture is applicable here. In infants the veins of the scalp may be used effectively if an assistant is available to hold the head for the duration of the procedure. The infant is restrained in a blanket and his head held at the edge of a table, where the operator may carry out the transfusion through manipulation of the stopcock and syringe, taking care not to allow movement of the needle once entry into the vein is made. The rate of infusion should not ordinarily exceed 10 ml. per minute, and in the case of cardiac failure or other serious disturbance may need to be much less (1 to 5 ml. per minute).

### SUBCUTANEOUS INFUSIONS

Subcutaneous fluid administration is limited to solutions of electrolytes of approximately isotonic strength. Solutions of glucose in water are unsuitable because they cause local irritation and may create movement of electrolytes into tissue spaces which defeats the aim of their administration. However, 2.5 per cent glucose in half-isotonic saline solution is well tolerated and is widely used. Solutions with less than this concentration of salt should not be used.

Fluid may be given under the skin on the lateral aspect of the thighs, in the axilla or, preferably, over the back of the trunk. The skin is prepared as for a venipuncture, a loose fold is picked up between the fingers, and the needle is pushed through at the base of the fold parallel to the underlying muscles to avoid penetration of them.

Prolonged subcutaneous infusions are usually given in the tissues of the anterior thigh with the patient restrained in the supine position. Infusions may be given into each thigh simultaneously with a Y adapter through 20-gauge needles, 2 or 3 inches in length. The needles must be securely anchored with adhesive tape. When the infusion is finished, the needle holes should be sealed with collodion.

In infants, when only a small amount of fluid is needed (not more than 40 ml. per kilogram), subcutaneous infusions may be given by syringe into tissues of the back. A long needle is inserted below the tip of the scapula and directed upwards into the interscapular and lateral areas of the back. Fluid is injected during the advance of the needle not exceeding in any position an amount which causes blanching of the skin over the tip of the needle. The needle is then almost completely withdrawn before being redirected in a like manner, so that trauma from redirection of the needle is kept at a minimum.

### INTRAMEDULLARY INFUSIONS

Owing to the danger of infection, the use of intraosseous infusions is limited mainly to emergency administration of blood plasma or other fluids in severe shock when there is collapse of peripheral veins. The sternal marrow may be used in children over five or six years of age, and the tibial and femoral marrows in younger children and infants. Special needles with stilets are recommended. The need for asepsis is of utmost importance. Care should be taken in performing the sternal puncture not to penetrate the mediastinum. The upper third of the tibia and the lower third of the femur are the sites chosen; the needle should be directed away from the epiphysis. The use of marrow infusions is contraindicated in septicemia and when it is necessary to introduce the needle through infected skin.

### BLOOD TRANSFUSION

Transfusion of whole blood or of products derived from whole blood may be specifically required in treatment of shock, in replacement of losses due to injury or surgical procedures, and in various hematologic disorders. Transfusion may be used less specifically as a supportive measure in many disturbances in infants and children. Adequate indications for transfusion of blood or blood derivatives should always be insisted upon, since blood transfusion is an expensive and often potentially harmful form of therapy.



Whole blood is most commonly used in transfusion, but often some fraction of whole blood or plasma will supply the patient's needs. For example, sedimented red blood cells may be preferred in the treatment of anemia; preparations rich in platelets, for the treatment of thrombocytopenia. "Platelet preparations" require silicone-coated glass or nonwetable plastic surfaces for collection and administration. Plasma or plasma derivatives may be preferable for certain hemorrhagic disorders or hypoproteinemias.

The safety of blood transfusions must be assured (1) by prevention of immediate reactions in the recipient resulting from antibodies ("natural" or acquired by prior transfusion) against the transfused cells, and (2) by prevention of formation of antibodies in the recipient, which might jeopardize future transfusions or cause hemolytic disease of the newborn in an offspring of a female recipient. The Rh (D or Rh<sub>o</sub>) antigens are the major untoward factors. Accurate typing of donor and recipient with respect to the A-B-O and Rh (D or Rh<sub>o</sub>) antigens and adequate cross-matching of the two bloods provide the necessary assurance.

The *cross-match*, which suspends donor's cells in recipient's serum (major cross-match) and recipient's cells in donor's serum (minor cross-match) determines (1) whether the recipient's blood contains antibody for donor's cells ("major mismatch") and (2) whether the transfused blood contains an antibody for the patient's cells ("minor mismatch"). The major mismatch is more dangerous than the minor, since the recipient has relatively large stores of antibody, whereas donor antibody is usually diluted in the recipient to an innocuous level.

A blood transfusion ought not to be given without cross-matching except in the most acute emergency; at such times group O blood which is Rh (D or Rh<sub>o</sub>) negative is probably safest. The use of group O blood, which contains anti-A and anti-B factors, as "universal donor" blood for A, B or AB recipients should be avoided if at all possible. When there is no alternative, blood should be chosen, if possible, which has low titers of anti-A and anti-B and in which the anti-A and anti-B are not hemolytic or resistant to neutralization by A and B specific polysaccharide substances. The addition of the latter substances to group O blood probably does not greatly reduce any potential danger from minor mismatch incompatibilities.

There are variations in the techniques of the cross-match, but certain factors appear to be basic. First, since antibodies formed in response to sensitizing transfusions are usually not active in a suspending medium of isotonic saline solution, the cross-match should be set up in the native serums of the donor and recipient, or in such mediums as 20 per cent bovine albumin or albumin-serum mixtures. If cells must be suspended in saline solution, their agglutinability may be enhanced by partial digestion by such enzymes as trypsin or papain. In recipients who have had previous transfusions all these techniques may fail to detect certain antibodies, notably anti-Kell and anti-Duffy, so that it is essential that the cross-matching procedure should demonstrate compatibility on the major side, at least, by the indirect antiglobulin technique (Coombs' test).\*

\* A positive antiglobulin reaction occurs when red blood cells become coated with specific antibody. The coating globulin antibodies often fail to cause agglutination of the coated cells in certain mediums. In such instances the globulin antibody may be detected indirectly through the phenomenon of precipitation with an antiglobulin serum.

Antiglobulin serum for the test is prepared in rabbits by injection of human serum. The rabbit forms antiglobulin precipitins which may be assayed by precipitin titration against normal serum. Animal serums so prepared are absorbed with human cells of various types to remove all species-specific cellular agglutinins. The serum precipitins remain.

The indirect antiglobulin test is carried out as follows: 2 drops of 2 to 5 per cent suspension of red blood cells in saline solution are added to 2 drops of the serum suspected of having antibodies for the chosen cells. After incubation for fifteen minutes at 37° C. the cells are washed three times in saline solution and reconstituted to a 2 per cent suspension. A drop or two of potent antiglobulin reagent is added, and the suspension is centrifuged at low speed for a minute. The tube is then lightly shaken; if agglutination is present, it indicates that the cells have been coated with antibody of the serum to which the cells were exposed. The observed agglutination is the by-product of the precipitation of globulin particles on adjacent cells.

In erythroblastosis fetalis and certain acquired hemolytic anemias the red blood cells of the patient may institute an immediate positive antiglobulin reaction after washing (*direct* antiglobulin reaction, or Coombs' test). In erythroblastosis fetalis the antibodies are transferred to the fetus through the placenta; in acquired hemolytic anemia auto-antibodies may be formed in the patient as part of the morbid process.

The antiglobulin reaction is the most sensitive method for detection of coating antibody, but it does not indicate the specificity of the coating particles. This identity must be established by studying the reactions of a number of cells of known types.

The possibility that a blood transfusion will sensitize the recipient and thus create the potential for future untoward transfusion reactions will practically be eliminated by avoiding the transfusion of Rh<sub>0</sub> (D)-positive blood to an Rh<sub>0</sub> (D)-negative recipient. Routine screening for less common incompatibilities is impractical. Rh<sub>0</sub> (D)-negative blood should be chosen for the Rh<sub>0</sub>-negative recipient so as to exclude the weakly reactive bloods known collectively as D<sup>u</sup> positive; such blood may be strongly antigenic in Rh<sub>0</sub>-negative persons. The safest method of exclusion at present is to test by the indirect antiglobulin technique (Coombs' test) all donor bloods which appears to be Rh<sub>0</sub> negative. Blood which has a positive reaction with anti-Rh<sub>0</sub> (anti-D) serum by this technique should be considered D<sup>u</sup> positive and be given only to Rh<sub>0</sub>-positive recipients.

Other reactions which may complicate transfusions include (1) febrile responses to pyrogens, (2) allergic reactions to ingested allergens or to reagins in the blood of the donor or to other factors in the plasma of the donor to which the recipient is sensitive, (3) severe toxic reactions caused by bacterial contamination of donor blood during collection or storage, (4) homologous serum hepatitis, (5) rarely, a toxic reaction to an elevated potassium level of the donor blood which normally occurs during storage.

Pyrogenic reactions are most often the result of improper cleansing of tubing and needles. Such reactions can be avoided or minimized by scrupulous cleanliness of equipment or by use of properly prepared disposable tubing for all intravenous therapy.

Allergic reactions can be avoided by delaying withdrawal of blood from the donor until after a suitable fasting interval and by rejection of allergic persons as donors. Reactions to plasma proteins occur most often in recipients of multiple transfusions, who may have febrile and urticarial responses regardless of how carefully the donor may be chosen. If the need is principally for red blood cells, sedimented cells may be given in place of whole blood to minimize the allergic response. Administration of aspirin and an antihista-

minic drug before and during transfusion provides additional precautions.

The severity of the toxic reaction to blood contaminated with bacteria necessitates the utmost care in the collection, storage and use of blood. Blood should remain in the bank until time for its use and should not be used if exposed to room temperature for more than a few hours.

Homologous serum hepatitis is less likely to occur after blood transfusion than after the administration of pooled plasma or plasma products. Its occurrence, however, is a strong argument against the unnecessary use of blood transfusions and against the choice of donors who have had jaundice.

Toxic reactions to elevated serum potassium levels in donor blood are most likely when large amounts of blood are used, as in exchange transfusions. Blood for this procedure should, under optimal conditions, be freshly drawn, and should in no instance be stored longer than four days. If a reaction is suspected during the course of an exchange transfusion, prompt administration of 5 to 10 ml. of 10 per cent calcium gluconate solution may prove lifesaving.

The amount of blood given in a transfusion should vary according to the clinical problem: the need during active hemorrhage may be for continuous transfusion; in an anemic newborn infant, for a relatively small transfusion of sedimented cells. Except for continuing hemorrhage or shock, transfusion should not exceed 10 ml. per pound (20 ml. per kilogram) of body weight if whole blood is used, or 5 to 7 ml. per pound (10 to 15 ml. per kilogram) if sedimented cells are used. Somewhat larger amounts of blood may be used if administered very slowly by intravenous drip, but the possibility of precipitation of cardiac failure and pulmonary congestion by intolerable increases in blood volume or viscosity should be guarded against. In such patients an *exchange transfusion* may permit efficient restoration of the oxygen-carrying capacity of the blood without changing, or with a salutary decrease in, blood volume.

VICTOR C. VAUGHAN, D



## TECHNICAL PROCEDURES

### COLLECTION OF SPECIMENS

**Urine.** The collection of urine specimens in infants and children who have not acquired voluntary sphincter control requires special techniques. In boys a smooth-glass test tube may be fastened over the penis with a 2- or 3-inch square of adhesive tape. The tube is slipped through a hole in the middle of the tape and made watertight with a band of adhesive. The square is then folded to the perineum. In girls a feeding cup from a bird cage may be substituted for the test tube, or a soft polyethylene diaper, which contains a reservoir for collection of urine, may be used.

Twenty-four hour specimens may be obtained from boys by securely fastening a soft rubber tube (Penrose tubing) or plastic tubing about the penis so as to make it watertight over the perineum and placing the open end in a collecting bottle. In girls plastic tubing may be taped to the vulva or fixed with skin cement. A metabolism bed is more effective.

If a specimen is urgently needed, catheterization may be performed. A small silk catheter, no. 9 or 10 French scale or no. 4 American scale, can usually be passed without difficulty. Utmost care should be used to avoid trauma and the introduction of infection. Catheterization should be used routinely only to secure urine for bacterial culture, to rule out external contamination in suspected pyuria in females, or to secure residual urine after voiding.

**Blood. Capillary blood.** Amounts up to 0.5 ml. of blood can often be obtained from finger or heel puncture. After preparation of the skin with alcohol solution or Zephiran, a stab is made, preferably on the *side* of the finger or heel, with a sharp, sterile (auto-sterilized) lancet. Only *disposable* lancets should be used, to avoid transmission of homologous serum hepatitis. For chemical determinations free flow of blood should be obtained, and milking or squeezing of the finger or heel should be avoided; otherwise, admixtures of tissue fluids may occur which vitiate the findings. After the puncture has been made and a free flow of blood obtained, the area should be wiped absolutely dry of any remaining sterilizing solution so that subsequent spreading of the blood due to reduction of surface tension is minimized.

**Venous blood.** In older children the veins

in the antecubital space are the most satisfactory for venipuncture. An uncooperative child may be held in the lap of an assistant, who holds the arm hyperextended while a tourniquet is lightly applied above the elbow. With the vein fixed in the tissues by hyperextension of the arm, the needle is inserted. If the vein appears to be readily available, penetration of the skin and vein may be made in one smooth motion. The most common errors are inadequate fixation, incomplete extension of the arm and improper direction of the needle toward the vein at an angle. The introduction and insertion of the needle should be in a plane nearly parallel to that of the vein.

In infants and young children blood is most readily obtained from the femoral and external jugular veins. Sometimes the scalp veins or those on the dorsum of the hand can be used. Rarely it may be necessary to use the internal jugular vein.

Use of the femoral vein requires an assistant to hold the leg flexed on the thigh with the knee maximally rotated outward and the thigh about half-abducted at the hip joint. The opposite leg may be put into a similar position and held there by the body of the assistant, who leans across an examining table to restrain the leg to be used. A 20- or 21-gauge needle with a 30-degree flat bevel should be used. The vein will be found just medial to the arterial pulsation, which can ordinarily be felt without difficulty at the inguinal crease. The needle is inserted through the skin about 1 inch below the inguinal crease and directed slightly cephalad to a position just medial to the artery under the guidance of the forefinger, which is kept on the pulsating artery. The vein is often transfixed, in which case the needle will usually strike the femur. Withdrawal of the needle for a short distance while slight negative pressure is maintained within the syringe will usually result in a spurt of blood into the syringe. When the specimen is obtained and the needle withdrawn, firm pressure over the vein should be maintained for a minute. If an artery is inadvertently entered, pressure should be continued longer. The cyanosis and mottling of the extremity which often accompany arterial puncture are usually transient.

For withdrawal of blood from the external jugular vein, the infant is wrapped securely

in a blanket and the supine body is steadied between the arms of the assistant, who holds the head extended and rotated between her hands over the side of the table opposite her. The external jugular vein is evident over the sternocleidomastoid muscle, and the needle may be inserted when the vein is distended by the crying of the infant.

The child must also be restrained in the foregoing manner for puncture of the internal jugular vein. A needle,  $1\frac{1}{2}$  inches in length, is inserted lateral to the sternocleidomastoid muscle at the junction of its upper and middle thirds, and advanced toward the tip of the index finger, which is placed in the supra-sternal notch. The vein is reached within  $\frac{1}{2}$  to  $\frac{3}{4}$  inch from the skin surface; if negative pressure is maintained in the syringe, entry into the vein will result in flow of blood into the syringe. Care should be taken to avoid the trachea and the pleura. This procedure should not be done unless the trachea is in the midline. When the needle is withdrawn from either the external or the internal jugular vein, the child should be put immediately in an upright position and pressure should be applied over the vein for a minute with a gauze sponge.

**Material for Bacterial Cultures from the Nasopharynx and Throat.** In bacterial pneumonias the pathogen can be isolated from the nasopharynx in a great many instances. A satisfactory swab can be prepared by attaching cotton with collodion to the end of a thin copper wire, which can then be autoclaved. With the child restrained, the tip of the nose is elevated with the thumb of one hand and the swab passed with the other hand into the nostril, along the floor of the nasal cavity close to the septum into the nasopharynx. The sensitive turbinates should be avoided unless a *nasal* swab is desired for culture or examination of a stained smear for eosinophils.

Material for a throat culture is obtained by swabbing the infected areas while the child is restrained and the tongue depressed. The exudate on the swabs *must* be streaked on appropriate mediums immediately, since it dries rapidly and pathogens may quickly become nonviable.

#### GAVAGE AND GASTRIC LAVAGE

**Gavage.** Feeding by stomach tube is indi-

cated for small premature infants who have inadequate sucking or swallowing function, and for infants and older children whose ability to swallow or retain nourishment is impaired.

In premature infants a small rubber catheter or small-bore polyethylene or other plastic tubing may be used, the latter having the advantage that it may be left in the stomach for several feedings. Polyethylene tubing for this purpose is available with a rounded tip to minimize danger of injury to the infant's tissues. It is not advisable to leave the tubing in place for more than a day or two because of the possibility of esophageal or gastric erosion. In older infants or children catheter or stomach tubes may be used. Here, too, there will be circumstances in which the use of continuous gavage by polyethylene or other plastic tubing will be advantageous.

Tubes for gavage should be moistened and passed with care through the nose or mouth and advanced slowly into the esophagus and stomach. If choking, coughing or aphonia suggests that the tubing may have entered the respiratory passages, it should be removed and reinserted. When the tube has been introduced a distance equal to that from the xiphoid to the nose, the tip will probably be in the stomach. Its position can be tested by introducing a few bubbles of air while auscultation is made over the left upper quadrant. Fluid given by gavage is best administered by gravity from an open container. The tube should be pinched off as it is removed to prevent leakage into the pharynx or respiratory tract.

**Gastric Lavage.** This procedure is used to remove stomach contents in instances of pyloric or high intestinal obstruction, delayed emptying, poisoning, and the like, or to obtain swallowed material of pulmonary origin for examination. The tube, which should be the largest practicable, should be passed in the manner described for gavage. Lavage may be accomplished by gravity, with the reservoir alternately raised and lowered to fill and siphon out the stomach contents, or more actively by the use of a syringe. A variety of washing solutions such as water, saline, bicarbonate solution and oils are used according to the clinical problem.

VICTOR C. VAUGHAN, M.D.



# DRUG THERAPY

## GENERAL CONSIDERATIONS

ational drug therapy is based on a clear understanding of the metabolic processes peculiar to the growing child, of the ways in which various diseases alter these processes, and of the mechanisms by which drugs may be remedial. Some medicinal therapy is still based on empirical knowledge, however, and such knowledge is essential to the practicing physician.

The success of therapy depends both on the adequacy of the treatment and on the method by which the treatment is administered. Owing to a lack of interest by physicians in supervising or even observing the administration of drugs, the actual benefit from many potentially useful agents may be lost. The administration of drugs to infants and toddlers is fraught with many problems. The task is not fulfilled when the diagnosis is made and therapy prescribed. Particular thought and instruction must be given to the methods and accuracy of administration to insure effective results.

Among the general considerations which should guide the practice of pediatric drug therapy are (1) symptomatic therapy, (2) the use of placebos, and (3) the possible dangers of medication in relation to the potential for benefit.

Specific therapy usually takes precedence over symptomatic therapy, but the value of the latter should not be overlooked. It may confer comfort and sleep to the parents as well as to the child. In most instances the prescription of drugs for a placebo effect should be avoided. The placebo, however, has its place; and all drugs, even specific ones, function to some degree as placebos. Many physicians prescribe drugs simply to give the mother something to do. However, this "something to do" can be bathing, the giving of fluids, and the like; it need not be drugs. The danger involved rests not in the drug itself, but in the possibility that parents will attribute an unwarranted dependence upon "medicine" and that the child may acquire the same unfortunate attitude. In considering these emotional factors one should also be aware that drug therapy may fail except as planned psychotherapy is added. This is especially true in the chronically ill child. The expected

benefits of medicinal therapy should always be balanced against the risks associated with the drug or with its administration. For example, edematous bleeding gingivae in primary herpetic stomatitis often heal better when left alone than after repeated, usually traumatic, local applications. When no drugs are prescribed, it is necessary that a complete explanation be given to the mother or the nurse.

## SPECIFIC CONSIDERATIONS

### THE CHOICE OF DRUGS

It is preferable to become familiar with a few drugs in each category rather than to prescribe a wide variety of similarly acting agents. For those drugs which the physician uses frequently he should know their characteristic routes and rates of absorption, their distribution in the body and their excretion or detoxification. Such information permits some discrimination in selecting a drug when secondary complications preclude the usual choice. For example, one avoids a barbiturate, which is excreted by the kidney, in the presence of renal disease. The normal inadequacy of many physiologic functions in the premature, the newborn and the older infant also affects the choice of drug, its route and frequency of administration and its dosage.

### GENERAL CLASSES OF DRUGS

The scope of this discussion does not permit transcribing complete pharmacologic data. Some of the drugs discussed below are treated more fully in other sections of this book. The drugs listed in this section are grouped according to their desired effect or area of action. Features peculiar to pediatric problems are brought out in the discussion of each group.

### CENTRAL NERVOUS SYSTEM DEPRESSANTS

#### SEDATIVES, HYPNOTICS, ANTICONVULSANTS AND NARCOTICS

The doses of these drugs vary greatly with the condition to be treated, but, in general, the more excited the child, the larger should be the initial dose. The dose should be titrated against effect.

Except in large anesthetic doses, barbitu-

rates are not analgesics and provide little relief for pain. When used alone, they may actually increase excitement of the child in pain. When combined with analgesics, sedatives form a valuable synergistic combination against pain and restlessness. The synergism of sedatives with antipyretics is useful in the prophylaxis of febrile convulsions.

The barbiturates are effective anticonvulsants, and usually should be administered intramuscularly (p. 1122). When administered intravenously, they must be in dilute solutions, and the dose should be titrated against the response. The rectal route is unreliable.

Extreme depression and death have followed average doses of barbiturates administered to patients with poliomyelitis, meningitis, respiratory obstruction or brain tumors. Prolonged but temporary depression also occasionally follows intravenous administration of barbiturates for anesthetic purposes.

Paraldehyde is a particularly safe drug and can be given by a number of routes. Children generally refuse it orally, even in its most palatable form, mixed with an equal quantity of tincture of sweet orange peel and added to sweetened iced water. Paraldehyde has an antibacterial action and can be given intravenously or intramuscularly as it comes in the ordinary bottle. When given intramuscularly to patients with chronic neurologic disturbances, it is liable to cause sloughing of tissue.

Chloral hydrate is another good sedative and soporific. It should not be used when there is gastric, renal or hepatic disease.

Narcotics (morphine, Demerol) are excellent drugs when used in appropriate doses for specific indications (preanesthetic, cardiac failure, and severe pain). The dangers of narcotic drugs in children are not as great as the statements in many textbooks of pharmacology would indicate. Addiction can follow continued use for as short a time as two weeks; the newborn of an addicted mother may also be addicted.

Nalline (nalorphine) is an effective specific antidote for poisoning by opium and its derivatives (morphine, codeine, and the like), Demerol (meperidine), methadone (Dolophine), levorphanol (Levo-Dromoran) and alphaprodine (Nisentil).

#### TRANQUILIZERS, ATARACTICS

Chlorpromazine (Thorazine), meprobamate (Miltown, Equanil), reserpine and other drugs of this class are being used in a number of psychotic and less severe emotional

problems, such as anxiety, tension and restlessness in children, with or without organic disease. Chlorpromazine is also an antiemetic and the drug of choice for the treatment of Sydenham's chorea. It is an antihypertensive agent, but a combination of reserpine and hydralazine is more effective. Meprobamate and others of this group have been used adjuncts in the treatment of enuresis; the value is not adequately defined.

Certain side reactions may be anticipated in the use of these agents. Chlorpromazine has been responsible for jaundice and parainfluenza symptoms. Drowsiness is occasionally encountered. Fever seems to be unrelated to dosage. Nasal congestion may be associated with the use of chlorpromazine or reserpine especially in infants.

#### CENTRAL NERVOUS SYSTEM STIMULANTS

Dexedrine (dextro-amphetamine) and related compounds are used in older children to aid in weight control, but it is doubtful whether there are many instances in which such use is justified. Their central stimulating properties may interfere with sleep and school activity.

The use of xanthines in apnea neonatorum is generally contraindicated. In depressant poisoning (by barbiturates) pentamethylenetetrazol (Metrazol), amphetamine or picrotoxin may be used with other supportive measures. Aminophylline (theophylline with ethylenediamine), if used as a bronchodilator in asthma, may cause central stimulation and poisoning when administered by any route.

#### ANALGESIC AND ANTIPYRETIC DRUGS

These drugs generally serve dual purposes—relieving pain and reducing fever. The value of antipyretics with anticonvulsants as prophylactics against febrile convulsions has been mentioned.

Aspirin is the most frequently used drug of this group. It is a valuable agent, but overdosage results in poisoning, especially when fever and dehydration exist. The potential dangers of preparations of aspirin or other drugs in candy-like form or in too pleasant tasting vehicles may outweigh their advantages.

Acetylamino-phenol (Tempra, Tylenol) is said to be less toxic than the salicylates, but more experience is needed to test this claim. Acetophenetidin (Phenacetin) used alone or in combination (A.P.C., Empirin Compound) has caused methemoglobinemia, particularly in infants.



## ANTIHISTAMINICS

Because it is impossible to be familiar with the available antihistaminics, it is best to limit one's use to a few and especially to those with recommended pediatric dosages. A variety of forms are available: fluid, tablet, capsule, chewing gum and granules (in capsules). The granules may be mixed with food, since they are enteric-coated. Antihistaminics have no value for rhinitis unassociated with allergy. Owing to their anticholinergic property, some antihistaminics are effective for motion sickness. They have varying degrees of sedative effect, a reaction which may prove helpful or annoying.

## ANTIFUNGAL AGENTS

Oral moniliasis (candidiasis) has been treated with a number of agents. Gentian violet should not be used in stronger concentrations than 0.25 per cent. Mycostatin (nystatin) seems to be effective for oral, gastrointestinal and cutaneous moniliasis.

## ANTIMICROBIAL AGENTS (ANTIBIOTICS AND SULFONAMIDES)

This group of drugs is perhaps the most useful and most misused of all therapeutic agents in pediatric practice. The effect of antimicrobial therapy on the shortening of periods of illness, on the avoidance of serious complications, on the reduction of mortality, and even on the prevention of illness constitutes the greatest therapeutic achievement in medical history. At the moment there is urgent need for greater discrimination in selecting the disease to be treated, in selecting the agent or agents to be used, and in determining the dosage and length of treatment.

The dangers inherent in the therapeutic agent itself are both direct and indirect. The direct dangers include damage to tissues by toxic, allergic or mechanical means. The indirect dangers are secondary to development of resistance to the therapeutic agent by existing bacteria, or to the establishment of new bacterial flora, including organisms not susceptible to the agent being administered, or to the establishment of new flora in the gastrointestinal tract which does not permit synthesis of vitamin K. The number of available agents necessitates an increasingly critical attitude toward the management of all patients and certainly toward those who are in the period of growth and development.

Most errors in antimicrobial therapy can

be grouped under three headings: (1) unnecessary therapy, (2) use of wrong agent, and (3) improper dose of the appropriate agent.

The obvious difficulties related to the management of the individual patient are (1) the immediate uncertainties, whether the infection is severe enough to justify specific therapy, and, if so, whether the infection is apt to be caused by an organism susceptible to any of the available antimicrobial agents; (2) the feeling of the physician that he must appear to be doing something for his patient; and (3) the insistence of the patient's parents that a drug be prescribed. The present practice of more or less indiscriminate medication contributes to a noncritical attitude on the part of both physician and layman. The economic saving in the country as a whole would be incalculable if only necessary medication were prescribed.

The use of the wrong antimicrobial agent in a particular situation is related initially to failure to establish an etiologic diagnosis or, when this is impossible, to appreciate the several etiologic possibilities and hence fail to provide therapeutic coverage for them. Subsequently the error lies in persistence of initially prescribed therapy when the clinical course has not been favorably affected. In the management of a child acutely ill with an infectious disease for which antimicrobial therapy is deemed necessary, the administration of it should not be delayed until bacteriologic identification is available, but appropriate material such as nasopharyngeal swabs and specimens of cerebrospinal fluid, blood, and/or urine should be obtained for smear and/or culture (including bacterial sensitivity to the commonly used antibiotics) before therapy is instituted. The initial selection of the antimicrobial agent(s) should be based on coverage of the most likely pathogens. Such decisions are particularly important in serious infections such as meningitis, osteomyelitis, septicemia, and any infection in the newborn infant. When laboratory data are available and response of the culture to the initially prescribed antimicrobial agent(s) has been observed, the decision can be made for continuation or change in the therapeutic program.

Inadequate therapy with an appropriate antimicrobial agent is usually the result of too small doses or too short a period of administration, or both. Such therapy may, on occasion, have disastrous results. The organism is not eliminated, but simply temporarily

suppressed. There may be a favorable initial response, followed by an exacerbation after therapy has been stopped. In such instances the clinical pattern may be sufficiently altered to be responsible for a delay in recognizing that the infection is still active. There are now a sufficient number of instances of chronic osteomyelitis and of permanent cerebral damage (from inadequately treated meningitis) to make it clear that suppressive in contrast to curative therapy is a major problem of the moment.

Chemotherapeutic agents may also be used prophylactically, but in general such use is not advisable. The use of penicillin to prevent initial and recurrent attacks of rheumatic fever is, however, generally accepted.

The use of a single antibiotic is generally preferable to a combination of several of them. When it is thought to be necessary to provide broader coverage than is possible with a single antibiotic, then the ones chosen should be prescribed individually and not in a commercially prepared combination. Combinations of penicillin and streptomycin as supplied commercially contain excessive streptomycin for infants when doses are calculated by penicillin content.

### CARDIAC GLYCOSIDES

Since these are potent and potentially dangerous drugs, preparations should be used which are primarily intended for pediatric patients. The preparations intended for adult use are usually too concentrated to allow accurate measurements for infants.

### CATHARTICS

These drugs are used more indiscriminately than any others readily available to the public. They should be used only when indicated, and then for a short time. There are extreme differences in individual responsiveness to the cathartics. In the few instances in which prolonged administration is indicated it is wise to start with a small dose and

increase it gradually as needed. Efforts should be made meanwhile to correct the underlying difficulty by means of improvements in diet and in toilet habits; the dose of the drug should then be gradually reduced until administration of the drug is discontinued.

### EMETICS

One or two teaspoonfuls of fresh ipecac syrup (U.S.P.) is an effective emetic. Some physicians recommend that it be kept in homes where there are infants and toddlers to be used in case of accidental poisoning or of croup. It is more effective than lavage in emptying the stomach, but there is also the risk of aspiration. If the vomiting center has been depressed by poisons (e.g., morphine), ipecac is dangerous in that the emetine retained may be toxic to the heart. Emetics are also dangerous in caustic or alkali poisoning.

### THE CALCULATION OF DOSES

Many rules exist for determining the dose of a drug for patients of various ages and weights. The multiplicity of these rules is evidence that no single rule is entirely satisfactory. Those most frequently used are listed at the bottom of the page.

Doses based on the factor of age have limited application; when the patient is usually heavy or light, the error may be considerable. Doses determined by the factor of weight also have limitations; for example, a dose calculated on the basis of a given amount of drug per unit of body weight may be satisfactory for infants, but excessive for older children.

Crawford and others have noted a close correlation of many physiologic processes when expressed in terms of surface area of the body. Doses of drugs can also be determined by this method, which is applicable for patients of various ages and weights. It is anticipated that drug dosage expressed in terms of  $D \times M$  (where  $D$  is the amount of drug per square meter of body surface and

Fried's Rule:

$$\frac{\text{Age in months}}{150} \times \text{Adult dose} = \text{Approximate dose for infants up to 2 years of age}$$

Clark's Rule:

$$\frac{\text{Wgt. in pounds}}{150} \times \text{Adult dose} = \text{Approximate dose for children over 2 years of age}$$

Young's Rule:

$$\frac{\text{Age in years}}{\text{Age in years plus 12}} \times \text{Adult dose} = \text{Approximate dose for children over 2 years of age}$$



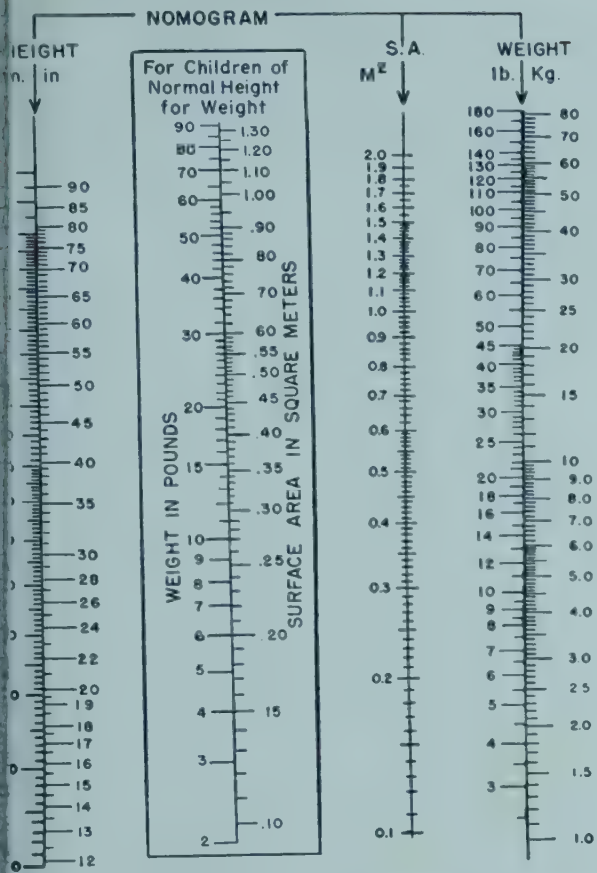


FIG. 36. Nomogram for estimation of surface area. The surface area is indicated when a straight line which connects the height and weight levels intersects the surface area column; or if the patient is roughly of average size, from the weight alone (in-closed area). (Nomogram modified from data of E. Lloyd by C. D. West.)

the surface area of the patient in square meters) will be more adequate for infants and children and perhaps for adults.

The surface area of a patient can be derived from a nomogram using the height and weight or, when the patient approximates average size, by using a weight-surface area nomogram (Fig. 36).

Doses based on surface area can be calculated by one of the rules listed at the bottom of the page.

Table 43 gives doses of frequently used drugs per square meter of body surface as well as by other standards.

By whatever method a dose is calculated, the result should be considered only an "average dose." It may not be the correct dose for a particular patient, although it is satisfactory for most patients of equal age and size.

Some drugs produce definite and visible

evidence of their effects; others require laboratory tests such as blood or urine analysis for evaluating the correctness of the dose. After the effect of the initial dose or doses has been noted subsequent doses should be adjusted to the individual patient's needs.

**PRESCRIPTION OF DRUGS**

Drugs should not be ordered in odd quantities. For example, 0.45 cc. should be expressed as 0.5 cc.; such a practice tends to prevent errors. For treatment of a child in his home it is advisable to prescribe only the amount of a drug estimated to be sufficient for a particular illness.

A teaspoonful is usually considered to be 4 to 5 ml. Since the capacity of teaspoons varies from 3.8 to 7.8 ml., the mother should be advised to select a teaspoon for administration of a prescribed drug which holds a quantity nearly equal to that of a standard measuring teaspoon. Prescriptions for drugs in liquid vehicles should then be written so that a single dose is contained in a full teaspoon rather than in a fraction of it. Similarly, drops vary considerably in size, dependent upon the aperture of the dropper. Calibrated droppers, now available, provide greater accuracy than the use of drops. See Appendix for list of common household measures.

Confusion can be avoided by adequately discussing the plan of therapy with the mother or nurse and by giving them written directions.

**ROUTES OF ADMINISTRATION**

The appropriate dose and frequency of administration of most drugs are closely related to the route by which they are to be administered. Some drugs, such as insulin, are effective by only one route.

**The Oral Route.** This is the preferred route, and should be used whenever practical. When there are gastrointestinal disturbances, such as anorexia, nausea or vomiting, some other route should be selected. Hours may be lost if a drug is given orally and vomiting ensues. When there is some doubt about the functional integrity of the oral route, the initial dose or doses may be given parenterally, and the drug may be administered orally as soon as it is deemed practical. (Text continued on page 227.)

$$\frac{\text{Surface area of patient in sq. meters}}{1.73 \text{ (adult surface area)}} \times \text{Adult dose} = \text{Dose for the patient}$$
$$\text{Surface area of patients in sq. meters} \times \text{Dose per sq. meter} = \text{Dose for the patient}$$

Table 43. Drugs and Drug Doses

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Acetaminophen (N-acetyl-p-aminophenol) (Tempra, Tylenol)	Under 1 year: 60 mg. 1-4 years: 60-120 mg. 4-8 years: 120-240 mg. 8-12 years: 240 mg. Single dose repeated every 6 hours (0) 0.7 gm./M <sup>2</sup> /24 hours, divided into 4-6 doses (0)	Tempra: Drops: 60 mg./0.6 ml. Syrup: 120 mg./5 ml. Tylenol: Drops: 60 mg./0.6 ml. Elixir: 120 mg./5 ml.
Acetylsalicylic acid (Aspirin)	Antipyretic: 65 mg./kg./24 hours 1.5 gm./M <sup>2</sup> /24 hours Maximum: 3.6 gm./24 hours Divided into 4-6 doses (0 or R) Avoid overdosage, particularly in infants To obtain salicylate level of 20 mg./100 ml. of blood: 3.0 gm./M <sup>2</sup> /24 hours (0)	Supplied in many forms Tablets: 30, 60, 75, 300 mg. ( $\frac{1}{2}$ , 1, $1\frac{1}{4}$ , 5 grains)
Adrenocorticotrophic hormone (Corticotropin, ACTH)	Infants: 20-40 units/24 hours Children: 1-2 units/kg./24 hours 50-100 units/M <sup>2</sup> /24 hours Aqueous: Divided into 4 doses I.M. Gel: I.M. once daily See individual diseases	Aqueous: Vials: 25, 40 units/ml. Ampules: 10 units/ml. Gel: Vials: 20, 40, 80 units/ml. Cartridge: 40 units/ml.
Amethopterin (Methotrexate)	Under 2 years: 1.25 mg./24 hours (0) 2-6 years: 2.5 mg./24 hours (0) Over 6 years: 5.0 mg./24 hours (0) CAUTION: Toxic	Tablets: 2.5 mg.
Aminophylline (Theophylline with ethylenediamine)	15 mg./kg./24 hours 0.5 gm./M <sup>2</sup> /24 hours Divide into 4 doses (I.V. or I.M.) Rectal dose: double the above dose Poisonous by all routes in overdosage	I.V.: 10-ml. ampules-0.25 gm. 20-ml. ampules-0.5 gm. I.M.: 2-ml. ampules-0.5 gm. R: Suppositories 0.125, 0.25 and 0.5 gm.
Ammonium chloride	75 mg./kg./24 hours 2.0 gm./M <sup>2</sup> /24 hours Divided into 4 doses (0) May produce acidosis by continued use	Tablets: 0.3 gm. (5 grains) Tablets enteric: 0.5 gm. ( $7\frac{1}{2}$ grains) 1.0 gm. (15 grains) Solutions and syrups
Ammonium mandelate	250 mg./kg./24 hours 6-8 gm./M <sup>2</sup> /24 hours Divided into 4 doses (0)	As chemical for solutions and syrups
<p>Key: M<sup>2</sup>, dose per square meter of body surface.</p> <p>I.M., intramuscular. I.Th., intrathecal. I.V., intravenous.</p> <p>O, oral. R, rectal. S.C., subcutaneous. T, topical.</p>		

All doses are average ones and are approximate. Variability of response may require alteration of dosage. Doses based on different criteria (body weight, surface area, and so forth) frequently do not correspond.

To change the dose per kilogram to the dose per pound, divide the dose by 2.2 (or, more conveniently, by 2). To change the dose in grams per kilogram to grains per pound, multiply the dose in grams per kilogram by 7.



Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
mobarbital sodium (Amytal)	Same as Phenobarbital	Ampules: 65 mg. (1 grain) 125 mg. ( $1\frac{7}{8}$ grains) 250 mg. ( $3\frac{3}{4}$ grains) 500 mg. ( $7\frac{1}{2}$ grains)
amphetamine sulfate (Benzedrine)	7.5–25 mg./24 hours 15 mg./M <sup>2</sup> /24 hours Divided into 3 doses or as Spansule in single dose (0)	Tablets: 5 and 10 mg. Spansules: 5, 10 and 15 mg.
amphotericin B (Fungizone)	0.25 mg./kg./24 hours Single dose diluted, 1 mg./10 ml. (I.V.) CAUTION: Toxic	Vials: 50 mg.
amprolisen (Pentolinium tartrate)	1.0 mg./kg./24 hours 30 mg./M <sup>2</sup> /24 hours Divided into 3 doses waking hours (O, S.C. or I.M.) Starting dose	Tablets: 20, 40 and 100 mg. Vials: 10 mg./ml.
Atropine sulfate	0.01 mg./kg./dose 0.3 mg./M <sup>2</sup> /dose Maximum: 0.4 mg. Preanesthetic or every 4–6 hours (S.C.)	Tablets: Several sizes Vials: 1 ml. = 0.4 mg. (1/150 grain)
Avertin (Tribromoethanol solution)	As single dose (R) in 3% sol.: 75 mg./kg. 2.0 gm./M <sup>2</sup>	Solution (U.S.P.): 1.0 gm./ml.
Bacitracin	For enteric infections: 500–2000 units/kg./24 hours, divided into 4–6 doses (0) 600–1200 units/kg./24 hours Maximum: 100,000 units Divide into 3–4 doses (I.M.)	1 mg. (50 units)
BAL (Dimercaprol, British Anti-Lewisite)	For arsenic, mercury and gold poisoning, in the following order: 2 mg./kg./every 4 hours for 2–4 doses (I.M.) 3 mg./kg./every 4 hours for 2 days (I.M.) 3 mg./kg./every 6 hours for 1 day (I.M.) 3–4 mg./kg./every 12 hours for 7–10 days (I.M.)	4.5-ml. ampules 10% in oil (100 mg./ml.)
Banthine (Methantheline bromide)	6 mg./kg./24 hours 150 mg./M <sup>2</sup> /24 hours Divided into 4 doses (O or I.M.)	Tablets: 50 mg. (scored) Ampules: 50 mg.
Barbiturates	See individual drugs	
Belladonna tincture	0.1 ml./kg./24 hours Not to exceed 3.5 ml./day 2.5 ml./M <sup>2</sup> /24 hours Divided into 3–4 doses (0)	Tincture (U.S.P.): 1 ml. = about 0.3 mg. of atropine (1/200 grain) Calibrated vitamin droppers offer accurate dosage

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Benadryl (Diphenhydramine hydrochloride)	5 mg./kg./24 hours Not to exceed 150 mg./ day 120 mg./M <sup>2</sup> /24 hours Divided into 4 doses (O or I.M.)	Capsules: 25 and 50 mg. Tablets enteric: 50 mg. Elixir: 10 mg./4 ml. Ampules: 50 mg./ml. Vials: 50 mg./ml.
Benodaine (Piperoxan)	Test dose: 0.25 mg./kg. (I.V.) 10 mg./M <sup>2</sup> (I.V.) Maximum: 20 mg.	Ampules: 2 mg./ml.
Bromides	60 mg./kg./24 hours 1.5 gm./M <sup>2</sup> /24 hours Divide into 3 doses (O)	Supplied in many forms
Caffeine with sodium benzoate	8 mg./kg./dose 250 mg./M <sup>2</sup> /dose Maximum: 500 mg. Repeat every 4 hours p.r.n. (S.C., I.V. or I.M.)	Ampules: 0.25 gm. (3 <sup>3</sup> / <sub>4</sub> grains) 0.5 gm. (7 <sup>1</sup> / <sub>2</sub> grains)
Calcium chloride (27% calcium)	0.40 gm./kg./24 hours 8.0 gm./M <sup>2</sup> /24 hours Give as 2% solution Divide into 4 doses every 6 hours (O) CAUTION: Acidifying. Give 2-3 days, then change to another calcium salt	Supplied as solutions of desired strength Ampules: 10%
Calcium disodium versenate (Edathamil calcium-sodium) (EDTA)	30-75 mg./kg./24 hours 1.7 gm./M <sup>2</sup> /24 hours Divide into 2 doses (I.V. or S.C.) I.V.: diluted to 0.2-0.4% solution S.C.: diluted to 2.5% solution Course: 2 doses/24 hours for 3 days; rest interval of 2 days Repeat course if needed	Ampules: 200 mg./ml.
Calcium gluconate (9% calcium)	0.5 gm./kg./24 hours 12.0 gm./M <sup>2</sup> /24 hours Divided doses (O or I.V.) I.V., diluted. Give slowly CAUTION: Bradycardia. Local necrosis with leakage from vein	Powder Ampules: 10% solution (I.V. only)
Calcium lactate (13% calcium)	0.5 gm./kg./24 hours 12 gm./M <sup>2</sup> /24 hours Divided doses (O)	Powder

Key: M<sup>2</sup>, dose per square meter of body surface.

I.M., intramuscular.

I.Th., intrathecal.

I.V., intravenous.

O, oral.

R, rectal.

S.C., subcutaneous.

T, topical.



Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
ascara, aromatic fluidextract	<p>Infants: 1.0—2.0 ml./dose</p> <p>Children: 2–8 ml./dose 5.0 ml./M<sup>2</sup>/dose Increase dose p.r.n. for effect (0)</p>	U.S.P. product
Castor oil	<p>Infants: 1–5 ml./dose</p> <p>Children: 5–15 ml./dose 15 ml./M<sup>2</sup>/dose Dose: (0)</p>	Oil or tasteless emulsion
Chloral hydrate	<p>50 mg./kg./24 hours Not to exceed 1 gm./dose 1.5 gm./M<sup>2</sup>/24 hours Divided into 3–4 doses (O or R)</p>	<p>Oral use: In solution</p> <p>Rectal use: In cotton seed oil</p>
Chloramphenicol (Chloromycetin)	<p>50–100 mg./kg./24 hours 1.5–3.0 gm./M<sup>2</sup>/24 hours</p> <p>Intervals: 4–6 hours (O) 6–8 hours (I.V.) 8–12 hours (I.M.)</p>	<p>Capsules: 50, 100 and 250 mg.</p> <p>Palmitate: 125 mg./4 ml.</p> <p>I.V.: 0.5-gm. ampules (diluted before use for I.V. drip)</p> <p>I.M.: 1.0-gm. vials</p> <p>Topical: Many forms</p>
Chlor-Trimeton (Chlorphenpyridamine maleate)	<p>0.35 mg./kg./24 hours 10.0 mg./M<sup>2</sup>/24 hours Divided into 4 doses</p>	<p>Tablets: 4 mg.</p> <p>Repetabs: 8 and 12 mg.</p> <p>Syrup: 2 mg./5 ml.</p> <p>Injection: 1-ml. ampules (10 mg./ml.) 2-ml. ampules (100 mg./ml.)</p> <p>Teldrin Spansules: 8 and 12 mg.</p>
Codeine	<p>For pain: 3 mg./kg./24 hours 100 mg./M<sup>2</sup>/24 hours Divide into 6 doses (O or S.C.)</p> <p>For cough: <math>\frac{1}{3}</math>–<math>\frac{1}{2}</math> above dose</p>	<p>Tablets: Many forms</p> <p>Cough syrups often contain 10 mg./5 ml.</p>
Compazine (Prochlorperazine)	<p>0.5 mg./kg./24 hours 10 mg./M<sup>2</sup>/24 hours Divide into 3 or 4 doses (O or R) I.M. dose: half of oral dose CAUTION: Catatonia or parkinsonian symptoms with overdose</p>	<p>Spansules: 10 and 15 mg.</p> <p>Suppositories: 5 and 25 mg.</p> <p>Syrup: 5 mg./5 ml.</p> <p>Tablets: 5 and 10 mg.</p> <p>Ampules: 5 mg./ml.</p> <p>Vials: 5 mg./ml.</p>

Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
Cortisone acetate	General use: Dosage varies with patient, disease and response  See individual diseases	Tablets: 5, 10 and 25 mg. Injection: 25 and 50 mg./ml.
Darvon (Dextro propoxyphene hydrochloride)	3 mg./kg./24 hours 100 mg./M <sup>2</sup> /24 hours Divide into 4-6 doses (O)	Capsules: 32 and 65 mg.
Demerol (Meperidine hydro- chloride)	6 mg./kg./24 hours 175 mg./M <sup>2</sup> /24 hours Maximum: 100 mg./dose Divide into 6 doses/24 hours (O, I.M. or S.C.)	Tablets: 50 and 100 mg. Elixir: 50 mg./5 ml. Ampules: 50 mg./ml. Vials: 50 mg./ml.
Deslanoside (Lanatoside C) (Cedilanid)	Digitalizing dose (rapid): 0.030 mg./kg. 0.75 mg./M <sup>2</sup> Best I.V. or I.M. In divided doses: Or as emergency: Single dose Patient should not have had digitalis or deriva- tives for 2 weeks or more Give slowly I.V. Watch EKG. Redigitalize with digitoxin or Digoxin after 24 hours	Cedilanid D ampules: 0.2 mg./ml.
Desoxycorticosterone acetate (DOCA)	1-5 mg./24 hours 1.5-2.0 mg./M <sup>2</sup> /24 hours Single dose in oil (I.M.)	Oil: 5 mg./ml. Aqueous: 5 mg./ml. Repository: 25 mg./ml.
Dexedrine sulfate (Dextro-amphetamine sulfate)	7.5-15 mg./24 hours 10-15 mg./M <sup>2</sup> /24 hours Divide into 3 doses/24 hours or as delayed action in single dose (O)	Tablets: 5 mg. Spansules: 5, 10 and 15 mg. Elixir: 5 mg./5ml.
Diamox (Acetazolamide)	10-30 mg./kg./24 hours 0.5 gm./M <sup>2</sup> /24 hours Single dose/24 hours or divide into 3 doses/24 hours (O or I.V.)	Tablets: 250 mg. Ampules: 500 mg.

Key: M<sup>2</sup>, dose per square meter of body surface.  
I.M., intramuscular.  
I.Th., intrathecal.  
I.V., intravenous

O, oral.  
R, rectal.  
S.C., subcutaneous.  
T, topical.



Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
digitalis (Leaf)	Digitalizing dose: Under 1 year of age: 0.045 gm./kg. 1-2 years: 0.040 gm./kg. Over 2 years: 0.030 gm./kg. 0.75 gm./M <sup>2</sup> Patient should not have had digitalis or derivatives for 2 weeks or more Divide total dose into 3, 4 or more portions with 6 hours or more between doses (O, I.V. or I.M.) Maintenance dose: Give 1/10 of digitalizing dose daily	Tablets: 0.1 gm. and fractions Tincture: 1 ml. = 0.1 gm. Digifolin: Ampules—50 mg./ml.
digitoxin	Digitalizing dose: Under 1 year of age: 0.045 mg./kg. 1-2 years: 0.04 mg./kg. Over 2 years: 0.03 mg./kg. 0.75 mg./M <sup>2</sup> /24 hours Patient should not have had digitalis or derivatives for 2 weeks or more Divide total dose into 3, 4 or more portions with 6 hours or more between doses (O, I.V. or I.M.) Maintenance dose: Give 1/10 of digitalizing dose daily	Tablets: 0.1, 0.15 and 0.2 mg. Ampules: 0.2 mg./ml.
digoxin	Digitalizing dose: Under 2 years of age: 0.09-0.12 mg./kg. Over 2 years: 0.045-0.09 mg./kg. 1.5 mg./M <sup>2</sup> Patient should not have had digitalis or derivatives for 2 weeks or more Divide total dose into 3, 4 or more portions with 6 hours or more between doses (O, I.V. or I.M.) Maintenance dose: Give 25% of digitalizing dose once daily	Tablets, scored: 0.25 and 0.5 mg. Elixir: 0.05 mg./ml. Ampules: 0.25 mg./ml.
digoxin (Diphenylhydantoin sodium)	3-8 mg./kg./24 hours 100-200 mg./M <sup>2</sup> /24 hours Divide into 3 doses (O or I.M.)	Tablets: 50 mg. (3/4 grain) Capsules: 30 and 100 mg. (1/2 and 1 1/2 grains) Suspension: 100 mg./4 ml. Vials: 50 mg./ml.

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Diocetyl sodium sulfosuccinate (Colace, Doxinate)	5 mg./kg./24 hours 150 mg./M <sup>2</sup> /24 hours Divide into 3 or 4 doses (O) Enema: Add 50–100 mg. to flushing enema (R)	Capsules: 50 and 100 mg. Liquid: 10 mg./ml. Syrup: 30 mg./5 ml.
Diuril (Chlorothiazide)	0.01–0.04 gm./kg./24 hours 0.3–1.2 gm./M <sup>2</sup> /24 hours Single dose or divided every 6 or 12 hours (O)	Tablets (scored): 250 and 500 mg.
Dramamine (Dimenhydrinate)	5 mg./kg./24 hours 120 mg./M <sup>2</sup> /24 hours Maximum: 150 mg./24 hours Divide into 4 doses (O, R or I.M.)	Tablets: 50 mg. Suppositories: 100 mg. Liquid: 12.5 mg./4 ml. Ampules: 50 mg./ml.
Ecolid (Chlorisondamine chloride)	First day: 15 mg./M <sup>2</sup> in morning (O) Second day: 15 mg./M <sup>2</sup> in morning (O) 15 mg./M <sup>2</sup> at night (O) Increase 15 mg./M <sup>2</sup> to gain effect Add hydralazine or reserpine for maximal control with minimal side effects	Tablets: 10, 25 and 50 mg. Ampules: 5 mg./ml.
Ephedrine sulfate	3 mg./kg./24 hours 100 mg./M <sup>2</sup> /24 hours Maximum, 30 mg./dose Divide into 4–6 doses/24 hours (O, S.C. or I.V.)	Capsules, Tablets: 25 and 50 mg. Syrup: 15 mg./4 ml. Ampules: 25 and 50 mg./ml.
Epinephrine hydrochloride (Adrenalin chloride)	Asthma or tolerance test: 1:1000 aqueous: 0.01 ml./kg./dose 0.3 ml./M <sup>2</sup> /dose Maximum, 0.5 ml. Repeat every 4 hours p.r.n. (S.C.) 1:100 aqueous: By nebulizer p.r.n. 1:500 oil: 0.01–0.02 ml./kg. 0.3–0.6 ml./M <sup>2</sup> Daily or every 12 hours (I.M.)	1:1000 aqueous: Ampules: 1 ml. Vials: 30 ml. Bottles: 30 ml. 1:100 aqueous: 5 ml. bottles 1:500 oil Ampules: 1 ml.

Key: M<sup>2</sup>, dose per square meter of body surface.

I.M., intramuscular.

I.Th., intrathecal.

I.V., intravenous.

O, oral.

R, rectal.

S.C., subcutaneous.

T, topical.



Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
tythromycin (lilotycin, Erythrocin)	20–50 mg./kg./24 hours 0.75–1.5 gm./M <sup>2</sup> /24 hours Divide into 4 doses/24 hours (O, I.V. or I.M.)	Tablets: 100 and 250 mg. Suspension: 100 and 200 mg./5 ml. Drops (oral): 5 mg./drop Ampules: 0.25, 0.5 and 1.0 gm. Vials: 50 mg./ml.
rous sulfate	Requirement: 6–16 mg. elemental iron (O) Anemia therapy: 100–200 mg. elemental iron/24 hours 0.5–1.0 gm. ferrous sulfate/24 hours Divide into 3 doses (O)	Ferrous sulfate: Tablets: 0.3 gm. Syrup: 0.20 gm./5 ml. (elemental iron): 0.04 gm./5 ml. Fer-in-Sol: Ferrous sulfate: 125 mg./ml. (elemental iron): 25 mg./ml.
radantin (Nitrofurantoin)	7.5 mg./kg./24 hours 200 mg./M <sup>2</sup> /24 hours Divide into 4 doses/24 hours (O)	Tablets: 50 and 100 mg. Oral suspension: 25 mg./5 ml.
gamma globulin (Immune globulin)	Hypogammaglobulinemia: 1 ml./kg. every 2–4 weeks (I.M. only) Measles: Preventive dose: 0.22 ml./kg. Attenuation: 0.05 ml./kg. (I.M. only) Hepatitis: Preventive dose: 0.022 ml./kg. (I.M. only)	16% solution U.S.P.
antrisin (Sulfisoxazole)	150 mg./kg./24 hours 4.5 gm./M <sup>2</sup> /24 hours Divide into 4 doses (O) 2.5 gm./M <sup>2</sup> /24 hours (I.V. or I.M.) Initial dose (loading) equals ½ of daily dose	Tablets (scored): 0.5 gm. Suspension: 0.5 gm./5 ml. Syrup: 0.5 gm./5 ml. Lipograntrisin: 1.0 gm./5 ml. Ampules: 2.0 gm./5 ml. 4.0 gm./5 ml.
Gentian violet (Methylosaniline)	Oral Monilia: Aqueous, 0.25–1% 3-day courses, (T), t.i.d. As coated tablets: 2 mg./kg./24 hours 50 mg./M <sup>2</sup> /24 hours Divide into 2–3 doses/24 hours (O) Treat 7–10 days Rest 7–10 days CAUTION: Not to be chewed	Tablets (coated): 10 and 30 mg.
Heparin	0.5 mg./kg. stat and every hour (I.V. drip) Check clotting time Titrate dose to yield 20–30 minute clotting time Continuous I.V.: 0.1 mg./ml. Antidote: Protamine sulfate (I.V. diluted) 5–8 mg./kg./24 hours	Ampules: 10 mg./ml.

Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
Hetrazan (Diethylcarbamazine)	Filariasis: 6 mg./kg./24 hours 150 mg./M <sup>2</sup> /24 hours (O) Divide into 3 doses/day Treat 7-10 days Ascariasis: 15 mg./kg./24 hours 500 mg./M <sup>2</sup> /24 hours (O) Single daily dose for 4 consecutive days	Tablets: 50 mg. Syrup: 120 mg./5 ml.
Hexylresorcinol	0.1 gm./year of age Maximum, 1.0 gm. Single dose (O) May repeat 3 days CAUTION: Not to be chewed	Crystoids: 0.1 and 0.2 gm.
Hydralazine (Apresoline)	0.15 mg./kg. 4 mg./M <sup>2</sup> With reserpine for hypertension Single dose every 12-24 hours (I.M.)	Tablets: 10, 25, 50 and 100 mg. Ampules: 20 mg./ml.
Hydrocortisone	$\frac{2}{3}$ of cortisone dose	Tablets: 5, 10 and 20 mg. Oral suspension: 10 mg./5ml. Ophthalmic suspension: 0.5-2.5% Topical: 1% Vials: For dilution, I.V.: 2-ml. vials 100 mg./ml. and 100 mg./20 ml. For I.M.: 5-ml. vials 50 mg./ml. Intra-articular: 5-ml. vials 20-50 mg./5 ml.
Imferon	Surface area in M <sup>2</sup> $\times$ 55 $\times$ (12.5—observed Hb.) = mg. of iron (I.M.) Add 20% for storage (Formula useful under age 3-4 years)	Equivalent of: 50 mg. elemental iron/ml.
Inversine (Mecamylamine hydrochloride)	Adult dose: 2.5 mg. twice daily p.c. (O) Increase 2.5 mg. at intervals of 2 or more days to response Average total adult dose: 25 mg. 1.5 mg./M <sup>2</sup> /24 hours Divide into 2 doses, p.c. (O) Increase to 15 mg./M <sup>2</sup> /24 hours	Tablets: 2.5 and 10 mg.
Ipecac syrup	Emetic dose: 5-10 ml. (O) Repeat in 20-30 minutes if needed	Syrup U.S.P.

Key: M<sup>2</sup>, dose per square meter of body surface.  
 I.M., intramuscular.  
 I.Th., intrathecal.  
 I.V., intravenous.

O, oral.  
 R, rectal.  
 S.C., subcutaneous.  
 T, topical.



Table 43. Drugs and Drug Doses (continued)

Drug	Dose	Supplied
niazid	5-15 mg./kg./24 hours 350 mg./M <sup>2</sup> /24 hours 3-4 doses/day (O or I.M.)	Tablets: 50 and 100 mg. Capsules: 50 and 100 mg. Syrup: 50 mg./5 ml. Ampules: 100 mg./ml.
namycin sulfate (Kantrex)	Systemic infections: 10-20 mg./kg./24 hours 0.5 gm./M <sup>2</sup> /24 hours Severe: up to 100 mg./kg./24 hours 3.0 gm./M <sup>2</sup> /24 hours Divide into 2-4 doses/24 hours (I.M.) Toxic reactions: Casts, red and white blood cells in urine; albuminuria; tinnitus, vertigo, deafness; skin eruptions; neutropenia Intestinal infections: 50 mg./kg./24 hours 1.5 gm./M <sup>2</sup> /24 hours Divide into 4 doses (O)	Vials: 0.5 gm. in 2 ml. 1.0 gm. in 3 ml. Capsules: 0.5 gm.
evarterenol bitartrate (Levophed, Norepinephrine)	1.0 ml. of 0.2% solution (0.1% base) in 250 ml. diluent Drip at 0.5 ml./min. to give 2 micrograms (base)/minute 2 micrograms/M <sup>2</sup> /minute Titrate dose with blood pressure CAUTION: Slough results from extravascular leakage	4-ml. ampules (0.2%)
magnesium hydroxide (Milk of magnesia)	Cathartic: 0.5 ml./kg./dose (O) 15.0 ml./M <sup>2</sup> /dose (O)	U.S.P. magma
magnesium sulfate (Epsom salt)	Cathartic: 0.25 gm./kg./dose (O) 8.0 gm./M <sup>2</sup> /dose (O) Hypertension: Intramuscular—50% solution: 0.1-0.2 ml./kg./dose 5 ml./M <sup>2</sup> /dose Repeat every 4-6 hours p.r.n. (I.M.) Intravenous—3% solution: 175 mg./kg./dose 5.8 ml./kg./dose 5 gm./M <sup>2</sup> /dose 170 ml./M <sup>2</sup> /dose I.V. during 1 hour	Ampules: 50%
Mandelamine	0.1 gm./kg./24 hours initially, then 0.05 gm./kg./24 hours 3.0 gm./M <sup>2</sup> /24 hours initially, then 1.5 gm./M <sup>2</sup> /24 hours Maximum, 3.0 gm./24 hours Divide into 3 doses/24 hours (O)	Tablets: 0.5 gm. Enteric coated: 0.25 gm.
Mebaral (Mephobarbital)	Same as Phenobarbital	Tablets: 30, 45, 100 and 200 mg.
Meproamate (Miltown, Equanil)	25 mg./kg./24 hours 0.7 gm./M <sup>2</sup> /24 hours Divide into 2-3 doses/24 hours (O)	Tablets: 200 and 400 mg. Suspension: 200 mg./5 ml.

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Mercaptomerin sodium (Thiomerein sodium) Meralluride sodium (Mercuryhydrin)	Below 6 kg.: 0.25–0.50 ml. (I.M.) Above 6 kg.: 0.50–1.0 ml. (I.M.) 1.0 ml./M <sup>2</sup> /24 hours (I.M.)	Ampules to yield 0.13 gm./ml.
6-Mercaptopurine (Purinethol)	Start: 2.5 mg./kg./24 hours single dose (O) Increase to 5 mg./kg./24 hours in 4 weeks if no response	Tablets: 50 mg.
Mesantoin	3–10 mg./kg./24 hours 100–300 mg./M <sup>2</sup> /24 hours Divide into 3 doses/24 hours (O)	Tablets: 100 mg.
Methimazole (Tapazole)	Start: 0.4 mg./kg./24 hours 12 mg./M <sup>2</sup> /24 hours Maintenance: 0.2 mg./kg./24 hours 6 mg./M <sup>2</sup> /24 hours Divide into 3 doses/24 hours (O)	Tablets: 5 and 10 mg.
Methylene blue	Methemoglobinemia: 0.2 ml./kg./dose 5 ml./M <sup>2</sup> /dose 1% solution (I.V.) Give over 5 minutes	Ampules: 1%
Metrazol (Pentylentetrazol)	0.2 ml./kg./dose Not over 5.0 ml. 5.0 ml./M <sup>2</sup> /dose Diluted (I.V.) Dose for marked barbiturate depression may be repeated every 15 minutes p.r.n.	Tablets: 100 mg. Ampules: 100 mg./ml.
Morphine sulfate (Paregoric yields 0.4 mg. of morphine/ml.)	Analgesic: Preoperative: 0.1–0.2 mg./kg./dose (S.C.) Maximum, 15 mg.	Stock tablets or solution
Mysoline (Primidone)	Infants and small children: 125 mg. b.i.d. and t.i.d. Over age 8 years: Up to 250 mg. t.i.d. 1.5 gm./M <sup>2</sup> /24 hours (maximum) Divide into 2–3 doses (O)	Tablets (scored): 0.25 gm. Suspension: 0.25 gm./5 ml.
Nalorphine hydrochloride (Nalline)	0.1–0.2 mg./kg./dose (I.V. or I.M.) May repeat in 15 minutes	Ampules: 5 mg./ml. Ampules for neonatal use: 0.2 mg./ml.

Key: M<sup>2</sup>, dose per square meter of body surface.

I.M., intramuscular.

I.Th., intrathecal.

I.V., intravenous.

O, oral.

R, rectal.

S.C., subcutaneous.

T, topical.



Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
embutal (Pentobarbital sodium)	Same as Phenobarbital	Capsules: 30, 50 and 100 mg. Suppositories: 30, 60, 120 and 200 mg. Elixir: 15 mg./4 ml. Ampules: 50 mg./ml. Vials: 50 mg./ml.
Neomycin sulfate	50-100 mg./kg./24 hours 1.5-3.0 gm./M <sup>2</sup> /24 hours Divided doses 4-6 times/24 hours (O) 7.5-15 mg./kg./24 hours 200 mg./M <sup>2</sup> /24 hours Divided doses 4-6 times/24 hours (I.V.) CAUTION: Toxic (I.V.)	Tablets: 0.5 gm. Mycifradin Pediatric Solution: 25 mg./ml. Vials: 0.5 gm.
Neostigmine (Prostigmin Bromide)	1-2 mg./kg./24 hours 30-50 mg./M <sup>2</sup> /24 hours Divided doses 3-6 times/24 hours (O)	Tablets: 15 mg.
(Prostigmin Methyl- sulfate)	0.04 mg./kg./dose (I.M.) 1.0 mg./M <sup>2</sup> /dose (I.M.)	Ampules: 0.25 mg./ml. (1:4000) 0.5 mg./ml. (1:2000)
Nikethamide (Coramine)	0.10 ml./kg./dose 3.0 ml./M <sup>2</sup> /dose Maximum, 10 ml. 25% solution (I.V. or I.M.) Repeat as needed	Ampules: 25%
Nitrogen mustard (Mustargen Hydrochloride)	0.1 mg./kg./24 hours for 4 days (I.V.) CAUTION: Toxic—slough if extravascular leak	Ampules: 10 mg.
Novobiocin (Albamycin, Cathomycin)	20-50 mg./kg./24 hours 0.75-1.5 gm./M <sup>2</sup> /24 hours Divided doses every 4-6 hours (O)	Capsules: 250 mg. Syrup: 125 mg./5 ml.
Nystatin (Mycostatin)	Infants: 400,000-800,000 units/24 hours Children: 1-2 million units/24 hours Divide into 3 doses/24 hours (O) Oral moniliasis: t.i.d. (T)	Tablets: 0.5 million units Suspension (O or T): 100,000 units/ml.
Ouabain (g-Strophanthin)	0.010 mg./kg. 0.3 mg./M <sup>2</sup> ½ dose stat (I.V.) Then fractions of dose every 30 minutes until response or total dose is given (I.V.) Redigitalize with long-acting drug 12 hours after onset of treatment Check patient and EKG before each dose CAUTION: Not to be given if a digitalis type of drug has been given in preceding 2 weeks	Ampules: 0.25 mg./ml.

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Pancreatin (Viokase, Panteric Granules)	Tablets: 1-2 tablets crushed with meals (O) Granules: $\frac{1}{4}$ - $\frac{1}{2}$ teaspoonful with meals (O) Gauge dose by quality of stools	Tablets: 0.3 gm. Granules: 1 and 4 oz. Powder
Papaverine	6 mg./kg./24 hours 200 mg./M <sup>2</sup> /24 hours Divide into 4 doses/24 hours (I.V. or I.M.)	Tablets: 30, 100 and 200 mg. Ampules: 30 mg./ml.
Para-aminosalicylic acid or salts (PAS)	200-400 mg./kg./24 hours 7.0 gm./M <sup>2</sup> /24 hours Divide into 3-4 doses/24 hours (O)	Tablets: 0.5 gm. Crystals: 0.5 gm.
Paradione (Paramethadione)	Under age 2 years: 0.3 gm./24 hours 2-6 years: 0.6 gm./24 hours Over 6 years and adults: 0.9 gm./24 hours Adjust subsequent doses by response (O) CAUTION: Blood dyscrasias	Capsules: 150 and 300 mg. Solution: 300 mg./ml.
Paraldehyde	0.15 ml./kg./dose 6.0 ml./M <sup>2</sup> /dose (O, R, I.M. or I.V. SLOWLY)	U.S.P. (Liquid)
Paregoric (Camphorated tincture of opium) (0.4 mg. of morphine/ml.)	Analgesic dose: 0.25-0.5 ml./kg./dose Smaller dose may be offered initially; increase to above as maximum Accurately measured with calibrated dropper (O)	U.S.P. tincture
Penicillin (aqueous) (1667 units/mg.)  (Procaine)	Infants: 20,000-50,000 units/kg./24 hours Older children: 300,000-600,000 units/24 hours Divided doses every 3-6 hours/day (O, I.M. or S.C.)  0.5-1.0 million units/M <sup>2</sup> /24 hours Single dose (I.M.)	Many forms and preparations
Penicillin benzathine (Bicillin, Permapen)	0.6-1.2 million units/dose at 24-72 hour intervals (I.M.) Rheumatic fever prophylaxis: 1-2 times/month	600,000 units/ml.
Penicillin V (1667 units/mg.)	100,000-300,000 units 4-5 times/day (O)	Many forms
Pentobarbital sodium (Nembutal)	Same as Phenobarbital	Same as Nembutal

Key: M<sup>2</sup>, dose per square meter of body surface.  
I.M., intramuscular.  
I.Th., intrathecal.  
I.V., intravenous.

O, oral.  
R, rectal.  
S.C., subcutaneous.  
T, topical.



Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Phenergan Hydrochloride (Promethazine hydrochloride)	0.5 mg./kg./dose 15 mg./M <sup>2</sup> /dose (O, R or I.M.) Antihistaminic: Full dose at night, $\frac{1}{4}$ dose A.M. or p.r.n. Nausea and vomiting: $\frac{1}{2}$ to full dose every 4-6 hours Preoperative: Full or double dose Motion sickness: Full dose, repeat 12 hours p.r.n.	Tablets (scored): 12.5 and 25 mg. Suppositories: 25 mg. Syrup: 6.25 mg./5 ml. Injection: 25 mg./ml.
Phenobarbital (Luminal)	Sedation: 6 mg./kg./24 hours 180 mg./M <sup>2</sup> /24 hours Divide into 3 doses (O, R, or I.M.) Anticonvulsant: 3-5 mg./kg./dose (I.M.) 125 mg./M <sup>2</sup> /dose (I.M.) Maximum dose, 300 mg.	Tablets: 15, 30 and 100 mg. Spansules: 60 and 100 mg. Elixir: 15 mg./5 ml. Ampules: 125 mg./2 grains 300 mg./5 grains
Picrotoxin	Barbiturate poisoning: 5 mg. (I.V. or I.M.) Repeat every 15 minutes	Ampules: 3 mg./ml.
Piperazine (as salts)	Pinworms: Up to 15 pounds: 250 mg. 15-30 pounds: 500 mg. 30-60 pounds: 1.0 gm. Over 60 pounds: 2.0 gm. 1.0 gm./M <sup>2</sup> Once daily before breakfast for 7 consecutive days (O) Roundworms: Up to 30 pounds: 1.0 gm. 30-50 pounds: 2.0 gm. 50-100 pounds: 3.0 gm. Over 100 pounds: 3.5 gm. 2.0 gm./M <sup>2</sup> Once daily for 2 consecutive days (O)	Tablets: 250 and 500 mg. Wafers: 500 mg. Syrup: 500 mg./5 ml.
Pitressin (Vasopressin)	Aqueous: 1-3 ml. (S.C.) Divide into 3 doses Tannate in Oil: 0.2 ml./dose (I.M.) Increase to 1-2 ml. 0.25-0.5 ml./M <sup>2</sup> (I.M.) Daily, twice daily or every other day (p.r.n.)	Vasopressin injection, U.S.P.: Aqueous: 20 units/ml. Pitressin Tannate in Oil: 5 units/ml.
Polymyxin B sulfate	Enteric infections: 10-20 mg./kg./24 hours 500 mg./M <sup>2</sup> /24 hours Divide into 3-4 doses/24 hours (O) Systemic infections: 1.5-2.5 mg./kg./24 hours (I.M.) 60 mg./M <sup>2</sup> /24 hours CAUTION: Nephrotoxic, neurotoxic	Tablets: 50 mg. Sterile powder: 50 mg./vial
Posterior Pituitary	Diabetes insipidus: Nasal insufflation p.r.n. (T)	Capsules of powder: 40 mg.

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Prednisone (Meticorten, Delt-Cortef Deltra)	See individual diseases	Tablets: 1.0, 2.5 and 5.0 mg. Suspension: 25 mg./ml.
Prednisolone (Deltasone Meticortelone, Hydeltra, Sterane)		
Probanthine (Propantheline)	1.5 mg./kg./24 hours 40 mg./M <sup>2</sup> /24 hours (O) Divide into 4 doses p.c. and h.s.	Tablets (coated): 15 mg. Ampules: 30 mg.
Procaine amide hydrochloride (Pronestyl)	30-50 mg./kg./24 hours 1.5 gm./M <sup>2</sup> /24 hours Divide into 4-6 doses/24 hours (O)	Capsules: 0.25 gm. Vials: 100 mg./ml.
Propylthiouracil	Start: Age 6-10 years: 50-150 mg./24 hours 10 years and over: 150-300 mg./24 hours 150 mg./M <sup>2</sup> /24 hours Divide into 3 doses every 8 hours (O) Maintenance: 50 mg. b.i.d. when euthyroid	Tablets: 25 and 50 mg.
Pyribenzamine Hydrochloride (Tripeleppamine hydrochloride)	5 mg./kg./24 hours 120 mg./M <sup>2</sup> /24 hours Maximum, 150 mg. Divide into 4-6 doses/24 hours (O)	Plain tablets (scored): 50 mg. Coated tablets: 25 mg. Delayed action tablets: 50 and 100 mg. Elixir: 25 mg./5 ml. Ampules: 25 mg./ml.
Quinidine sulfate	Test dose: 2.0 mg./kg. 60 mg./M <sup>2</sup> (O, I.V. or I.M.) Therapeutic dose: 30 mg./kg./24 hours 900 mg./M <sup>2</sup> /24 hours Divide into 5 doses/24 hours (O, I.V. or I.M.)	Ampules: Other salts 40, 65, 80, 200 and 600 mg./ml. Tablets: 100, 200 and 300 mg. Capsules: 100, 200 and 300 mg.

Key: M<sup>2</sup>, dose per square meter of body surface.  
I.M., intramuscular.  
I.Th., intrathecal.  
I.V., intravenous.

O, oral.  
R, rectal.  
S.C., subcutaneous.  
T, topical.



Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Reserpine	General: 0.02 mg./kg./24 hours 0.6 mg./M <sup>2</sup> /24 hours Divide into 1 or 2 doses/24 hours (O) Hypertension: 0.07 mg./kg./dose 2.0 mg./M <sup>2</sup> /dose With hydralazine every 12–24 hours (I.M.)	Tablets: 0.1, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mg. Ampules: 5.0 and 10.0 mg.
Scopolamine	0.006 mg./kg./dose 0.20 mg./M <sup>2</sup> /dose (O or S.C.)	Tablets: various sizes
Secobarbital sodium (Seconal)	Same as Phenobarbital	Tablets (coated): 50 and 100 mg. Capsules: 30, 50 and 100 mg. Suppositories: 30, 60, 125 and 200 mg. Elixir: 15 mg./5 ml. Injection: 50 mg./ml.
Streptomycin	25–40 mg./kg./24 hours (I.M.) 1.0 gm./M <sup>2</sup> /24 hours (I.M.) See Tuberculosis (pp. 465 and 470)	Ampules: (1) Streptomycin (2) Dihydrostreptomycin (3) Mixtures
Sulfadiazine (or combinations of sulfonamides)	150 mg./kg./24 hours 4.0 gm./M <sup>2</sup> /24 hours Maximum, 6.0 gm./24 hours Divide into 4–6 doses/24 hours (O) Initial dose, 1/2 of 24-hour dose Under 2 months of age: 60–100 mg./kg./24 hours 1 dose/24 hours as 5% solution (S.C.) Over 2 months of age: 100 mg./kg./24 hours 2.25 gm./M <sup>2</sup> /24 hours Divide into 3 doses/24 hours (S.C.) Divide into 4 doses/24 hours (I.V.) Rheumatic fever: Prophylaxis: Under 30 kg.: 0.5 gm./24 hours (O) Over 30 kg.: 1.0 gm./24 hours (O)	Tablets: 0.5 gm. Suspension: 0.5 gm./5 ml. Ampules (sodium): 0.25 gm./ml.
Sulfamethoxypyridazine (Kynex, Midicel)	Initial dose: 10 kg.: 0.125 gm. 20 kg.: 0.250 gm. 40 kg.: 0.50 gm. 80 kg.: 1.0 gm. 0.6 gm./M <sup>2</sup> Single dose (O) Maintenance dose: 1/2 of initial dose/24 hrs. (O) For severe infections, double above dose	Tablets (scored): 0.5 gm. Syrup: 250 mg./5 ml.

Table 43. Drugs and Drug Doses (*continued*)

<i>Drug</i>	<i>Dose</i>	<i>Supplied</i>
Sul-Spansion (Sulfaethylthiadiazole)	Maintenance dose: Under 75 pounds: 0.5 ml./kg./24 hours Adults and children over 75 pounds: 20 ml./24 hours 2.0 gm./M <sup>2</sup> /24 hours (15 ml./M <sup>2</sup> /24 hours) Divide into 2 doses/24 hours (O) Initial dose: double maintenance dose For severe infections: double maintenance dose	Tablets: 0.65 gm. Liquid: 0.65 gm./5 ml.
Tetracyclines	25-50 mg./kg./24 hours 0.75-1.5 gm./M <sup>2</sup> /24 hours Divided doses: 3-4 doses/24 hours (O) 2-3 doses/24 hours (I.M.) 2 doses/24 hours (I.V.)	Tablets: 50, 100 and 250 mg. Capsules: 50, 100 and 250 mg. Suspension: 250 mg./5 ml. Syrup: 125 mg./5 ml. Drops: 5 mg./drop Intramuscular—vials: 100, 250 and 500 mg.
Thorazine (Chlorpromazine)	General use: 2.0 mg./kg./24 hours 60 mg./M <sup>2</sup> /24 hours Divide into 3-4 doses (O or I.M.) Rectal dose: double above See individual diseases <b>TOXIC REACTION:</b> Jaundice (reversible)	Tablets: 10, 25, 50 and 100 mg. Spansules: 30, 75, 150 and 200 mg. Suppositories: 25 and 100 mg. Syrup: 10 mg./5 ml. (120-ml. dark bottles) Ampules: 25 and 50 mg.
Triamcinolone (Aristocort)	General: Initial: 0.5 mg./kg./24 hours 10-15 mg./M <sup>2</sup> /24 hours Maintenance: 0.1 mg./kg./24 hours 2.5 mg./M <sup>2</sup> /24 hours Divide 24-hour dose into 4 equal doses (O)	Tablets: 2 and 4 mg.
Triethylene melamine (TEM)	Initial: 5.0 mg. Maintenance: 1.0 mg./24 hours <b>CAUTION:</b> Toxic	Tablets (scored): 1.0 and 5.0 mg. Vials: Powder

Key: M<sup>2</sup>, dose per square meter of body surface.

I.M., intramuscular.

I.Th., intrathecal.

I.V., intravenous.

O, oral.

R, rectal.

S.C., subcutaneous.

T, topical.



*ext continued from page 209)*

Liquid preparations are preferable for children under five years of age. They may be made with pleasant vehicles such as syrup of chocolate, cinnamon or lemon. The amount of alcohol in elixirs and some other liquid preparations need usually cause no concern.

Although solid medications are usually taken poorly by children under five years of age, toddlers, when left alone, ironically imitate themselves with swallowed tablets or other solids. The risk of aspiration from the forced administration of tablets or capsules is great; they are usually safe for children five years or older. If the patient objects, tablets may be crushed or capsule contents emptied and added to syrups, jellies, Jello applesauce. One should, however, generally avoid adding drugs to the formula or to a favorite food.

**The Sublingual Route.** Older children will often hold drugs in their mouths long enough for absorption directly into the systemic circulation, thus avoiding passage of the drug through the portal system and the liver, where much of a drug may be lost.

**The Rectal Route.** One cannot expect uniform results from rectal administrations. If the ampulla is full, a capsule, tablet or suppository may soon be discharged with the stool. A cleansing, nonirritating saline enema

given prior to the medication offers the best chance of absorption. Suppositories which melt at body temperature are more effective than those which depend upon solution for their action.

Drugs in liquid form may also be administered rectally. The drug should be dissolved or suspended in 10 to 30 ml. of fluid and injected into the rectum. The buttocks are held or taped to prevent expulsion.

Rectal therapy is ineffective in the presence of diarrhea or dehydration.

**The Parenteral Route.** No child looks forward to a "needle," but the parenteral route is often preferable for the treatment of severe or potentially severe illness, especially when vomiting precludes oral treatment. The speed of drug absorption by this route varies with (1) the tissue injected, (2) the absorbability of the drug or vehicle, and (3) the adequacy of circulation. Except in a few clearly stated instances, the contents of an ampule are not intended to be a single dose for a child.

A drug to be administered by some route not described above, as for example intradermally or topically, is so indicated in the discussion of the particular disease.

HARRY C. SHIRKEY  
WILLIAM P. BARBA, II

## ANESTHESIA FOR CHILDREN

In order to provide adequate anesthesia for the pediatric patient, one must have (1) a working knowledge of the anatomic, physiologic and psychologic problems peculiar to the various age periods from birth to adolescence, (2) a thorough understanding of the surgical problem in each situation, (3) the ability to prescribe and evaluate fluid and electrolyte therapy, and (4) complete familiarity with the principles and techniques of sedation and of anesthesiology.

### PREOPERATIVE EVALUATION

Preparation for anesthesia begins with a detailed history, which should include information about previous anesthetic experiences and reactions to such drugs as barbiturates, opiates and derivatives of belladonna, and regional anesthetic agents such as procaine and pontocaine. It is also essential to know whether the child has recently had therapy with any

drug which might alter his response to sedatives and anesthetic agents as, for example, with the steroid hormones, anticonvulsant or tranquilizing drugs, antihypertensive agents or cardiac stimulants. Knowledge of previous transfusion or serum reactions or of prolonged bleeding or easy bruising may serve to forewarn of an otherwise unexpected complication. If there is any indication of an abnormal bleeding tendency, appropriate laboratory studies must be obtained. Evaluation of the functional capacity of a child with known cardiac or respiratory disease is essential to an accurate evaluation of his ability to withstand anesthesia and operation. An upper respiratory tract infection within a period of two weeks may increase the likelihood of laryngeal and tracheal complications. Recent loss of weight or failure of an adequate gain in weight may alter the expected response to sedative and anesthetic agents. Hypothyroidism or hyper-

thyroidism, adrenal insufficiency, diabetes mellitus and myasthenia gravis are examples of diseases which should alter the management during anesthesia and during the preoperative and postoperative periods.

A hemoglobin determination, a white blood cell count and a urinalysis constitute the minimal laboratory data which must be obtained within twenty-four hours of a procedure.

#### PREOPERATIVE PREPARATION

**Psychologic Aspects.** Children are frightened by leaving the security and familiarity of home and going to a strange hospital. Not knowing what to expect or on whom to call for assistance and sympathy generates fear and anxiety. The greatest incidence of psychic trauma following hospitalization is said to occur in infants and children one to three years of age, since they are unable to understand the purpose of hospitalization and do not realize that they can soon return home. Beyond this age there is increasing comprehension when the child is properly and adequately prepared for his hospitalization. Gross changes in the child's personality may follow traumatic emotional experiences.

A detailed description of what to expect is unnecessary. The child should know the general purpose of the proposed operation. If special equipment, such as an oxygen tent, is contemplated postoperatively, it is wise to introduce him to it a day before the operation so that he may "practice" with it and become accustomed to it. The unexpected should be avoided, if at all possible. No "white lies" should be told, but rather he should know that a certain amount of discomfort is necessary in order to get well.

Preparation for an elective operation should include a visit to the hospital a day or so before the scheduled admission in order that the child may become familiar with its appearance and with the principal personnel who will care for him. Children sense the tension and apprehension of parents and will reflect these attitudes; thus the parents must display confidence and cheerfulness. The child should bring a favorite toy or blanket to the hospital in order to alleviate some of the strangeness of his new environment. Every effort should be made by the surgeon and the child's physician to instruct the parents in preparation of the child emotionally before admission to the hospital. If the operation is a disfiguring one, such as an amputation or

the creation of a permanent colostomy, a psychiatrist or other physician, familiar with the problems of children, should assist in preparation of the child and his parents before operation. The anesthesiologist should visit the child, if possible in the presence of the parents, so that he will understand that the anesthesiologist is a friend who will care for him during the operation.

The immediate postoperative period is one of great emotional strain for the child; if possible, the parents should be with him to comfort and reassure him. Liberal visiting hours for parents should be encouraged as long as they do not seriously interfere with the hospital routine.

**General Medical Aspects.** Any acidosis, alkalosis, dehydration or hyperpyrexia must be corrected before induction of anesthesia to avoid precipitation of convulsions. Even emergency operation is rarely so urgent that time cannot be taken to improve the child's condition. For a major surgical procedure an intravenous infusion should be operating prior to induction of anesthesia, so that a means of administering blood, plasma or appropriate electrolyte solutions before and during operation is available. Hyperpyrexia may be lowered by external methods of cooling and by rectal administration of aspirin. In the presence of an acute infection necessitating a surgical procedure the temperature should not exceed 101° F. rectally, and the pulse rate should not exceed 120 per minute at the time anesthesia is begun. Cooling should be continued during anesthesia, if necessary, until a normal temperature is approached. Dehydration and abnormal concentrations of plasma electrolytes should be corrected by administration of appropriate fluids, which should also contain glucose (see p. 186).

A hemoglobin level of less than 10 gm. per 100 ml. is indicative of anemia, and elective operation should be postponed until it has been corrected. When the anemia is the result of recent rapid loss of blood, transfusion of whole blood is indicated, but only rarely is it indicated for an elective surgical procedure.

Obstruction of the respiratory tract by aspiration of regurgitated food during general anesthesia and in the immediate postoperative period is a major hazard. Solid food and milk should be withheld from all children for eight hours before induction of anesthesia; clear liquids to which additional sugar has



en added may be given within four hours; s is particularly important for small in- ts, and especially during hot weather. When the operation involves manipulation the upper gastrointestinal tract, a Levin be should be placed in the stomach before uction of anesthesia as a safeguard against gurgitation and aspiration of material into e tracheobronchial tree.

**Preanesthetic Medication.** Ideally, the pa- nt should arrive in the operating suite in rowsy, tranquil state. Quiescence is accom- shed by psychologic preparation and by the e of narcotic or sedative drugs.

Preanesthetic drugs (sedatives, narcotics d belladonna derivatives) are administered (1) to allay fear and apprehension, (2) to ecrease secretions from the respiratory tract, (3) to decrease the amounts of anesthetic gents required, and (4) to decrease unde- rable reflex activity, especially that of para- mpathetic origin.

Barbiturates allay apprehension more effec- tively than opiates (Dripps and Beecher). atients who receive short-acting barbiturates, uch as secobarbital or pentobarbital, pre- peratively will also awaken more quickly om general anesthesia and will regain their rojective pharyngeal and cough reflexes more apidly. This is particularly important for ndoral surgery, such as tonsillectomy or den- al procedures, in order to minimize aspiration f blood or secretions during the immediate ostoperative period. Barbiturates are classi- ed according to the duration of their action nd to their modes of inactivation and excre- tion. Pentobarbital and secobarbital are inacti- vated chiefly by the liver and have a relatively hort action; they should not be prescribed if here is hepatic damage. Phenobarbital and

barbital are long-acting barbiturates and are excreted by the kidneys. Thus the choice of the proper barbiturate depends on renal and hepatic function as well as on the duration of action desired. If a child has been receiving a barbiturate or other drug as an anticonvul- sant, it should be continued, and the usual preoperative medication should be prescribed in addition.

The narcotic drugs most commonly used for preoperative medication are morphine, meperidine (Demerol) and alphaprodine (Nisentil). There are four prime indications for their use: (1) for analgesia, (2) to lower oxygen requirements in the child with cya- notic heart disease, (3) for additional seda- tion and euphoria when operation is to be performed with regional analgesia, and (4) for intrathoracic surgery. Morphine is more effective than the other narcotics, but, in gen- eral, is more likely to cause nausea, vomiting and respiratory and circulatory depression.

The belladonna alkaloids used before oper- ation are atropine and scopolamine. Their purpose is to reduce secretions within the respiratory tract and to minimize undesirable autonomic reflexes. Scopolamine, when com- bined with a narcotic or barbiturate, produces a desirable degree of amnesia, and is a more effective drying agent than atropine. Atropine is superior for its protective action on cardiac and bronchial reflexes. Overdoses of either drug may cause hyperpyrexia, especially in the presence of even mild dehydration or in a hot, humid environment; Negroes require slightly larger doses, owing to their tendency to form excessive secretions. Scopolamine may cause agitation, and for this reason the dose is slightly smaller than that of atropine.

The anesthetist should refrain from using

Table 44. Preanesthetic Medication for Infants and Children

Age	Weight (Lbs.)	Nembutal (Mg.)	Morphine (Mg.)	Demerol (Mg.)	Atropine (Mg.)	Scopolamine (Mg.)
1 day-3 months.....	5-10	—	0.5-1	—	0.05-0.1	—
3-6 months.....	10-20	15-30	1-2	—	0.1-0.12	—
6 months-1 year.....	15-25	25-40	1.5-2.5	—	0.12-0.15	—
1-3 years.....	20-35	30-50	2-3.5	15-25	0.15-0.2	0.15-0.17
3-6 years.....	35-60	50-90	3.5-6	25-40	0.2-0.3	0.17-0.24
6-12 years.....	60-100	90-150	6-10	40-75	0.3-0.4	0.24-0.32
12+.....	100+	150-200	10	75-100	0.4-0.6	0.32-0.43

All drugs are given by the intramuscular route.

Nembutal is available in solution in multiple-dose vials containing 50 mg. per ml.

Scopolamine is available in ampules containing 0.32 or 0.43 mg. per ml.

Morphine should be prepared in solutions containing 4 mg. in each ml.

Average doses: Morphine, 0.1 mg. per lb.; Nembutal, 1.5 mg. per lb.; Demerol, 0.75 mg. per lb. These doses must be modified by certain conditions such as anemia, dehydration, malnutrition, asthma and drug sensitivity.

Approximately twice the foregoing doses can be given on basis of mg./kg. body weight.

any drug during anesthesia whose action is not thoroughly familiar to him. Weight is the most satisfactory basis for determining the dose for the average child; however, in special instances surface area and the metabolic activity of the patient must be considered. Narcotics such as morphine and Demerol should be prepared in dilute solutions to minimize errors in calculating the prescribed dose. The intramuscular route of administration is preferred.

The usual practice is to combine a barbiturate or an opiate with one of the belladonna derivatives; a particularly apprehensive child may be given all three drugs. They are administered sixty to ninety minutes before induction of anesthesia in the doses listed in Table 44.

INDUCTION OF ANESTHESIA

Induction of anesthesia in children should be accomplished with a minimum of crying and struggling and without the need for forcible restraint. With proper preanesthetic preparation it is usually possible to induce anesthesia by allowing cyclopropane or nitrous oxide to flow over the face by gravity. Conversation about subjects dear to the heart of the child will often serve to distract him during the early phase of induction. When the patient comes to the operating room with an intravenous infusion apparatus in place, induction may be accomplished with small doses of sodium pentothal injected directly into the tubing. Only when the child is completely unconscious is the mask slowly lowered and

fitted to the face. Anesthesia may then proceed by any desired method.

PHYSIOLOGIC CONSIDERATIONS DURING ANESTHESIA

Table 45 summarizes some of the data relative to the respiratory and circulatory systems which are useful to the anesthesiologist.

The circulatory system of infants and children is vulnerable to minute stresses and reacts vigorously and rapidly to them. The pulse rate in anesthetized infants varies between 80 and 180 per minute. A cardiac rate below 80 per minute in a young infant must be regarded as bradycardia and as a sign of impending hypoxia. The oxygen consumption of a newborn infant is approximately 7 ml. per kilogram per minute and is often higher in children one to three years of age. Owing to this high metabolic rate, even minor degrees of hypoxia are poorly tolerated.

Less often, bradycardia during general anesthesia is of autonomic reflex origin, frequently precipitated by a surgical stimulus, such as traction on the viscera. If the stimulus is released, the pulse rate usually returns to its previous level. Atropine, intravenously, will also often abolish bradycardia of parasympathetic origin.

The child not uncommonly has a slight lowering of blood pressure after moderate or heavy preoperative sedation; it is no cause for concern if he appears well otherwise.

The blood volume of a newborn infant is 400 to 500 ml., or 7.5 to 8.5 per cent of body weight. The loss of 30 ml. of blood by

Table 45. Respiratory and Circulatory Data of Children of Value in Anesthesia\*

Weight (Lbs.)	Average Tidal Volume (Ml.)	Average Minute Volume (Ml.)	Size of Endotracheal Tube O.D.† (Mm.)	Length of Endotracheal Tube (Cm.)	Resp. Rate in Sleep	Blood Volume (Ml.)	Average Hemoglobin Concentrations (Gm.)	Blood Pressure	Average Pulse Rates (per Minute) Asleep Anesthetized	
8	16-21	750-1175	4.6	10	20-80	450-500	15-21	(4.5 cm. cuff) 78/50	130	120-200
10	23	800-1270	4.6	10	20-80	550	11-12	90/60	130	100-180
12	41	1200-1650	5.3	10	40	600	10-11	95/60	130	80-180
15	51	1750-1950	6.0	11	38	750	11-12	100/70	120	80-180
21	78	2650-3000	6.3	12.5	38	1000	12	100/70	112	80-180
31	138	4410	7.6	14.0	32	1500	12	(9 cm. cuff) 100/70	95	80-150
36	140	4480	8.0	15.5	32	1800	13	110/70	90	80-150
45	215	5375	8.6	17.0	25	2250	13		85	75-140
60	281	5540	9.6	18.5	24	3000	14		85	75-140
77	355	7810	10.0	20.0	22	3500	14		80	70-110
85	395	7900	10.6	22.0	20	4250	14	115/75	80	70-110

From R. Dripps, J. E. Eckenhoff and L. D. Vandam: Introduction to Anesthesia, The Principles of Safe Practice.  
\* Data of Margery VanN. Deming, M.D.  
† O.D. = Outside Diameter.



six-months old infant is estimated to be equivalent to a loss of 500 ml. by an adult. It is essential to estimate the loss of blood during a major operation and to be prepared to replace any significant loss, volume for volume.

Owing to the relatively large surface area of infants and young children, and the immaturity of their neural heat regulatory mechanism, it is often difficult to control their temperatures. It is not uncommon for the temperature of a small infant to fall to 94° after a two- or three-hour surgical procedure in which a nonbreathing anesthetic technique is used. It is undesirable, however, to have the body temperature rise above normal, since this increases oxygen requirements. External warming and cooling devices should be used judiciously to keep the child's temperature 1 to 2 degrees below normal.

Generalized convulsions occur more frequently under general anesthesia in children than in adults. The factors which predispose to convulsions are hypoxia, hyperthermia, dehydration, disturbances of acid-base equilibrium, overdoses of atropine and scopolamine and certain anesthetic agents. Immediate therapy of a convulsion is aimed at preventing permanent cerebral damage by avoiding or correcting hypoxia and by stopping the seizure. Oxygen should be administered through a patent airway, with endotracheal intubation when necessary, and rapidly acting barbiturate administered intravenously to control the seizure. The surgical procedure should be terminated, and the factor responsible for the convulsion corrected before anesthesia is administered again.

The safety of any anesthetic procedure depends largely on the training, skill and experience of the anesthesiologist. Unless the surgical requirements demand a specific method of anesthesia, the simplest technique should be used by the anesthetist of limited

experience. Generally, the choice of anesthetic agents and methods of administration will depend on the anesthetist's ability, the seriousness of the child's illness and the contemplated operative procedure.

**FLUID THERAPY** (See page 183)

### POSTOPERATIVE CARE

The immediate postoperative period is a critical one; a "recovery room" adjacent to the operating suite should be available for observation of the child during this time. Nurses specially trained to observe postoperative patients for signs of respiratory obstruction, circulatory failure, silent regurgitation and other emergencies should be assigned to this unit, which contains equipment for suctioning, resuscitation, transfusions and other emergency measures. Members of the anesthesia and surgical staffs should be available for any necessary consultation and assistance. The child should leave the recovery area and return to his own room only after he has reacted adequately from anesthesia, when his pulse rate and blood pressure are stable, there is no respiratory depression, and the pharyngeal and cough reflexes are active.

In respiratory disturbances, particularly following endotracheal anesthesia in young children, breathing is facilitated by humidification of the environmental air, with oxygen added when necessary.

JACOB FRIEDMANN

### REFERENCES

- Dripps, R. D., Eckenhoff, J. E., and Vandam, L. D.: Introduction to Anesthesia, The Principles of Safe Practice. Philadelphia, W. B. Saunders Company, 1957.
- McQuiston, W. O.: Anesthesia for Pediatric Surgery. S. Clin. North America, 36:1441-52, 1956.
- Stephen, C. R.: Elements of Pediatric Anesthesia. Springfield, Ill., Charles C Thomas, 1954.

## CONVALESCENT CARE

Convalescent care as a phase of medical responsibility in the management of the sick child is often overlooked. Its importance in certain diseases, notably rheumatic fever and crippling orthopedic conditions, is generally recognized, but the average busy practitioner gives little consideration to the completion of the recovery process in his patients. When the

active phase of an acute illness or an acute exacerbation of a chronic one has passed, the patient is likely to be dismissed with indefinite instructions to take things easy for a few days.

Literally, the term "convalesce" means to grow or become strong; in common usage it implies to recover from illness, to become well

or healthy again. Childhood is the period of rapid growth and development; no definition is sufficient which does not take these factors into consideration. Perhaps a more adequate definition would be the attainment of optimal physical, mental and social health after illness. Such a connotation has the advantage that the recovery level is gauged by the delimiting factors of the individual child and his increasing age. A child with no physical residuals would thus be expected to attain a state of robust health in contrast to a child with a damaged myocardium from a rheumatic lesion who might have sufficient permanent damage that his state of optimal health would be at a lower level. Such a concept is important, not only for the sake of setting the goal for each child, whenever possible, at a level higher than that of the pre-illness state, but also to determine, as accurately as possible, for the handicapped child the limits of his capacity. The physician must also be aware that illness may interfere with the normal development of the mental and social status of the child. Convalescence cannot be considered complete unless the child has also attained his optimal mental and social levels.

In a broad sense, any child who is below par physically is in need of convalescent care. In a stricter and perhaps more practical sense the term "convalescent care" should be reserved for the management of the more serious deviations from states of health which are the result of an acute or chronic illness, and for which at least some degree of improvement can be expected.

Convalescence from short-term acute illnesses in previously healthy children should be completed in a relatively short time, not longer than that of the acute stage of the illness. In such instances gradual increases in activity with special attention to essential factors in the diet are usually all that is required. When the illness has been prolonged or unusually severe, greater attention is necessary.

The care of the convalescent child should be designed to follow natural patterns as far as possible. The principal factors are (1) provision for adequate rest; (2) increasing but graded physical activity; (3) diets which take into account increased need for such essential items as protein, vitamins and minerals; (4) play and occupational therapy; (5) continuation of formal schooling by the visiting teacher in the private home or by a resident teacher in institutions; and (6) an environment which stimulates self-confidence

in the child and at the same time provides an adequate sense of security. Though the child should be managed in such a way that he does not have a sense of self-pity, attempts at developing the Spartan attitude are often overdone. A fine degree of understanding is necessary to guide the child who requires a long period of convalescence.

Rest is perhaps the most efficient tool for repairing the ravages of disease, yet we know all too little of its quantitative administration. Those who have worked in the recovery wards of hospitals or in convalescent homes, or have observed convalescent children in their own homes, have noted the extreme degrees of restlessness and even of unhappiness in children whose activity was limited beyond what appeared to be their natural desires, especially when there was inadequate provision for occupational and play therapy. Paradoxical as it may seem, physical activity may at times be reduced by permitting greater latitude in movement. The restless child may expend more energy in continuous activity in bed than he would if allowed short periods out of bed. In the evaluation of the benefits to be derived from rest, such general but diametrically opposed concepts as recovery of structure and function with rest and the atrophy or disuse must be considered. Retention of calcium and nitrogen during periods of enforced inactivity may be less than on corresponding intakes during states of normal activity, and there may even be negative balances on otherwise adequate dietary intakes.

A workable plan for grading activity from bed rest to full activity is as follows: When the temperature is normal and other evidences of infection have subsided, the child should be allowed some activity, provided there is no residual damage which requires special consideration, such as cardiac damage from rheumatic fever or crippling orthopedic conditions. When there is no evidence of fatigue, the child may be permitted to sit for increasing periods of time at a table or window or on a porch to provide changes in activity or view. Bathroom privileges can usually be allowed as soon as the child is out of bed, and dining room privileges within another day or two. Otherwise, until there is a good return of physical strength, activity should be limited to the child's room or to the porch or terrace in suitable weather. Exposure to the sun should be encouraged so long as burning is avoided. The next increase in activity may include walking, croquet and playing catch with a ball. After this stage full activity



permitted. The rate at which activity is increased depends on the child's response. So long as additions do not cause a loss in weight and are below the fatigue level, they may be considered safe. Evidences of fatigue will be reflected by facial appearance, body posture and emotional responses. When an increase in activity is not well tolerated, it should be reduced to a lower level until the child again seems ready for greater activity.

Rheumatic fever patients with cardiac involvement require special consideration (p. 13). Besides the general criteria for determining the times for starting and increasing activity, attention must also be given to the possibility of continued infection as measured by the sedimentation rate and to the possibility of cardiac decompensation. The size of the heart, the pulse rate at rest and after exercise, the temperature curve uninfluenced by salicylates, and the general response to exercise must be evaluated. Some children with residual cardiac damage will never be able to tolerate full physical activity, and it is of the greatest importance to determine the upper level of activity compatible with their cardiac capacity and to inform them and their parents of their physical limitations.

The convalescent care of orthopedic patients must be governed by their physical limitations; they should have the benefit of expert supervision.

Children in need of convalescent care simply because of nutritional deficiency present special problems, particularly in subsequent home care if the convalescent period has been spent in an institution. If the undernutrition has been due to economic factors, every effort should be made to see that ample food supplies are available. When the undernutrition has resulted from poor eating habits, which frequently are due to poor training and disturbed parent-child relationships, reconstructive work must be carried on with the parents as well as the child.

The private home can usually be adjusted for short-term convalescent periods, but is only adequate for a long time when the family is capable of making the necessary adjust-

ments. Foster homes, if adequately supervised, can be of great benefit when the child's own home is inadequate. They are also safer places than large institutions for children under the age of two or three years, owing to the high susceptibility to respiratory infections during infancy and early childhood.

Properly conducted convalescent homes have proved their worth for children who require a long period of convalescence. They have the advantage that the child is in contact with other children whose problems are similar and thus require similar methods for their solution. Institutions, however, cannot provide adequate substitutes for family living, and even the best of them can to advantage be integrated with a home-care program. In such a plan the child who requires prolonged convalescence would spend alternate periods at the convalescent home and in his own home. General convalescent homes may also serve a useful function in providing a place of recuperation for children in need of mental rest and psychologic adjustment because of disturbed situations within their own homes. Such institutions are adequate, however, only so far as they satisfy the physical, mental, social, educational and religious demands of the individual child.

In most areas there are either inadequate or no facilities for institutional convalescent care for children, so that the responsibility for supervision of long convalescence within the child's own home falls upon the physician. If he assumes this responsibility, he must recognize that he must provide for the whole child. He will do well to enlist the aid of persons who can provide play and occupational therapy and schooling within limits which stimulate but do not overtax the child. In some instances the mother may be adequate for this task; in others, dependence will have to be placed upon such persons as visiting teachers and visiting nurses. Communities which do not have convalescent institutions could with advantage organize such home-care service for convalescent patients.

WALDO E. NELSON

# Prenatal Disturbances

## PRENATAL FACTORS IN DISEASES OF CHILDREN

### GENETIC AND ENVIRONMENTAL FACTORS

The interplay of many factors determines health or disease of children. The physician who observes many persons exposed to equal traumas, infections or deficiencies notices that they react differently to injuries of the same type and intensity. Such differences are conveniently explained as due to varying "constitutions." It may be useful to attempt an analysis of latent or remote factors underlying this differential behavior. Some of these factors were at work before the child was born, and obviously it is difficult to study them. However, the remoteness or latency of these factors does not make them less real, and they deserve as much study and, if possible, treatment as the factors which finally elicit the disease.

**The Fertilized Ovum.** The child's life begins with fertilization of the ovum. The structure and composition of the fertilized egg (zygote) determine the somatic and mental traits of the new individual, but a favorable environment is also indispensable for coordinated embryonic differentiation and intrauterine growth. Abnormalities of the elements of the zygote as well as prenatal environmental disturbances may result in congenital defects or the formation of points of minor resistance in the new organism. Congenital deviations are often at the root of chronic and intractable diseases of children.

The fertilized ovum consists of the cytoplasm and the nuclear substance. The latter contains the chromosomes and their constituents, the genes. The structure of the cytoplasm is of great importance for the development of the embryo; abnormalities of the cytoplasm apparently may lead to such severe impairment that the resulting embryos seldom reach postnatal life. Abnormalities of the chromosomes and genes cause many defects

encountered in children. In addition, injurious environmental factors are capable of altering the development of an otherwise healthy zygote and are thus responsible for the production of abnormalities. Such factors should be more accessible to preventive measures than other prenatal pathogenic factors.

**Injurious Factors.** Injurious genetic and prenatal environmental factors will be discussed separately, although they are difficult to distinguish in practice. Prenatal development is regulated by a continuous interaction of genes with their surrounding cytoplasm, the latter reacting in turn with the intramaterial and extramaterial environments. This continuous process may be regarded as a chain of complicated physical and chemical reactions, which may be interrupted by genetic as well as by environmental interference. The end result of different disturbing influences may be the same. Genetically determined abnormalities may be imitated by environmental disturbances and result in nonhereditary "phenocopies" of hereditary defects.

### GENETIC FACTORS

In man the nuclear substance of the zygote and of all the somatic cells derived from it contains forty-eight chromosomes, the carriers of the genes.\* The germ cells (gametes) contain only half the number of chromosomes. The union of two gametes, sperm and ovum, re-establishes in the fertilized ovum the number of chromosomes characteristic for the somatic cells of the species. Thus twenty-four of the forty-eight chromosomes of each cell can be traced back to the paternal and twenty-four to the maternal germ cells. The paternal as well as the maternal series of chromosomes

\* Until recently it was thought that man has forty-eight chromosomes, but more accurate counts have established the normal number as forty-six.



contains a complete assortment of genes and therefore a complete set of developmental potentialities. With the exception of the sex chromosomes, the paternal and maternal chromosomes resemble each other so closely that they can be grouped in twenty-three homologous pairs containing twenty-three homologous sets of genes. Thus every hereditary trait is determined by a pair or several pairs of genes. In general, the members of a pair of genes have a similar principal function: They regulate some phase of the development of the same organ or system. They may differ somewhat in their qualitative or quantitative potentialities, or may be identical. A person who carries a pair of genes which tend to produce identical results is considered *homozygous* for the trait they determine. If the two members of the pair tend to produce somewhat different results, the person is *heterozygous*. In that case one of the genes usually assumes leadership, and the other fails to express itself. The stronger gene is called "dominant," the suppressed one, "recessive." Though a recessive gene cannot express itself in a heterozygous person, it can act if united with an equivalent recessive gene in a homozygous person.

The dominant genes usually determine the traits of heterozygous persons. Since the recessive genes are not expressed in heterozygous persons, the appearance, or *phenotype*, of such persons differs from their genetic constitution, or *genotype*.

A reduction division precedes formation of the germ cells. The members of each chromosome pair separate, and only one member of the pair enters the final germ cell. Therefore each germ cell contains twenty-four (twenty-four?) chromosomes. It is a matter of chance whether it is the maternal or paternal member of the pair that is included in a germ cell. Thus any one germ cell will contain a mixture of maternal and paternal chromosomes, and all possible combinations may occur by the laws of chance. Though the chromosomes dissociate and segregate freely, certain genes are linked by their common location on the same chromosome and tend to remain together in inheritance.

A few types of morbid inheritance will be cited as examples of prenatal factors in the etiology of diseases of children. No attempt will be made to simplify a complicated subject. For more complete details of normal and morbid inheritance, the reader is referred to the literature cited.

### DOMINANT PATHOLOGIC TRAITS\*

A person who has a dominant abnormal trait is usually heterozygous. Such a person has one dominant, pathologic gene ( $P$ ) and one recessive, normal gene ( $p$ ) for the trait in question. The person shows the pathologic trait, since the abnormal gene expresses itself, and the action of the normal one is suppressed. Such a person ( $Pp$ ) usually marries a person who is free of the same pathologic trait and has two normal recessive genes ( $pp$ ) for the character in question. The abnormal person forms two kinds of germ cells in about equal numbers, those containing the gene  $P$  and others containing the gene  $p$ . All the germ cells of the normal mate contain the gene  $p$ . Figure 37 illustrates the results to be expected from such a mating: Half of the offspring ( $Pp$ ) can be expected to carry and exhibit the pathologic trait, but the other half ( $pp$ ) will be entirely free of it. A dominant abnormality appears in every generation of a kinship, and each offspring of an affected parent has an equal chance of being affected or unaffected. If one of these affected children marries a normal person, he must expect to see the trait in half of his offspring. However, those children who do not show the trait will have entirely normal offspring if their mates are normal.

Figure 38 presents a pedigree in which a pathologic trait, multiple exostoses, is inherited as a dominant factor. The abnormal trait is transmitted from affected parents to approximately half of their children, while the other members who are free of the trait have only healthy offspring. Ratios predicted from the type of diagram illustrated on page 237 actually occur in genetic experiments when large numbers of plants or animals are

\* Designations for genes (for the present discussion the following arbitrary symbols for genes are used):

#### Dominant Traits

$P$  = Dominant pathologic gene  
 $p$  = Recessive normal gene

#### Recessive Traits

$N$  = Dominant normal gene  
 $n$  = Recessive pathologic gene

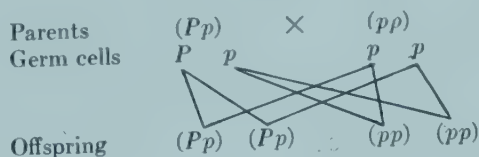


FIG. 37

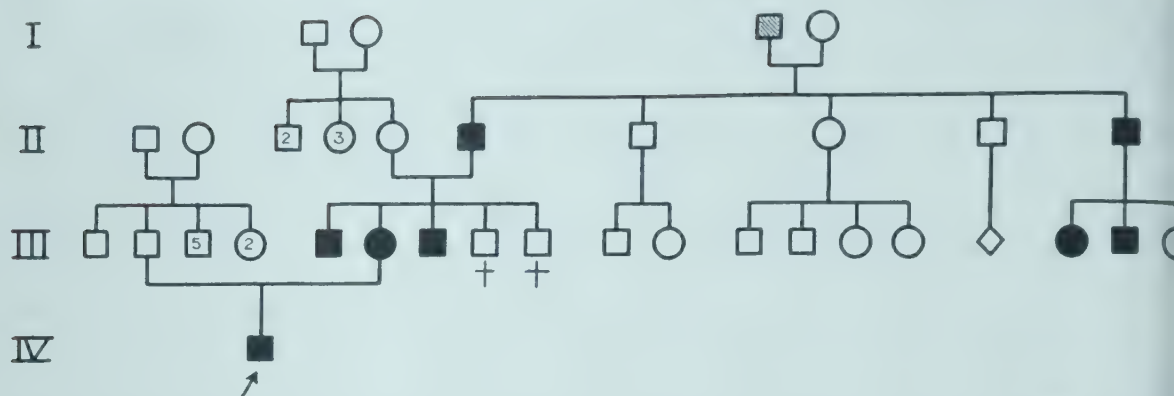


FIG. 38. Pedigree of a sibship in which multiple exostoses occurred in several members. The abnormal condition was transmitted by the affected members to part of their offspring, but the children of the unaffected members remained free. This suggests a dominant mode of inheritance. The pedigree was drawn according to the report of the mother of the propositus (↗), a 4-year-old patient of the Children's Hospital, Cincinnati, Ohio.

■ ● Persons with multiple exostoses.

▨ Man with a "bone disease" considered tuberculous (?).

See Figure 39 for explanation of other symbols.

crossed. In small human families, however, the actual ratio of normal to abnormal offspring may differ from the statistical expectancy, owing to random variation.

A number of pathologic conditions are inherited as dominant traits: multiple exostoses, osteopsathyrosis, coloboma iridis, aniridia, night blindness (without myopia), Huntington's chorea, neurofibromatosis (von Recklinghausen), spherocytosis and sickle anemia. In addition, certain forms of the following disorders may be inherited in a dominant manner: diabetes insipidus, brachydactyly, split hand, polydactyly, syndactyly, chondrodystrophy, microphthalmus, cataract, glioma retinae, optic atrophy, cerebellar ataxia, Friedreich's ataxia, hereditary spastic paraplegia, progressive muscular dystrophy, myotonia congenita, peroneal atrophy and epidermolysis bullosa. (See also Recessive Pathologic Traits, p. 238.)

*Inheritance of a pathologic trait in one or several pedigrees does not imply that the trait in question is always hereditary, nor that it is always inherited in the same manner.*

**Modification of Hereditary Traits. Skipping of a generation.** Contrary to the rule developed, a dominant trait may appear to skip a generation. Thus the abnormal trait may not be apparent in a person who has inherited the abnormal gene and transmits it to one half of his offspring. This behavior may be due to reduced *expressivity* of the gene, which may cause only a slight abnormality not obvious to the casual observer. In some instances the abnormality may be found in a mild form (microform). In some

cases of hereditary malformations, such as brachydactyly or exostoses, apparent skipping can be explained by roentgenographic demonstration of the abnormality in a mild form in an apparently normal parent who transmits the anomaly to some of his children. In other instances chemical or hematologic methods reveal that the transmitting person carries a basic hereditary anomaly (hyperuricemia in spherocytosis) without clinical manifestation (gout, hemolytic jaundice).

Breeding experiments often fail to produce the expected number of abnormal offspring, but since some of the phenotypically normal parents transmit the abnormal trait to some of their offspring, it must be assumed that the pathologic gene failed to manifest itself in the parents. Skipping of a generation in this manner is attributed to reduced *penetrance* (the percentual frequency with which a heterozygous dominant or a homozygous recessive gene manifests itself). Other genetic or environmental factors may be responsible for the varied expression of the abnormal trait.

**Environmental effects.** Environment plays an important role in the postnatal manifestation of hereditary diseases, in which only a "tendency" is genetically transmitted. The disease may be manifest in a person with the abnormal tendency only if he encounters certain environmental conditions. Thus tendencies to allergic conditions are inherited, but manifestations may be absent if exposure and sensitization to an allergen do not occur.

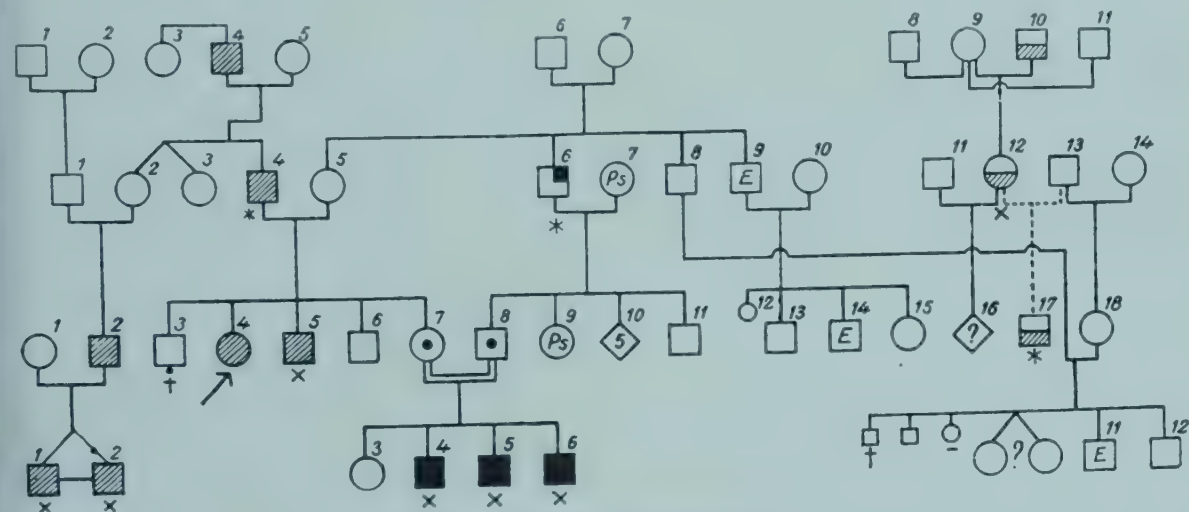
The basis for such pathologic tendencies may be anatomic, histologic or functional



ions from the normal which often are not manifest clinically. Thus unusual thickness of the red blood corpuscles (spherocytosis) may be observed in certain families as a dominant hereditary trait. Some carriers of spherocytosis are completely unaware of their abnormal trait, whereas in others there is an increased hemolysis of the abnormal cells, with resultant anemia, jaundice, splenomegaly and a variety of other clinical manifestations. The clinical patterns of those with the same disease vary markedly, and members of an affected family may have no symptoms in common. Thus spherocytosis, inherited as a simple dominant, may cause a confusing variety of clinical symptoms (pleiotropism), which may not be recognized as being related without hematologic studies. Patients with hemolytic jaundice can be freed of their disabling symptoms by splenectomy. This shows that a hereditary disease can be effectively

treated postnatally and refutes the false but widely accepted opinion that "nothing can be done about hereditary diseases." Splenectomy, however, does not change the patient's genetic make-up, and he can transmit the abnormal trait to half of his offspring.

Another example of multiple symptoms of one dominant hereditary trait is represented by a *mesenchymal dysplasia*, which manifests itself in bluish scleras and long, gracile bones. Such bones may fracture with the slightest trauma. Some affected persons have a tendency to dislocations of joints, some to otosclerosis. In taking a history of the sibship of an affected person one may learn that one member suffered from deafness and multiple dislocations, and other members were subject to multiple fractures (Fig. 40). Unless the observer knows the disease entity, he will not recognize the dominant inheritance of the underlying trait.



EXPLANATION OF SYMBOLS

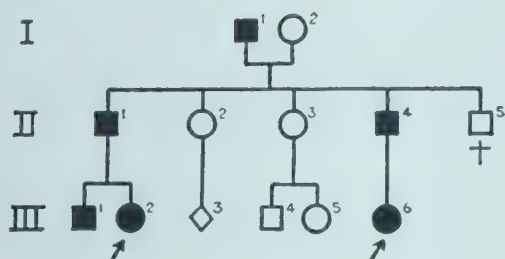
Standard for all Pedigree-Charts:

- = Male
- = Female
- = Sex unknown
- = Sex unknown number unknown
- = 5 Children sex unknown
- x = tested by investigator himself
- \* = tested by other competent person (who?)
- = abortive male
- = premature male
- = deadborn male
- † = died in infancy
- ↗ = points to probandus
- = non identical twins
- = identical twins
- = twins uncertain if identical or not
- = carrier
- = parents
- = children
- = parents not married
- = illegitimate child
- = consanguineous marriage
- Roman figures to the left indicate generations in ascending and descending line
- Pr = generation of the probandus
- Arabic figures locate individuals (thus Pr 7 = the woman in the generation of the probandus who married her cousin. AII 9 = the woman in the second ascending generation who married 3 times (resp with AII 8 10 and 11)).

Especially devised or selected for this particular pedigree-chart:

- = polydactyly
- = deafmuteness
- = deafness
- Ps = psychopathic
- E = epileptic.
- = strongly curled hair
- Other symbols may be used and added.

FIG. 39. Standard symbols for pedigree charts. (Bureau of Human Heredity, London.)



■ ● Persons with blue sclerae.

FIG. 40. Pedigree of a family in which blue sclerae occurred in several members. In addition, the following associated symptoms were seen by the recorder or reported by a member of the family (II<sub>4</sub>): III<sub>1</sub>: long, gracile bones in roentgenograms; III<sub>2</sub>: multiple fractures (osteopsathyrosis); III<sub>6</sub>: multiple fractures; II<sub>1</sub>: multiple fractures; II<sub>4</sub>: multiple dislocations, otosclerosis.

The abnormal condition which manifested itself in various symptoms was transmitted as a dominant trait.

■ ● Persons with blue sclerae.

**Incompatibility of Parental Genetic Factors.** The degree of complexity with which genetic factors may interact with other factors in the etiology of disease is well-illustrated in erythroblastosis fetalis. In this condition the interaction of *normal* genes of the parents is associated with a pathologic condition in the fetus or newborn infant which stems directly from these normal genes.

Approximately 85 per cent of white persons of European origin carry on their red blood cells an antigen, the Rh<sub>o</sub> (D) factor, determined by a corresponding gene Rh<sub>o</sub> (D). These persons are designated "Rh positive" and appear as homozygous Rh positive (Rh Rh) or heterozygous Rh positive (Rh rh), according to whether the Rh gene was inherited from only one or from both parents. Persons lacking the gene are "Rh negative" (rh rh) and are homozygous.

Figure 41 shows how the three major Rh types can be formed in a family in which the parents are heterozygous and indicates that the relative frequencies of offspring in such families will be one Rh-positive homozygous and one Rh-negative person for each two heterozygous persons.

If transfusions of Rh-positive blood are made into Rh-negative persons, antibodies (agglutinins) to the Rh-positive red blood cell will usually develop. These antibodies may be the cause of transfusion reactions, or, in female recipients who later become pregnant with Rh-positive infants, the antibodies may cause hemolytic disease (erythroblastosis fetalis) in the infant as a result of their trans-

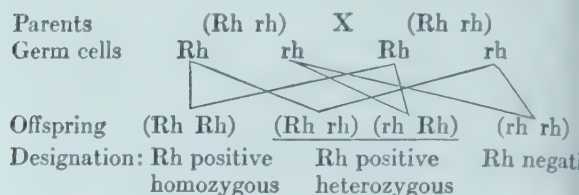


FIG. 41.

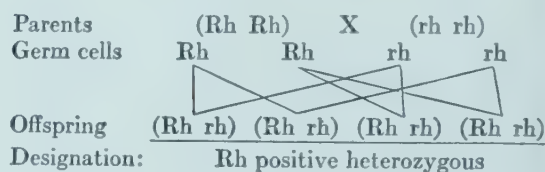


FIG. 42.

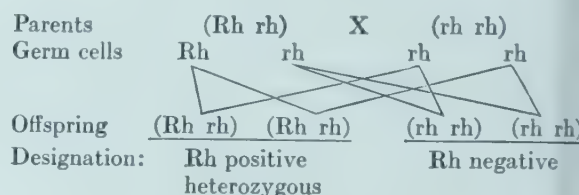


FIG. 43.

fer across the placenta. An Rh-negative mother who has *not* been transfused with Rh-positive blood may have infants with hemolytic disease after stimulation by red blood cells which cross into her circulation from an Rh-positive fetus. When maternal sensitization occurs as a result of pregnancy alone, the first child almost always escapes, but subsequent children. Once sensitization is established, however, subsequent Rh-positive children will usually have some degree of hemolytic disease. The tendency for the first child to be free of the disease is unlike a phenomenon seen with the action of ordinary dominant or recessive genes.

In an Rh-negative sensitized woman married to a homozygous Rh-positive husband all children will be Rh positive (Fig. 42) whereas, if the father is heterozygous, the children will have a 50 per cent chance to be Rh negative (Fig. 43).

#### RECESSIVE PATHOLOGIC TRAITS\*

A person with an abnormal recessive gene paired with a normal dominant gene appears normal and produces normal offspring with a mate who has two normal genes for the trait in question. If, however, such a heterozygous person marries a person who is similarly heterozygous, then each child has one chance in four of being homozygous and showing the pathologic trait. In Figure 44 the two apparently normal but actually heterozygous

\* See footnote, page 235.



ents are represented by  $(Nn)$ ,  $N$  representing the normal dominant and  $n$  the pathologic, recessive gene:

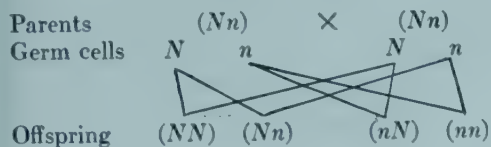


FIG. 44.

One abnormal offspring has the genetic constitution  $(nn)$ . Three fourths of the offspring appear phenotypically normal, but only one fourth  $(NN)$  is genotypically normal. One half of the children  $(Nn)$  are heterozygous, like the parents; they appear normal, but carry the pathologic gene. Since such carriers have one recessive abnormal gene appear normal, there is the possibility that they may carry unknowingly a carrier of the same pathologic trait. The chances of such a mating are related to the frequency of the pathologic gene in the general population. Consanguineous marriages favor the appearance of recessive traits. If a recessive gene is rare in a population, a homozygous, affected individual may appear only once in a pedigree. Thus the lack of a pathologic trait in the traceable genealogy does not exclude its genetic determination.

An interesting situation arises if a homozygous person with a pathologic trait caused by recessive genes  $(nn)$  marries an apparently normal person who is actually a heterozygous carrier of the same pathologic gene  $(Nn)$  (Fig. 46). In this case half of the

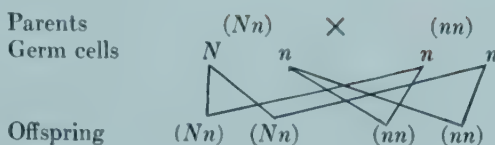


FIG. 46.

children appear normal and the other half exhibit the pathologic trait. To the observer such a family will appear like the one represented by the diagram on page 235, where an abnormal person, heterozygous for a dominant pathologic gene  $(Pp)$ , married a normal person  $(pp)$ . In both cases one of the parents and half of the children show the defect. But the genetic make-up of the children is different. In the case of the dominant pathologic trait the unaffected children are genetically entirely normal. They neither show nor carry the abnormal gene. In the case of the recessive abnormal character the children who appear normal carry the pathologic gene and transmit it to half of their children.

Thus a family history which includes only the parents and their children is insufficient to determine whether a pathologic trait is inherited as a dominant or a recessive one.

If two persons who exhibit an abnormal recessive trait and are therefore homozygous  $(nn)$  marry, the expectation is that all their offspring will be abnormal (Fig. 47). Such

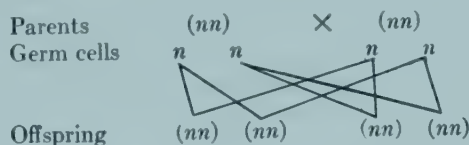


FIG. 47.

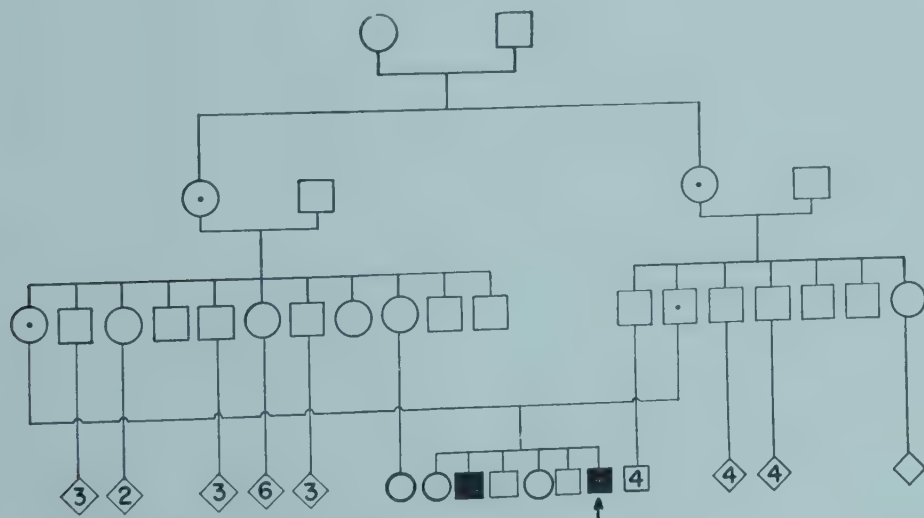


FIG. 45. Werdnig-Hoffmann muscular atrophy (■) occurring in offspring of a consanguineous marriage. The disease does not appear in the collateral close relatives, but because the recessive disease-producing gene has been received by both parents from one of their common ancestors, each of their offspring has one chance in four of being homozygous  $(nn)$  for it and developing the disease.

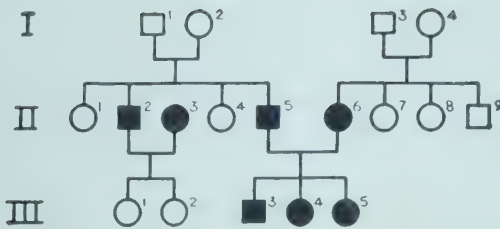


FIG. 48. Deaf-mutism (■ ●) in a pedigree recorded by Albrecht, inherited as a recessive trait. The deaf-mutism of all the affected persons is genetically determined with the exception of that of II<sub>3</sub>, who acquired deafness as a sequel of scarlet fever in infancy. (After Blacker.)

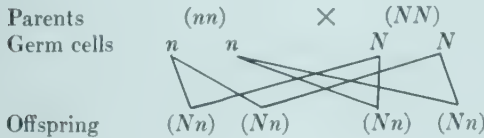


FIG. 49.

matings occur sometimes with deleterious effects among hereditary deaf-mutes. On the other hand, there is no objection to the marriage of persons whose deaf-mutism is acquired and not genetically determined. Figure 48 represents a pedigree in which two marriages of deaf-mutes occurred: II<sub>5</sub> and II<sub>6</sub> suffered from hereditary deaf-mutism, and all children were deaf-mutes. The marriage of II<sub>2</sub> and II<sub>3</sub> resulted in the birth of two normal children. Though II<sub>2</sub> was genetically a deaf-mute, II<sub>3</sub> was genetically normal and acquired deafness as a sequel of scarlet fever in infancy. Only normal children, all carriers of the pathologic trait, will be expected from such a marriage (Fig. 49). It is also possible that two deaf-mute persons who are affected by different genes for deaf-mutism may have normal children.

The following pathologic conditions are apparently inherited as recessive traits: albinism, Gaucher's disease, Tay-Sachs disease, Niemann-Pick disease, alcaptonuria and congenital ichthyosis. Certain forms of the following disorders can also be inherited as recessive traits: Fanconi's rachitic syndrome, polydactylism, atypical chondrodystrophy, Morquio's disease, gargoylism, osteopetrosis, microcephaly, microphthalmus, optic atrophy, cerebellar ataxia, Friedreich's ataxia, hereditary spastic paraplegia, progressive muscular dystrophy, peroneal atrophy, fibrocystic disease of the pancreas, galactosemia, phenylpyruvic oligophrenia, Wilson's disease, Laurence-Moon-Biedl syndrome and epidermolysis bullosa. (See also Dominant Pathologic Traits, p. 235.)

A number of clinical entities may be inherited as either dominant or recessive traits.

#### SEX-LINKED RECESSIVE PATHOLOGIC TRAITS

Of the forty-eight chromosomes of human cells, only forty-six can be arranged in twenty-three homologous pairs. The remaining pair, the sex chromosomes, requires special discussion. In males this pair consists of two chromosomes of unequal size: a large X chromosome and a small Y chromosome. In females there are two large X chromosomes. The every somatic cell of the male organism contains twenty-three pairs of homologous chromosomes (autosomes) plus one X and one Y chromosome, and every somatic cell of the female organism contains twenty-three pairs of autosomes and two X chromosomes. Meiosis, which leads to the formation of germ cells, produces two types of sperm cells: one containing twenty-three autosomes and a small Y chromosome and another containing twenty-three autosomes and a large X chromosome. All the germ cells produced by the male contain twenty-three autosomes and an X chromosome. Fertilization may result, therefore, in the formation of one of two types of zygotes: one which receives an X chromosome from both father and mother, the resulting offspring being female (XX), and another which receives a Y chromosome from the father and an X chromosome from the mother, the offspring being male (XY). The large X chromosome carries many genes, the small Y chromosome few, if any. Since most characters depend genetically upon the action of a pair of homologous chromosomes, the genes of the X chromosome of the male are in an exceptional position in this respect because they are not matched by corresponding genes of the Y chromosome. If a pathologic gene is located in the X chromosome of the male, it can manifest itself even if it is recessive, since it is not checked by a normal gene of the Y chromosome. A similar recessive pathologic gene in the X chromosome of a female may be kept in check, however, by a normal dominant gene in the other X chromosome. In this manner certain hereditary pathologic traits may appear in the males of a family without becoming manifest in females. Hemophilia, color blindness, some forms of gargoylism, progressive muscular dystrophy, peroneal atrophy, microphthalmus, night blindness with myopia, and the atrophic type of ectodermal dysplasia are sex-linked traits.

Figure 50 illustrates the transmission of



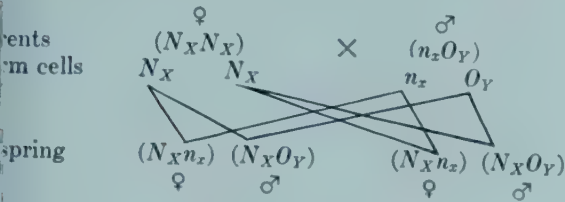


FIG. 50.

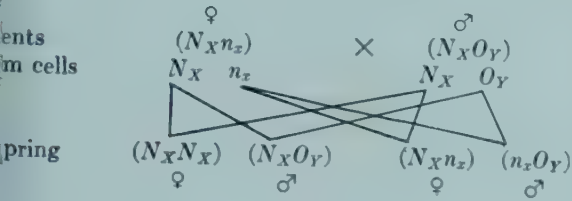


FIG. 51.

recessive pathologic gene located in an X chromosome ( $n_x$ ). There is no corresponding gene in the Y chromosome ( $O_Y$ ). The affected father's pair of genes is represented by the formula ( $n_x O_Y$ ). If the mother has two normal dominant genes in her X chromosomes ( $N_X N_X$ ), the following results are to be expected: The sons ( $N_X O_Y$ ) are all normal, having received their normal X chromosome from their mother. All the daughters ( $N_X n_x$ ) appear normal, but carry a recessive pathologic gene ( $n_x$ ) in one of their X chromosomes. If such a carrier-daughter marries a normal man ( $N_X O_Y$ ), half of her sons ( $n_x O_Y$ ) will show the abnormal trait of the paternal grandfather, and half will be genetically normal ( $N_X O_Y$ ). Half of the daughters will be genetically normal ( $N_X N_X$ ), and half ( $N_X n_x$ ) will carry the pathologic trait on one X chromosome (Fig. 51).

Figure 52 shows the sex-linked recessive inheritance of progressive muscular dystrophy in a sibship. This type of pathologic trait appears chiefly in males, but in rare cases females will also have it. If an affected

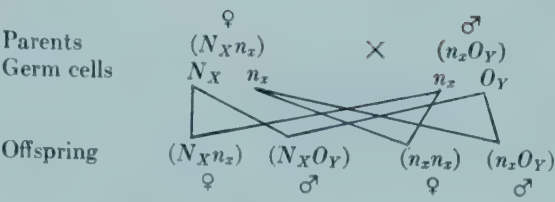


FIG. 53.

man ( $n_x O_Y$ ) marries a carrier ( $N_X n_x$ ), half their daughters ( $n_x n_x$ ) will have the disease and half will be carriers ( $N_X n_x$ ); half their sons will be affected ( $n_x O_Y$ ), and half will be genetically normal ( $N_X O_Y$ ) (Fig. 53).

PATHOLOGIC TRAITS WHICH DEPEND ON MULTIPLE GENETIC FACTORS

The hereditary traits discussed so far are attributable to one gene or one pair of genes. Hereditary characters may depend on the combined action of several genes, however. If these genes are located in different chromosomes, they associate and dissociate in different matings according to the laws of chance. Obviously the chances of the manifestation of a pathologic trait are diminished if it is dependent upon several genes. In simple recessive inheritance two genes of a pair determine the manifestation of a recessive trait. The chances that they unite in the offspring of a pair of carriers ( $Nn$ ) are 1 in 4. If a pathologic trait depends upon several pairs of recessive genes located in different chromosomes, the chances that they will become homozygous in one person are rather small. Thus the chances of the appearance of the trait are so diminished that one can expect to see it only rarely in a human pedigree. This illustrates again that the lack of a pathologic trait in the traceable genealogy does not exclude its genetic determination.

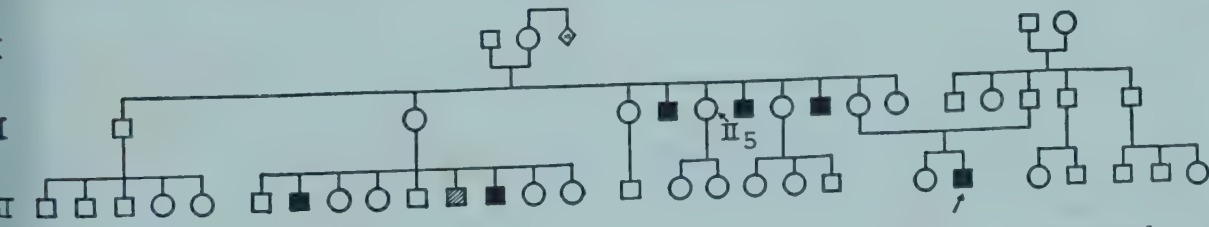


FIG. 52. Pedigree in which progressive pseudohypertrophic muscular dystrophy was transmitted as a sex-linked recessive trait. The pedigree was drawn according to the report of the mother of the proband (II-5), a 5 year old patient in the Children's Hospital, Cincinnati, Ohio.

The maternal grandmother of the patient was obviously a carrier of the abnormal trait, which was transmitted to 3 of her sons. A fourth son, who did not inherit the disorder to a part of their sons. Since this pedigree was drawn the daughter marked II-5 had 2 sons; both have progressive muscular dystrophy.

- Patients with progressive muscular dystrophy.
- ▨ Patient with a mild case of muscular dystrophy who recovered, according to the reporter.

### LETHAL TRAITS

A gene or a combination of genes may lead to developmental defects incompatible with life. Severe defects cause intrauterine death; the responsible genes are called "lethal genes." Milder defects may be compatible with intrauterine life, but cause death soon after birth; responsible genes are termed "sublethal."

Lethal genes may be dominant or recessive. They may produce only slight effects in heterozygous persons, but may cause death in the homozygote. For example, a dominant gene is known which, in heterozygous subjects, leads to brachyphalangia, a shortening of the second phalanx of the second fingers and toes. Such a defect is of no practical importance to the affected person. If, however, two heterozygous persons with this defect marry, one fourth of their offspring may be homozygous. Such a homozygous person may have no fingers and toes and have other osseous defects incompatible with normal postnatal life. This dominant gene is sublethal in homozygous persons.

Congenital ichthyosis may be cited as an example of a disorder which appears in children homozygous for a recessive sublethal gene. The parents of such children appear normal, but carry the abnormal gene, and some of their offspring present hyperkeratosis incompatible with life.

### ENVIRONMENTAL FACTORS

In mammals prenatal development is protected, since it takes place in the uterus, but this protection is not complete. Mechanical, actinic, chemical, nutritional and infectious agents may cause prenatal injury.

Intrauterine life may be divided into an *embryonic period* (approximately the first trimester) and a *fetal period* (from the twelfth week to birth). This division is arbitrary, but it distinguishes the period in which organogenesis takes place from the period which is chiefly devoted to growth. Severe injuries lead to prenatal death, but milder injuries may result in changes compatible with life. Environmental interference during the embryonic period leads to arrest of development and to malformations. A noxious agent may be harmless at certain stages of this period and deleterious at others, since the various organs are sensitive to noxious agents at periods of rapid differentiation and less sensitive to them in resting stages. It can be assumed that agents responsible for malformations act early in prenatal life, probably

within the first two or three months of gestation. Later, during the fetal period, injuries result in changes which more closely resemble those of postnatal damage, such as scars and mutilations.

**Mechanical Injuries.** Mechanical injuries may result in fetal death. External, intra-abdominal or intrauterine pressure has been said to lead to malformations, but only a few specific possibilities are seriously considered at present. In extrauterine pregnancies the fetus is often deformed. The deformity cannot be attributed to mechanical causes alone, however, since an ectopic embryo is embedded in an abnormal decidua, and faulty nutrition may be the cause. Malformations in a twin can in some instances be attributable to pressure exerted by the other twin. It is often asserted that intrauterine malposition of the fetus leads to malformations; it seems just as reasonable, however, to consider malposition secondary to the malformation. There is a possibility that a deformed fetal part which assumes an abnormal position impairs the normal development of another part and thus causes secondary deformities (mutilations). Amniotic bands are sometimes associated with malformations, but there is no proof that they are the cause of the deformities. More probably they are the result of the genetic or environmental disturbance that caused the malformations.

**Chemical Injuries.** Certain chemicals are capable of destroying the embryo, and, in lower animals, malformations can be produced by adding toxic substances to the environment. The evidence for similar effects on mammalian embryos is scant. Alcohol, benzene, nicotine, lead, mercury and iodine have been suspected as injurious agents, but experimental results have been contradictory. Quinine taken by the mother during pregnancy may cause congenital deafness in her child.

**Nutritional Disturbances.** Nutritional disturbances may adversely influence the embryo. Faulty implantation of the ovum and degeneration of the chorion may interrupt the nutrition of the embryo and disturb its development. Malformation in fetuses derived from ectopic pregnancies is mentioned above. Deficiencies of other nutritional constituents of the maternal diet and deficiency of oxygen have been responsible for defective offspring in animal experiments, but there is no proof that these observations can be applied to human beings. In many regions of Europe, Asia and South America endemic goiter of the parents is associated with endemic cretinism.



the children. The serious mental and physical retardation of the offspring is usually attributed to a lack of iodine in the maternal diet. However, a positive goitrogenic factor may also contribute to this anomaly.

Extensive studies have shown a significant relation between the diet of pregnant women and the physical condition of newborn infants. Stillborn, premature and functionally immature children are born more often to mothers whose diet is poor during pregnancy than to mothers whose diet is adequate. General starvation, as in war or famine, leads to a sharp fall in the conception rate which is associated with amenorrhea. Infants born after periods of dietary deprivation show a reduction in birth weight and birth length.

**Injuries from Infection.** Severe maternal infections during early pregnancy often result in abortion. Mothers who have had German measles during the first two or three months of pregnancy may give birth to infants with congenital cataracts and other congenital defects. Prenatal toxoplasmosis may also result in congenital hydrocephalus, microcephaly and chorioretinitis, as well as widespread disease.

Infections of the fetus during the latter stages of prenatal life cause manifestations which more closely resemble those of postnatal life. Smallpox has been observed in fetuses older than three months; the fetus may recover and be born with scars. Rare

cases of fetal measles and scarlet fever have been reported. Placental transmission of typhoid and tubercle bacilli occurs occasionally, and that of *Treponema pallidum* is common in infected, untreated mothers.

**Actinic Injuries.** Roentgen rays and radium rays are capable of arresting embryonic development and producing malformations. Microcephaly, mental retardation, spina bifida, deformities of the extremities, and the like, have been ascribed to such intrauterine injuries.

**Other Factors.** In addition to the pathogenic environmental factors considered, there may be others still unrecognized. The possibility that abnormal endocrine factors influence the development of the embryo deserves consideration. Diabetic mothers treated with insulin often have abortions and stillbirths, and the neonatal death rate of their infants is high. Cortisone injected into pregnant mice or rabbits may induce cleft palate and other malformations in the fetus.

The etiology of mongolism appears to be related in some way to the age of the mother at the time of the birth of the mongolian idiot. The average age of mothers at such times is significantly higher than the average age of mothers at the birth of normal children.

Advanced maternal age may also play a role in the etiology of other congenital defects such as chondrodystrophy.

## CONGENITAL MALFORMATIONS

More deaths occur in the first month of life than in the remaining months of the first year, and the decline in the infant mortality rate in recent years is less in the neonatal period. This is not surprising if the neonatal mortality is regarded in part as a continuation of the process of "natural selection" which eliminates defective embryos and fetuses throughout the intrauterine period.

Structural anomalies of the embryo play a leading role in the mortality of the first trimester of intrauterine life. Most abnormal embryos die early, but structural anomalies may be compatible with intrauterine life. Shortly before and after birth (perinatal period) the fetus must adjust itself to the profound physiologic changes associated with the onset of extrauterine life. Many abnormal fetuses are incapable of doing so and die at

this time. They contribute considerably to the peak of mortality, which occurs in the perinatal period. About 20 per cent of the deaths occurring in the third trimester of gestation and about 15 per cent of those in the neonatal period are attributed to gross congenital malformations. Although the elimination of deformed children decreases markedly after the first month of postnatal life, the process of natural selection continues throughout infancy and childhood.

According to the vital statistics of the United States, 20,012 deaths were attributed in 1953 to congenital malformations. In the same year whooping cough, measles, diphtheria, scarlet fever and poliomyelitis combined caused 2544 deaths. A comparison of these data illustrates the relative importance of malformations as a cause of death.

Many children with congenital malformations are permanently disabled. Malformations such as clubfoot, dislocation of the hip, spina bifida, and the like, are among the leading causes of crippling in childhood.

The role of congenital malformations in the causation of diseases of children is difficult to evaluate. Some defects, such as those of the osseous system, the heart and the intestinal tract, are well recognized, but many malformations are encountered in disguise. Many congenital defects may go unnoticed for years, particularly those within the body. The affected organs may function for some time, but fail when faced with increased demands. Congenital malformations are often predisposing factors to disease because they represent points of inadequate resistance; they can be damaged by minor infections, toxins or traumas which are usually tolerated by the normal organism without serious consequences. Diseases resulting from such a combination of circumstances may be attributed to the eliciting factor, while the underlying malformation is overlooked.

The primary cause of so-called renal rickets may be a congenital obstruction of the urinary tract. Dwarfism, malnutrition, osseous changes, polyuria, polydipsia, renal insufficiency, chemical changes of the blood, infections of the urinary tract or other symptoms may dominate the clinical picture. Obviously treatment of the symptoms enumerated will not meet with success, whereas early detection and removal of the congenital obstruction may lead to permanent cure.

Many cases diagnosed as chronic pyelitis, chronic pneumonia, malnutrition, birth injury, and the like, represent symptoms of diseased congenital defects; certain nervous disorders and endocrine disturbances are caused by prenatal developmental errors. Many tumors of infancy and childhood can be attributed to congenital malformations (see p. 1347). Congenital defects of the brain play an important role in mental deficiency.

Congenital malformations need not be grossly demonstrable, but may be defects of histologic structure. The role of misplaced cells in the genesis of certain tumors is well known. Some disorders of the nervous system or the endocrine glands must be attributed to histologic congenital defects. Spherocytosis is a congenital anomaly. The intimate relation of certain forms of anemia to malformations is indicated by their association in syndromes. For example, in some forms of aplastic anemia, association with congenital

defects of the skeleton, heart and genital tract points to the developmental origin of the disorder (e.g., Fanconi's anemia).

#### ETIOLOGY AND PATHOGENESIS

Little is known about the causes of congenital malformations in man. Maternal rubella in the first trimester of pregnancy, toxoplasmosis and exposure of the mother to roentgen rays are probably the only known events for which a causative relationship is recognized. A great deal is known, however, about mechanisms and circumstances which favor developmental errors. Such knowledge is derived from clinical observation of patients, from investigation of their families and their environment, and from animal experiments.

Many congenital anomalies are genetically determined. Such anomalies are caused by mutations of genes or chromosomal aberrations which occurred in an immediate or remote ancestor of the affected person. In plants and animals, mutations can be induced experimentally by radiation, but nothing is known about the causes of mutations in man. Some congenital defects are inherited like mendelian unit characters. The laws of inheritance explain the mechanism of the transmission and make possible statistical predictions concerning their reappearance in the offspring of affected persons and their relatives.

Animals often inherit congenital malformations with great regularity of pattern, and it is possible to make a systematic examination of their embryos of different ages to ascertain step by step the deviations from normal development. In this way the action and mechanism of the abnormal gene can be investigated at the development of the finished character observed.

The embryo requires adequate nutrition for normal growth and differentiation. Interruption of nutrition results in death of the embryo, and it is suggested that minor disturbances of the metabolic exchanges between mother and embryo may lead to malformations of the developing organism. The chorion of pathologic embryos is frequently diseased but it is difficult to decide whether the chorionic changes are responsible for the abnormal development or whether an inherent anomaly of the fetus incompatible with life leads to secondary changes of the chorion. Abnormal fetuses are sometimes found in uterus which appears histologically normal. On the other hand, there is a high incidence of congenital defects in fetuses derived from ectopic pregnancies, which have been attributed to faulty implantation.



Experimental observations indicate that chemical changes of the environment can alter the development of the embryo. At certain stages of development minor abnormalities can produce severe anomalies. Maternal diseases and hormonal disturbances could change the chemical environment of the human embryo. Suggestive of such a causal relationship is the relatively high incidence of congenital malformations in children of diabetic mothers and of mothers in their late childbearing period. The mechanism of abnormal development in such cases is not understood, but possibly an undetected anomaly of the chemical environment of the embryo may be responsible.

As previously noted, severe infections of the mother in early pregnancy often result in abortion, and relatively mild infections with the rubella virus in the first trimester of gestation may result in a variety of congenital anomalies of the fetus. There is no proof that these viruses have a comparable teratogenic effect.

*Although the origin of most congenital defects in man is obscure, some general conclusions can be drawn. Congenital malformations are the result of prenatal pathologic processes which can be determined by the genetic constitution of the embryo and take their course in spite of favorable environmental conditions, or a genetically normal embryo can be deformed by adverse environmental circumstances. It follows that not all congenital malformations are hereditary. It is likely, however, that most congenital malformations are the result of interaction between genetic and nongenetic (environmental) factors.*

Teratogenic factors are not specific, and the lack of specificity manifests itself in two ways. An injurious agent may cause various types of abnormalities, according to the time or intensity of its action, as illustrated by the wide variety of congenital anomalies induced by maternal rubella. Maternal roentgen-ray irradiation results in abnormalities in the offspring, which vary with the dose applied and the gestational period in which the exposure took place. An abnormal gene may manifest itself in various abnormalities and exercise a pleiotropic effect. Conversely, a specific type of malformation may be caused by different etiologic factors. For example, each of the three pathologic conditions illustrated in Figures 54, 55 and 56 can be attributed to three different causes. Hereditary and nonhereditary forms may resemble each other; it should not be concluded, therefore, that all forms of

cleft palate or syndactylysm are hereditary because heredity has been proved in some instances.

In spite of the variability of syndromes, it is of definite value to study and record combinations of defects frequently encountered. A knowledge of such syndromes may be an aid in diagnosis and prognosis, particularly if one keeps in mind that the association of defects may vary. This will be illustrated by two examples. Night blindness may be due to a deficiency of vitamin A, but it is also a symptom of retinitis pigmentosa, a degenerative process of the retina which is a constituent of the Laurence-Moon-Biedl syndrome. Night blindness in a child with polydactylysm, obesity and mental retardation assumes, therefore, a different aspect from that in an otherwise normal child. The diagnosis of mental retardation is difficult in the neonatal period. The presence of hypertelorism, epicanthal folds, slanting eyes and other somatic anomalies makes possible, however, the diagnosis of mongolism, with all its prognostic implications, immediately after birth.

Besides such well established syndromes, many combinations of congenital defects are encountered which have not been described or named. Thus, in children with congenital heart disease, conditions such as cleft palate, polydactylysm, malformations of the kidney, atresia ani, encephalocele, hydrocephalus and mongolism are more frequent than in the average children's population. The occurrence of external and skeletal defects in children with mental deficiency is well known. Such visible defects have been considered "stigmata of degeneration." Though this term is ill chosen, it is correct that malformations are found more often in patients with mental deficiency of prenatal origin than in mentally normal children. It is useful to keep this principle of multiplicity of malformations in mind when there is doubt whether one is dealing with a congenital or an acquired disorder in a patient. The finding of one or several additional malformations makes prenatal origin of the disorder more likely.

Malformations may occur sporadically or repeatedly in a sibship (p. 234). Identical malformations, such as cleft palate, may be found in several members of a pedigree. In other instances, one member may have microphthalmus and another glioma retinae. Entire syndromes may recur in families. Thus gargoylism or the Laurence-Moon-Biedl syndrome has been observed repeatedly in a single family. But the various symptoms of a

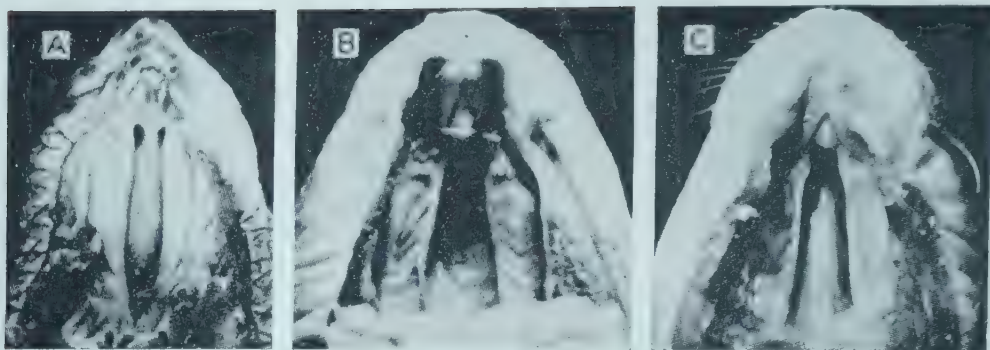


FIG. 54.

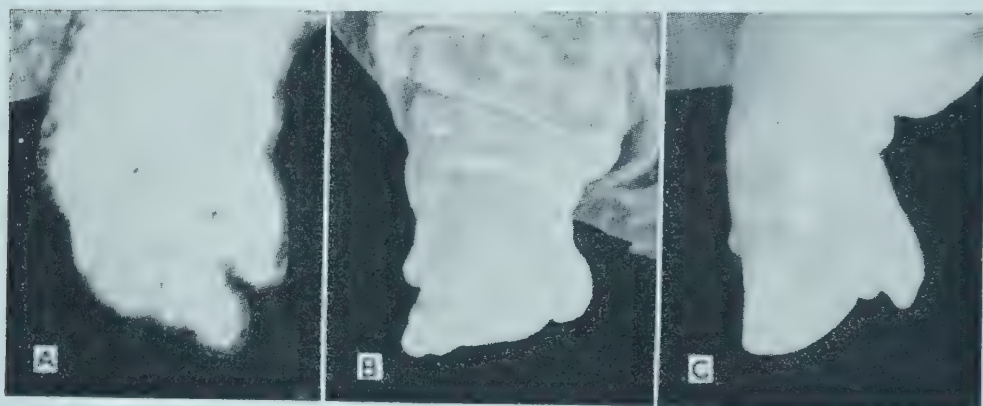


FIG. 55.



FIG. 56.

FIG. 54. Cleft palates of different etiology: A, mouse, derived from strain in which harelip and cleft palate were hereditary. (Steiniger: *Ztschr. f. menschl. Vererb.-u. Konstit.*, Vol. 23.) B, Rat whose mother was deficient in riboflavin; C, rat whose mother was exposed to roentgen rays on day 15 of gestation.

FIG. 55. Syndactylism of different etiology: A, mouse, derived from strain with hereditary congenital defects. (Bagg: *Am. J. Anat.*, Vol. 43.) B, Rat whose mother was deficient in riboflavin; C, rat whose mother was exposed to roentgen rays on day 13 of gestation.

FIG. 56. Microcephaly of different etiology: A, in a child who had 2 siblings with microcephaly and normal siblings and a paternal granduncle who was mentally deficient. (Goldblatt: *Arch. f. Psych.*, Vol. 70.) B, In a child with toxoplasmosis. (Levin and Moore: *J. Pediat.*, Vol. 21.) C, Child of a mother irradiated with roentgen rays during the second and third months of pregnancy. (Engelking: *Klin. Monatschr. f. Augenh.*, Vol. 94.)

(All figures from Warkany, in *Advances in Pediatrics*. Interscience Publishers, Inc., Vol. 2.)

syndrome may also be dissociated in a family, one member showing one symptom or one group of symptoms, and other members showing another part of the syndrome. Thus one child may have the entire Laurence-Moon-

Biedl syndrome, while another child of the same family is mentally retarded and obese, and a third child has mental retardation and polydactylism. In spite of such irregularity the family history is often a great aid in



gnosis and prognosis of the disease of an individual.

It is useful to regard congenital malformations as one form of reproductive failure. Whenever environmental or genetic factors are unfavorable for reproduction, various manifestations of reproductive failure are observed. The most unfavorable conditions are sterility. Between this extreme and the most favorable one which leads to normal reproduction, abnormal borderline states exist. Stillbirth, premature birth and perinatal death may be expressions of such borderline conditions. Malformations contribute to all degrees of reproductive failure and are a substantial cause of abortions in the first trimester. Deformed fetuses which reach the end of the normal gestational period and are born in the perinatal period or survive birth represent a relative reproductive "success" when compared with sterility or early abortion. This possibility makes it understandable that an improvement of reproductive conditions may result in a higher incidence of

congenital malformations. It explains why the true incidence of malformations cannot be estimated without a thorough examination of the aborted and stillborn fetuses.

In experiments one can produce congenital malformations in animals by planned creation of adverse borderline conditions or by applying injurious agents which damage the embryo without killing it. However, starvation, severe infection of the mother or traumatic injury of the embryo may not result in malformations, because they are lethal for the embryo. Even genetically determined malformations may not become "congenital"; i.e., the embryo may not live to the period of birth if two abnormal genes direct the development. Between the lethal homozygous state and normality there may be a borderline condition, the heterozygous state. The heterozygous person is viable and affected with a congenital malformation. These examples illustrate how closely related are the causes of congenital malformations to other forms of reproductive failure.

## ADVISABILITY OF PARENTHOOD

Interest in prenatal pathogenic factors originated with the desire to prevent their disastrous results. In many instances eugenic measures or advice may contribute to the well-being of children as yet unborn.

If a person or one of his close relatives suffers from a congenital defect, he may ask his physician whether he should have children; or parents who have had a defective child may ask whether they should have more offspring. Such questions can rarely be answered adequately, but a knowledge of the facts discussed in the foregoing pages may serve as a guide.

In general it is preferable to give the parents all the available facts concerning the etiology, the theoretic chance of transmission of the disorder, and its clinical course rather than to advise them whether or not to have children. Many factors not medical enter into such a decision, such as the parents' desire of having children, the size of the family, the age of the parents, economic circumstances and religious convictions.

It is important to ascertain whether a given defect or disorder is hereditary or not, since the prognosis for procreation will differ greatly in cases of genetic origin from those of

postconceptional damage. In certain instances such a differentiation can be made without difficulty; in many it may not be possible. Before a statement is made concerning the heredity of a trait the following considerations should be taken into account.

Not all congenital anomalies and defects are hereditary, and not all hereditary anomalies are congenital. The defects produced in the fetus by maternal rubella or toxoplasmosis are congenital, but not genetically determined and, therefore, not hereditary. On the other hand, hereditary traits such as Friedreich's ataxia, Huntington's chorea, diabetes mellitus, retinitis pigmentosa and many others are not congenital, but develop at various periods of postnatal life. The terms "congenital" and "hereditary" are not synonymous.

The widespread belief that anomalies which occur repeatedly in a family are hereditary, whereas those which appear sporadically are not, is not necessarily correct. A defect may be genetically determined, although only one known member of the sibship shows the trait. The defective person may be the first to manifest the genic mutation. In the case of a dominant hereditary trait, his ancestors and siblings are free of the trait, but half of his

children have a chance to have the anomaly and to pass it on to half of their children. This illustrates that sporadic occurrence of a congenital anomaly does not assure normal offspring to the (first) affected member. Similarly, genetically determined defects may appear sporadically if they depend upon recessive factors or if by chance a limited pedigree does not include other defective members. The repeated occurrence of a defect in a pedigree does not prove, however, that it is genetically determined, since several members of a sibship may be exposed to the same pathogenic environmental factors. Thus endemic goiter, rickets, pellagra, and the like, are often familial, but they are usually not hereditary and may be prevented by a change of dietary habits. "Familial" and "hereditary" are not synonymous terms.

Differentiation between hereditary and nonhereditary anomalies is further complicated by the fact that the clinical picture of a nonhereditary modification may resemble closely that of a hereditary mutation. Thus congenital cataract is hereditary in some families, but cataract in an infant whose mother had German measles during the first two months of pregnancy is of environmental origin. Epileptiform convulsions can be inherited or may be due to natal or postnatal trauma. Similarly, syndactyly, cleft palate, microcephaly, spina bifida, microphthalmus and many other congenital defects may be due to genetic mutation, to environmental modification, or to a combination of the two.

The history of pregnancy should include a description of the mother's state of health during the early weeks of pregnancy and of any roentgen ray or drug therapy. Organogenesis is finished at approximately twelve weeks of gestation, and most severe malformations such as congenital heart disease, spina bifida, colobomas of the eye and cleft palate are determined by that time. The rest of gestation is devoted essentially to growth of the fetus. Interference during the latter phase of development may result in a different type of congenital anomaly, such as hydrocephalus, microphthalmus, chorioretinitis and malposition of the extremities. Threatened abortions, diseases and traumas of the mother should be recorded.

The birth history may indicate that physical and mental anomalies can be attributed to injuries received during delivery.

Taking the family history is a time-consuming but necessary procedure. The mother's and the father's ages should be recorded, and

the parents should be asked whether they are blood-related (consanguineous). It is usual to make a pedigree chart (p. 237), but this is usually impractical in a busy clinic. Initially, the medical history of the patient (propositus) is recorded, then that of his brothers and sisters. Miscarriages, stillbirths and causes of deaths of siblings are also recorded. Healthy persons as well as the defective ones must be included in the family history. Next the medical histories of the grandparents, their siblings and siblings' offspring, and so on, are obtained until the pedigree is traced backwards and collaterally as far as the information is reasonably reliable.

If a pathologic trait known to be usually dominant appears in a family and if the pedigree of that family suggests dominant inheritance, it is possible to give a eugenic prognosis. An affected parent who marries a mate normal for the character in question can be told that his children have only a 50% chance to be normal. However, if the parent comes from a family affected by a dominant pathologic trait without showing it, he cannot be assured that he will not transmit the trait to his offspring. Before such assurance is given it should be established that the inheritance of the trait has complete penetrance and expressivity (p. 236), since otherwise a person may appear normal, but transmit the trait. In cases of variable expressivity a person may appear normal on superficial examination, but reveal an abnormal trait in a mild form when subjected to special examinations.

Multiple exostoses are usually well developed in affected males, but in affected females may be so small that the carriers may not be conscious of them. If roentgenograms of the prospective mother reveal slight osseous excrescences in places where exostoses usually occur, she is likely to transmit the disorder, and her sons could be severely affected.

At times laboratory tests can aid in detecting carriers of an abnormal trait with variable expressivity. A member of a family affected with hemolytic jaundice may be clinically well, but have spherocytosis and increased fragility of the red cells which is revealed only by special tests. "Carriers" of gout can be discovered by chemical examination of the blood, since they have hyperuricemia. In addition, before a member of an affected family is declared free, one must be sure that he has reached an age after which the onset of the disease is unlikely. Since cerebellar ataxia may not begin before the fourth decade, no member of an affected family should



considered normal before reaching the age forty years. These examples demonstrate that even in dominant inheritance a eugenic prognosis must be made with caution.

Analysis and prognosis of a recessive trait is more difficult. Such a gene can be carried in the heterozygous form through many generations without causing visible effects, and the abnormal trait can appear in about one-fourth of the children of normal parents who are both heterozygous carriers. Such cases are sometimes so sporadic that their distinction from nonhereditary similar conditions (anecdotical cases) may be impossible. On the other hand, if a homozygous person who has the trait marries a heterozygous carrier who appears normal, the children have a 1:1 chance to be homozygous and to exhibit the trait. Such a pedigree simulates that of a family in which a dominant trait is transmitted through two generations. When two persons homozygous for a recessive trait marry, all the children must be expected to be abnormal.

Deaf-mutism is sometimes genetically determined, the gene being recessive. A deaf-mute is homozygous for the trait. If two persons of this type marry, one can predict that their children will be deaf-mutes (see Fig. 48). If, however, a person with such hereditary deafness marries a normal mate or a person with acquired deafness, all the children can be expected to have normal hearing, although they will be carriers of the abnormal trait (Figs. 48, 49). If two carriers who have an abnormal (homozygous) child ask about the chances of a second child, they must be told that the following child has again one chance in four to be affected. The chances that two heterozygous carriers meet are enhanced by consanguineous marriages in families in which recessive pathogenic genes occur.

A man who manifests a sex-linked recessive trait will—with a normal wife—have sons who neither show nor transmit the trait; but all his daughters will be carriers. The sons of such female carriers will have a 1:1 chance of showing the abnormal trait; those sons who do not manifest the disorder do not transmit it. All the daughters will appear normal, but have a 1:1 chance of being carriers like their mother. There is usually no way to distinguish the carrier daughters from their normal sisters unless their offspring reveal their heterozygous state.

Hereditary traits may be transmitted differently in different sibships. It was mentioned

before that polydactylism, chondrodystrophy, glioma retinae and many other anomalies are sometimes inherited in a dominant and sometimes in a recessive manner. Progressive muscular dystrophy, peroneal atrophy and microphthalmus are transmitted in some families as dominant, in some as recessive, and in others as sex-linked recessive traits.

If a congenital anomaly was caused by an environmental accident, the prognosis for a subsequent pregnancy will depend upon the kind of interfering agent. If the child's anomalies are due to maternal rubella or toxoplasmosis, the prognosis for a second child is good. If they are due to administration of therapeutic doses of roentgen rays or toxic drugs and a repetition of the faulty treatment can be avoided, the prognosis is good.

The etiology of mongolism is unknown, but the theory has been advanced that abnormal heredity and environment may act in combination. In this case the environment is thought to be rendered abnormal by factors resulting from the advanced age of the mother. Two or more cases of mongolism have occurred in one family, but this is exceedingly rare. Young mothers who have given birth to a mongoloid child have a good chance to have normal children subsequently.

When neither a definite genetic nor a known environmental factor can be made responsible for a congenital defect, the chances for the outcome of a subsequent pregnancy cannot be estimated.

When possible, it is helpful to indicate to parents the approximate chances for normal or abnormal children. Such empirical risk figures have been worked out for some congenital disorders such as epilepsy, diabetes mellitus, cardiac malformations, facial clefts, clubfoot and others. Since such disorders are of heterogeneous origin, empirical risk figures represent merely average risks for the disorder in question, which should be used only when actual risk figures cannot be had.

If, for instance, normal parents have a child with harelip (with or without cleft palate), the average risk for another child having a similar malformation is about 5 per cent. If the parents have had two affected children, the risk of having still another is about 10 per cent. If one parent has the anomaly, the average risk for a child is 2 per cent. If, however, in a family one parent and one child are affected, the risk for other children being affected is about 12 per cent. The risk figures are somewhat different for cleft palate without harelip. If the parents are

unaffected, but one child has cleft palate, the risk of having this malformation is about 3 per cent for subsequent children. If one parent has the anomaly, the risk for a child is said to be 7 per cent, but this estimate is questionable, since it is derived from a small sample. If one parent and one child are affected, the risk for other children is said to be 17 per cent.

Such risk figures are better than none at all, but they should be considered merely provisional estimates.

**Protection of the Mother.** Eugenic measures and advice are not restricted to the genetic aspects of prenatal life. The normal development of the fetus should be assured as far as possible by protection of the expectant mother from adverse environmental influences. Roentgen ray treatment must be avoided whenever there is the possibility of a pregnancy. It is of great importance to point out that the first three months of pregnancy are decisive in the formation of the organs of the child, and that the embryo in its early stages is more vulnerable than the fetus.

JOSEF WARKANY  
F. CLARKE FRASER

## REFERENCES

- Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene. The Embryo. Edinburgh, W. Green and Sons, Ltd., 1904.
- Bass, M. H.: Diseases of the Pregnant Woman Affecting the Offspring. *Advances Int. Med.*, 5:15, 1952.
- Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C.: Nutrition Studies during Pregnancy. *Am. J. Obst. & Gynec.*, 46:38, 1943.
- Corner, G. W.: *Ourselves Unborn*. New Haven, Yale University Press, 1945.
- Ebbs, J. H., Tisdall, F. F., and Scott, W. A.: Influence of Prenatal Diet on Mother and Child. *J. Nutrition*, 22:515, 1941.
- Fraser, F. C.: Medical Genetics in Pediatrics. *Pediatr.*, 44:85, 1954.
- Fraser, F. C., Walker, B. E., and Trasler, D. G.: Experimental Production of Congenital Cleft Palate. Genetic and Environmental Factors. *Pediatr.* 19:782, 1957.
- Goldschmidt, R. B.: *Physiological Genetics*. New York, McGraw-Hill Book Company, Inc., 1938.
- Goldstein, L., and Murphy, D. P.: Etiology of Health in Children Born after Maternal Pelvic Irradiation; Defective Children Born after In-utero Pelvic Irradiation. *Am. J. Roentgenol.* 22:322, 1929.
- Gregg, N. M.: Congenital Cataract Following German Measles in the Mother. *Tr. Ophth. Soc. Australia*, 3:35, 1942.
- Gruenewald, P.: Mechanisms of Abnormal Development. *Arch. Path.*, 44:398, 495, 648, 1947.
- Hale, F.: Relation of Vitamin A to Anophthalmos. *Pigs. Am. J. Ophth.*, 18:1087, 1935.
- Ingalls, T. H., Curley, F. J., and Prindle, R. A.: Anoxia as a Cause of Fetal Death and Congenital Defect in the Mouse. *Am. J. Dis. Child.*, 80:3, 1950.
- Mall, F. P.: Pathology of the Human Ovum, Keibel, F. K. J., and Mall, F. P.: *Manual of Human Embryology*. Philadelphia, J. B. Lippincott Company, 1910.
- Neel, J. V.: The Clinical Detection of the Genetic Carriers of Inherited Disease. *Medicine*, 26:1, 1947.
- Potter, E. L., and Adair, F. L.: Fetal and Neonatal Death. Chicago, University of Chicago Press, 1940.
- Smith, C. A.: Effects of Maternal Undernutrition upon the Newborn Infant in Holland. *J. Pediatr.* 30:229, 1947.
- Snyder, L. H.: *Medical Genetics*. Durham, N. C., Duke University Press, 1941.
- Sorsby, A. (ed.): *Clinical Genetics*. London, Butterworth & Co., Ltd., 1953.
- Stern, C.: *Principles of Human Genetics*. San Francisco, W. H. Freeman & Co., 1950.
- Warkany, J.: Etiology of Congenital Malformations. *Advances in Pediatrics*. New York, Interscience Publishers, Inc., 1947, Vol. 2.
- Warkany, J.: The Role of Congenital Anomalies in the Etiology of Chronic Diseases. *J. Chron. Dis.* 3:46, 1956.

## INBORN ERRORS OF METABOLISM

Sir A. E. Garrod's classic paper (1902) on the abnormal human biochemical trait, alcaptonuria, presented the first evidence that each gene was concerned with a specific biochemical process in cellular metabolism. Extensive studies by biochemical geneticists in plants, bacteria and animals greatly stimulated the clinical interest in the human hereditary biochemical disorders, which Gar-

rod had named *inborn errors of metabolism*. Investigation of inherited flower color differences, for example, defined the specific role of numerous single genes in modifying chemically the organic nucleus, 2-phenylbenzopyrylium, to form the different anthocyanin and anthoxanthin compounds which are the blue, red and yellow pigments of flowers. Many of the demonstrated complexities



etic control of the pathways for biosynthesis of vitamins, amino acids and the like, the protoplasm of the fungus, *Neurospora*, and their prototypes in the human cell. Studies of the synthesis of nucleic acids in mutant strains of *Escherichia coli* and phages are furnishing knowledge of the chemical nature of the gene and of basic biochemical mechanisms under genetic control, which is applicable to all cellular metabolism. The detection of two inherited enzymatic activities in the rabbit, xanthophyllase, which defines the deposition of yellow fat, and ascorbic acidase, which inactivates atropine, is a forerunner of the expanding body of human observations which forms the basis for the concept of human biochemical individuality—that the uniqueness of each human being derives from the genetically determined chemical patterns in his cells.

Important additions to the knowledge of normal human dynamic biochemistry are being made by the recent rapid growth of clinical and investigative interest in the inborn errors of metabolism. The current concept is that each gene is normally responsible for the production of a specific biologically functional macromolecule which is often, but not necessarily, an enzyme. To emphasize the association of a specific molecular abnormality with a mutant gene, Pauling renamed the disorders, "the molecular diseases." Several different mechanisms are postulated to explain the ways in which the molecular diseases produce clinically detectable biochemical abnormalities:

1. By producing a metabolic block at one stage in a series of chemical transformations, resulting in either (a) an accumulation of a normally occurring metabolite, present in undetectable amounts, e.g., the accumulation and excretion of phenylpyruvic acid in phenylketonuria; or (b) a failure of production of an essential normal end product, e.g., the absence of melanin pigments in albinism.

2. By the abnormality or absence of an enzymatically regulated renal tubular transport mechanism, leading to (a) excessive urinary loss of an essential metabolite because of tubular reabsorptive failure, e.g., cystine in cystinuria; or (b) accumulation of a catabolic end product in the body fluids because of excessive tubular reabsorption, e.g., uric acid in gout.

3. By replacement of a normally occurring enzyme or enzymatic process by another with different activity, resulting in the synthesis

of compounds unlike those usually found in man, e.g., the abnormal hemoglobins.

Patients with the same molecular disease may show individual differences in clinical findings, ranging from complete absence of signs and symptoms to severe illness of varying duration. Such variability may be due to a peculiarity of the genetic defect itself, which is termed the *degree of penetrance* of the mutant gene. In persons carrying the same mutant gene, *genotypes*, variations in degree of penetrance of the gene account for differences in clinical appearances or manifestations, *phenotypes*. More amenable to medical intervention, however, are the influences of environmental factors in determining the clinical manifestations or phenotypes of a given molecular disease. This is referred to as the *degree of expressivity* of the genetic defect. The prevention of the symptoms of galactosemia by a galactose-free diet exemplifies this latter concept.

A meaningful classification of the ever-growing number of molecular diseases would be one based upon the framework of normal human dynamic biochemistry. The fragmentary knowledge of this vast area, and the ignorance of the specific genetically determined biochemical defect in most molecular diseases, make this impossible at present. A temporarily convenient grouping, which lists the inborn errors of metabolism under the chemical species by which they are detectable clinically, is the following:

Table 46. Inborn Errors of Metabolism ("Molecular Diseases")

#### I. Errors in Protein Metabolism

##### A. Defective synthesis of plasma proteins (dysproteinemias)

1. Familial idiopathic dysproteinemia
2. Idiopathic hypoproteinemia
3. Congenital afibrinogenemia
4. Hemophilia (A) and mild hemophilia (AHG)
5. Hemophilia B (plasma thromboplastin component, PTC, deficiency or Christmas disease)
6. Plasma thromboplastin antecedent (PTA) deficiency (hemophilia C)
7. Hageman factor (HF) deficiency
8. Labile factor deficiency (parahemophilia or Owren's disease)
9. Stable factor deficiency (serum prothrombin conversion accelerator, SPCA, deficiency)
10. Stuart factor deficiency
11. Congenital hypoprothrombinemia
12. Agammaglobulinemia

Table 46 (continued)

13. Congenital absence of specific beta-2-globulin with immunologic paralysis
14. Absence of  $\beta$ -2-globulins (haptoglobins) causing hemoglobinuria
15. Ceruloplasmin deficiency in Wilson's disease
16. Congenital analbuminemia
- B. Defective hemoglobin synthesis
  1. Abnormal hemoglobin (S, C, D, E, G, H, I, J, K, L, M, N, O, P, Q, Bart's hemoglobin), diseases and traits
  2. Thalassemia major and minor
  3. Sickle cell variants (combinations of 1 and 2)
- C. Defective amino acid metabolism and transport of amino acids
  1. Of phenylalanine and tyrosine
    - a. Alcaptonuria
    - b. Phenylketonuria
    - c. Tyrosinosis
    - d. Albinism
    - e. Sporadic goitrous cretinism (p. 1170)
  2. Of cystine (and glutathione)
    - a. Cystinuria, the prototype of inherited syndromes of renal tubular dysfunction. Includes glycinuria, beta-aminoisobutyric aciduria, renal glycosuria, vitamin D-resistant rickets, nephrogenic diabetes insipidus, pseudohypoparathyroidism, variants of the Fanconi syndrome and others
    - b. Cystinosis
    - c. Hereditary tendency to drug-induced (primaquine, etc.) hemolytic anemia (involving glutathione)
  3. Of tryptophane
    - a. Congenital hypoplastic anemia (erythrocytogenesis imperfecta)
    - b. Hartnup (H) disease
    - c. Autism with hereditary error in tryptophane metabolism
  4. Of lysine
    - a. Hypoglycemia (idiopathic)
  5. Of valine, leucine and isoleucine
    - a. Maple sugar disease
- II. *Errors in Carbohydrate Metabolism*
  - A. Defective mucopolysaccharide metabolism
    1. Hurler's disease (gargoylism) (p. 1238), Marfan's syndrome (p. 1243) and osteogenesis imperfecta (p. 1241)
  - B. Defective glycogen metabolism
    1. Glycogen storage disease of liver and kidneys (von Gierke)
    2. Glycogen storage disease with hepatic cirrhosis (brancher enzyme defect)
    3. Glycogen storage disease of liver and muscle (debrancher enzyme defects)
    4. Glycogen storage disease of heart and muscles

Table 46 (continued)

5. Glycogen storage disease of skeletal muscle
- C. Defective disaccharide metabolism
  1. Congenital sucrosuria
- D. Defective hexose metabolism
  1. Essential fructosuria
  2. Galactosemia (congenital galactosuria)
- E. Defective pentose metabolism
  1. Essential pentosuria (xylulosuria)
- III. *Errors in Lipid Metabolism*
  - A. Defective neutral fat metabolism
    1. Idiopathic hyperlipemia
  - B. Defective cholesterol metabolism (p. 1002)
    1. Primary xanthomatosis of the hypercholesterolemic type (hereditary hypercholesterolemic xanthomatosis) manifested as the following clinical syndromes:
      - a. Xanthoma tuberosum et planum (skin)
      - b. Xanthoma of the tendons
      - c. Xanthoma of the intima of blood vessels and heart
      - d. Forme fruste, i.e., hypercholesterolemia alone
      - e. Xanthomatous biliary cirrhosis
    2. Congenital adrenal hyperplasia, syndromes of (virilizing adrenal hyperplasia)
      - a. Early virilization in either sex, pseudohermaphroditism in females
      - b. Early virilization, precocious growth and hypertension
      - c. Early virilization, precocious growth and disturbed electrolyte metabolism (salt losers)
  - C. Defective diaminophosphatide (sphingomyelin) metabolism
    1. Niemann-Pick disease (sphingomyelin lipoidosis) (p. 1000)
  - D. Defective cerebroside metabolism
    1. Gaucher's disease (cerebroside lipoidosis) (p. 999)
  - E. Defective ganglioside metabolism
    1. Tay-Sachs disease (amaurotic familial idiocy) (p. 1094)
- IV. *Errors in Pigment Metabolism*
  - A. Defective porphyrin metabolism, the porphyrias
    1. Congenital (erythropoietic) porphyria
    2. Acute intermittent porphyria
    3. Cutanea tarda type of porphyria
  - B. Defective bilirubin excretion
    1. Hereditary obstructive jaundice
  - C. Defective hemoglobin pigment
    1. Hereditary methemoglobinemias
    2. Hereditary sulfhemoglobinemia
  - D. Hemochromatosis
- V. *Unclassified*
  - A. Hypophosphatasia (p. 1224)
  - B. Congenital spherocytic anemia (p. 944)
  - C. Oxalosis (p. 1054)



## INBORN ERRORS IN PROTEIN METABOLISM

Genetic abnormality of the various body proteins, estimated to number 100,000, could produce a staggering variety of structural and functional human hereditary disorders. Basic chemical defects are being uncovered in human genetic diseases, once known only by their morphologic and functional features. Exemplifying this are arachnodactyly, in which a widespread connective tissue defect

is apparently based upon disordered structure of fibrous proteins or upon abnormal basic molecules of collagen and elastin; and muscular dystrophy, in which abnormality of the contractile proteins of muscle cells is a basic defect. Because the disordered chemistry of these two true molecular diseases is still somewhat ill-defined, they and many others are omitted from this section.

### *Defective Synthesis of Plasma Proteins*

The number of genetic errors in the synthesis of plasma proteins continues to increase. For example, the isolation of gamma globulin and the demonstration that it is a carrier of immune antibodies made possible the discovery that a group of children who failed to acquire immunity to various infectious agents suffered from a congenital defect in the synthesis of gamma globulin. And the congenital absence of certain single fractions of the globulins which enter into the complex mechanism of blood clotting has been shown to be responsible not only for hemophilia, but also for an array of disorders with abnormal bleeding tendencies. The term "dysproteinemia" has been applied to hereditary disorders of plasma proteins.

#### **FAMILIAL IDIOPATHIC DYSPROTEINEMIA**

Familial idiopathic dysproteinemia is a hereditary disorder characterized by hypoproteinemia with or without abnormalities in the electrophoretic patterns in the plasma. In the family in which the disorder was first detected four adults of one generation, two of their paternal uncles and four members of the second generation had hypoproteinemia with a variety of changes in concentration of various serum protein fractions. Edema occurred in adult members of the family, with ulcers of the legs in male members and low oscillometric readings in females.

#### **IDIOPATHIC HYPOPROTEINEMIA**

Congenital and persistent hypoproteinemia is a rare disorder. The two cases recorded in this country had fluctuating edema associated with low globulin and albumin values. One patient, a twelve-year-old child, had not had

recurrent infections, even though serum gamma globulin was absent by electrophoretic analysis. The second, a child three years of age, showed atrophic liver changes at autopsy. Whether these were the cause or the result of the hypoproteinemia is not known. In both instances, however, it appears that a defect in the synthesis of serum protein was responsible for the hypoproteinemia. Congenital hypoproteinemia is unrelated to the recently delineated syndrome of hypoproteinemia and anemia of a transitory nature in young infants, which has been named transient dysproteinemia.

#### **CONGENITAL DEFECTS IN THE SYNTHESIS OF PLASMA PROTEINS ACCOMPANIED BY HEMORRHAGIC DIATHESIS**

The relationship of the hemorrhagic disorders dependent upon a deficiency or absence of one or another of the plasma proteins concerned in the clotting mechanism is shown in Figure 57.

A clot forms when soluble fibrinogen is converted to insoluble fibrin through the enzymatic activity of thrombin. For its activation to thrombin, prothrombin requires the following five substances: (1) thromboplastin, which is derived from platelets (platelet factor 3) or tissue extracts and becomes active through modification by four separate components of plasma protein, antihemophilic globulin (AHG), plasma thromboplastin component (PTC), plasma thromboplastin antecedent (PTA) and Hageman factor (HF); (2) calcium (ionic); (3) labile factor in an active form derived from an inactive form by the action of small amounts of thrombin; (4) stable factor; and (5)

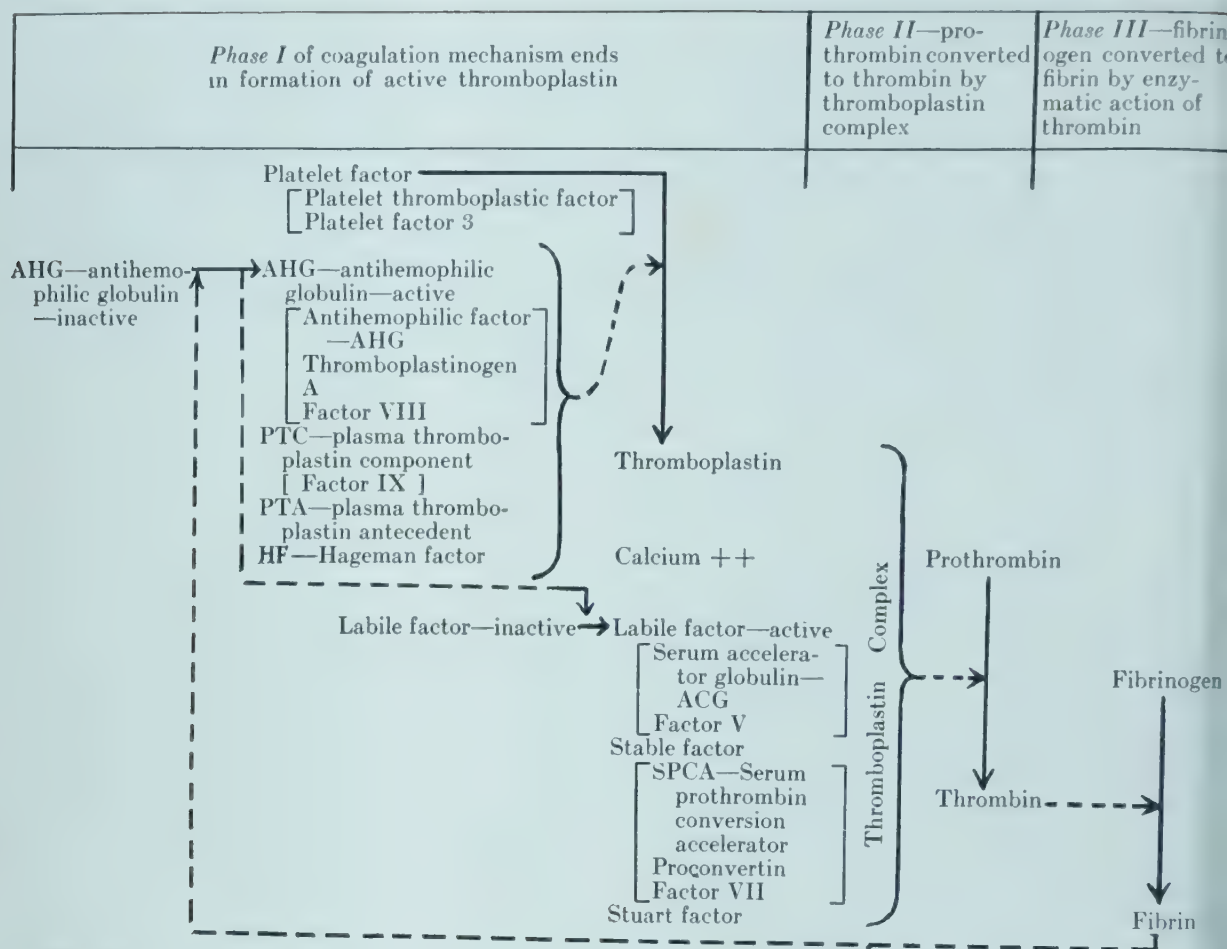


FIG. 57. Schema of postulated blood coagulation process. Solid arrows indicate conversion of one substance to another. Broken arrows indicate activation of the process; other commonly used names for individual constituents are listed under each one between brackets. At the top of the figure is depicted the division of the coagulation mechanism into its three phases ending in thromboplastin, thrombin and fibrinogen formation, respectively. Clinical entities are associated with inherited defects in formation of fibrinogen (afibrinogenemia), antihemophilic globulin-AHG (classic hemophilia A), plasma thromboplastin component-PTC (Christmas disease or hemophilia B), plasma thromboplastin antecedent-PTA (hemophilia C or PTC deficiency), Hageman factor-HF (Hageman trait), labile factor (parahemophilia or Owren's disease), stable factor (serum prothrombin conversion accelerator, SPCA deficiency), Stuart factor deficiency, prothrombin (congenital hypoprothrombinemias, types I and II).

Stuart factor. The formation of a clot ceases when the small amount of thrombin which initiated the process is absorbed upon the fibrin clot so formed.

*Afibrinogenemia* (p. 482) or hereditary absence of fibrinogen from the blood is due to a rare recessive gene. Thirty-one cases, affecting both sexes, are recorded. Though death in early infancy and early childhood is common, one patient was in excellent health at the age of twenty-one years.

*Hemophilia* (p. 977) (classic hemophilia or hemophilia A) is due to a failure or deficiency in synthesis of the antihemophilic globulin (AHG). In *mild hemophilia*, an allelic form of hemophilia, AHG is present in variable amounts up to 25 per cent of normal, so that bleeding is less severe than in hemo-

philia. Both degrees of hemophilia are sex-linked recessive traits, carried by females and appearing in males. The mild form is not completely recessive, however, since certain female carriers tend to bruise easily and to have menorrhagia. In several families hemophilia has occurred in females. A variety of hemophilia in which, in addition to the customary findings of reduced AHG concentration and prolonged coagulation time there is an increased bleeding time and capillary fragility, has been termed *vascular hemophilia* or *pseudohemophilia* (p. 980). It is apparently transmitted by an autosomal dominant gene of high penetrance and variable expressivity.

*Hemophilia B* (p. 980) (plasma thromboplastin component, PTC, deficiency; Christ



nas disease or deuterohemophilia) is inherited as a sex-linked recessive trait, causing an absence or deficiency of PTC. Less severe than hemophilia in males, there is a greater incidence of bleeding manifestations in heterozygotes for the PTC factor. From 10 to 20 per cent of the entire group of hemophilic diseases are due to PTC deficiency.

*Plasma thromboplastin antecedent deficiency* (PTA deficiency, hemophilia C) (p. 980) is a mild bleeding disease occurring in both sexes, transmitted by an autosomal dominant gene of high penetrance and variable expressivity. As a result, the disorder may occur in varying degrees, even within a single family.

*Hageman factor deficiency* (HF deficiency) is a hereditary defect in the coagulation mechanism discernible only *in vitro*, since patients with the defect have no clinical evidences of a bleeding tendency. It has been discovered in a few families by the finding of a prolonged coagulation time in either glass or siliconized tubes during the performance of routine preoperative coagulation tests on patients with no known tendency to bleed. The Hageman factor is apparently necessary along with AHG, PTC and PTA for thromboplastin formation. It is thought to be transmitted by an autosomal recessive gene.

*Labile factor deficiency* (parahemophilia) (p. 981) was described by Owren in 1947 in a female with menorrhagia. It is caused by absence or deficiency of the labile factor (factor V or accelerator globulin). Occurring in both sexes, its mode of transmission is not certain, but it is thought to be carried by a partially dominant gene. Deficiency of the labile factor causes prolongation of the one-stage prothrombin time, which is restored to normal by the addition of fresh plasma.

*Stable factor deficiency* (serum prothrombin conversion accelerator, SPCA, deficiency; proconvertin deficiency) is a hereditary hemorrhagic disorder apparently transmitted by an autosomal dominant gene. Recently a factor closely allied to it in activity has been segregated and named the *Stuart factor*. It appears to be inherited as an incompletely recessive characteristic of high penetrance.

Two types of *congenital hypoprothrombinemia* have been described by Quick. Type I is supposedly due to a deficiency of prothrombin caused by impaired enzymatic synthesis. In type II the total amount of circulating prothrombin is normal, but a postulated hereditary defect prevents the liberation of active prothrombin from the normal quanti-

ties of the inactive form. It has been suggested that the families described by Quick may be suffering from SPCA deficiency rather than from hypoprothrombinemia.

## AGAMMAGLOBULINEMIA

### (BRUTON'S DISEASE)

Hereditary defective synthesis of gamma globulin was discovered by Bruton (1952) in a boy who had had nineteen attacks of sepsis. A sex-linked recessive mutant gene transmits the disorder. A mother who is a carrier may pass the *disease* to half of her sons and the asymptomatic carrier state to half of her daughters. Failure of gamma globulin production is due to the absence of plasma cells in the hypoplastic lymphoid tissue characteristic of these patients. The hypoplasia of the adenoid tissue can be demonstrated roentgenographically and is of diagnostic help.

Children with the disorder are quite normal except for their inability to form antibodies to pyogenic bacteria (staphylococci, streptococci, pneumococci, meningococci and *Hemophilus influenzae*) or to such antigenic substances as diphtheria toxoid, typhoid vaccine, pneumococcal polysaccharides, heterologous tissues and the like. Absence of the appropriate isohemo-agglutinin from the blood, e.g., lack of anti-A antibodies in a child with a group B blood type, is another facet of this immunologic paralysis. The properdin system and complement activity of serum are unimpaired, and account for the normal resistance of these patients to infections with gram-negative bacteria. Unlike the hypersusceptibility to recurrent pyogenic infections, response to viral infections such as measles, mumps and poliomyelitis is normal with the development of lasting immunity. Paradoxically, circulating antibodies do not develop after immunization with viral vaccines. Smallpox vaccination has been done successfully without complication in at least ten children. However, four instances of vaccinia gangrenosa have occurred after vaccination of children with agammaglobulinemia. Administration of specific hyperimmune gamma globulin to two of the children helped arrest the life-threatening process. The failure of transplanted heterologous skin and other tissues to evoke an antibody response which in normal persons destroys these tissues permits their survival in agammaglobulinemic children.

Newborn infants with the defect have normal adult serum levels of gamma globulin,

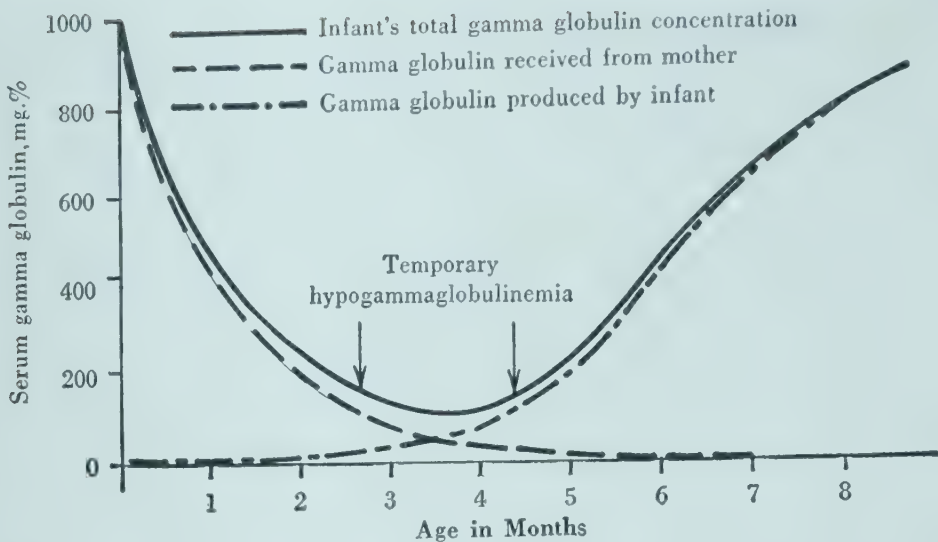


FIG. 58. Physiologic hypogammaglobulinemia in the infant. (From Barrett and Volwiller: J.A.M.A., Vol. 164.)

averaging 900 mg. per 100 ml., derived entirely by passive transfer from the maternal circulation in the later months of gestation. Depletion of this store is complete at six months of age (Fig. 58). Increased susceptibility to infection occurs when the level of gamma globulin falls below 100 to 150 mg. per 100 ml., by two to four months of age.

Lymphopenia is a customary finding, and cyclic neutropenia occurs in some patients. During infectious episodes extreme polymorphonuclear leukocytosis (50,000 to 60,000 per cubic millimeter) is not unusual. Recurrent localized infection has led to such complications as bronchiectasis, impaired hearing and obstructive hydrocephalus. Many of the children have chronic rheumatoid arthritis.

The disease is suspected in a male child who has repeated bacterial infections or has a persistently positive Schick test or negative Widal test after adequate immunizations. Demonstration of a low level or absence of gamma globulin by immunochemical methods establishes the diagnosis; the zinc turbidity test and electrophoretic procedures are useful as screening procedures.

Prevention of infection is the major objective of medical management. Administration of prophylactic antibiotics and reasonable attempts at avoidance of infections are means to this end. Bacterial cultures are mandatory during illness as guides to appropriate intensive antibiotic therapy. Monthly intramuscular injections of 0.7 ml. of gamma globulin (solution) per kilogram of body weight will maintain minimal but effective serum levels of 100 to 150 mg. per 100 ml. The initial

dose of gamma globulin (priming dose) is twice the maintenance dose, or 1.4 ml. per kilogram; some patients require higher maintenance doses.

#### BETA-2-GLOBULIN DEFICIENCY ASSOCIATED WITH IMMUNOLOGIC PARALYSIS

Recently the presence of a disturbance which duplicated the findings of agammaglobulinemia was reported in a four-year-old boy with normal serum gamma globulin levels. However, the absence of two specific beta-2-globulins was demonstrable, and the condition is proposed as a new molecular disease.

#### HAPTOGLOBIN DEFICIENCY

Hereditary deficiency of the haptoglobins, the plasma beta-2-globulins which bind free hemoglobin, has been suggested as an explanation for some instances of hemoglobinuria. Although the amount of hemoglobin which the haptoglobins bind is the same (125 mg. per 100 ml.), there are variations in the types of haptoglobin in different normal persons. A given person may have either one, three or four distinct haptoglobins, depending upon whether he is homozygous or heterozygous for a single pair of allelomorphous genes.

Increased hemolysis of red blood cells during strenuous exercise is a recognized phenomenon in defective persons. Usually the released hemoglobin is not excreted by the kidney, because of its union with haptoglobin. However, in persons with *march*



*hemoglobinuria*, hemoglobin appears in the urine after a long walk or race. Decreases or absence of haptoglobin appears to be the hereditary basis for this benign type of hemoglobinuria.

## HEREDITARY CERULOPLASMIN DEFICIENCY

Ceruloplasmin, a blue-colored alpha-2-globulin containing eight copper atoms per molecule, comprises 0.5 per cent of the total plasma proteins. The average normal concentration is 24 mg. per 100 ml. (range, 16 to 33 mg.). Low levels are found in newborn infants, presumably owing to immaturity of the synthetic mechanisms, and in patients with active nephrosis, in which ceruloplasmin is lost in the urine. In *Wilson's disease* (hepatolenticular degeneration, p. 1098), a hereditary disorder transmitted by an autosomal recessive gene, low levels of ceruloplasmin, averaging 5 mg. per 100 ml. (range, 0 to 14 mg.), are apparently responsible for the abnormal accumulations of copper in tissues. It appears likely that the primary genetic defect in *Wilson's disease* is in the

synthesis of ceruloplasmin. By permitting increased absorption of ingested copper and increased deposition in tissues, the ceruloplasmin deficit is responsible for injury to organs most susceptible to damage by copper, i.e., the brain, liver and kidneys. Although the mechanism of copper intoxication is not clear, the clinical features of *Wilson's disease*, including the Kayser-Fleischer corneal ring, are reflections of disturbances in the organs with an abnormally high copper content.

## ANALBUMINEMIA

Total absence of serum albumin as a genetic defect was reported by Bennhold (1954) in a German woman aged twenty-five years, and her thirty-three-year-old brother. Another sister and 150 members of the family who were studied were normal in this respect. Except for slight edema of the ankles after an arduous day's work, the lack of clinical findings is remarkable. An American woman with the same defect is under study. Apparently many of the functions of albumin are taken over by globulin fractions, which are increased in concentration.

## Defective Hemoglobin Synthesis

### ABNORMAL HEMOGLOBINS

These disorders, described elsewhere, are inborn errors in synthesis of the globin moiety of hemoglobin. Following Pauling's fundamental discovery of an abnormal hemoglobin (S) in "sicklers" (1949), numerous other hemoglobin variants have been identified (hemoglobins S, C, D, E, G, H, I, J, K, L, M, N, O, P, Q and Bart's).

The genes which control the formation of hemoglobin are found at three chromosomal loci. Various combinations of different genes at these sites form the numerous genotypes which are manifested clinically as the abnormal hemoglobin diseases and traits.

There is a single locus for the gene controlling normal hemoglobin (A) production and the mutant alleles responsible for the presence of the abnormal hemoglobins. The mutant genes are incompletely recessive, so that homozygous subjects differ from heterozygotes in the magnitude of their abnormality, rather than in the usual all-or-none fashion of completely recessive traits. This is well exemplified by persons with hemoglobin S;

the more serious sickle cell disease is a manifestation of homozygosity, whereas the heterozygote has less abnormal hemoglobin and has only the sickle cell trait. The finding of two abnormal hemoglobins in the same person, e.g., S and C or S and D, is evidence of heterozygosity for both genes.

The genes which control the *rate* of synthesis of normal hemoglobin reside in a second site, the so-called thalassemia locus. Homozygosity for the mutant gene in this location causes *thalassemia major*; the phenotype for heterozygosity is the milder trait, *thalassemia minor*. Double heterozygosity for the thalassemia major and the thalassemia trait is a well recognized occurrence.

Fetal hemoglobin, normally found in the fetus and young infant, is represented by a gene situated at a third focus. Interference with the formation of normal adult hemoglobin (A), e.g., in subjects with abnormal hemoglobins, evokes resumption of production of fetal hemoglobin. Thus patients with *sickle cell anemia* and *thalassemia* have circulating hemoglobin F.

The hemoglobin of sickle cell anemia

differs from hemoglobin A by the replacement of a glutamic acid residue by a valine residue in the polypeptide chain of 300 molecules of

amino acid which forms the protein. In hemoglobin C disease a lysine residue replaces the glutamic acid residue.

Defective Amino Acid Metabolism

ERRORS IN PHENYLALANINE AND TYROSINE METABOLISM

Congenital defects in the intermediary metabolism of the amino acids phenylalanine and tyrosine are the bases for a number of inter-

esting clinically defined disorders. Phenylalanine is an essential amino acid; i.e., the body is unable to manufacture it. Tyrosine may be derived by oxidation of phenylalanine in the body and is thus termed a dispensable amino acid. The location of the chemical de-

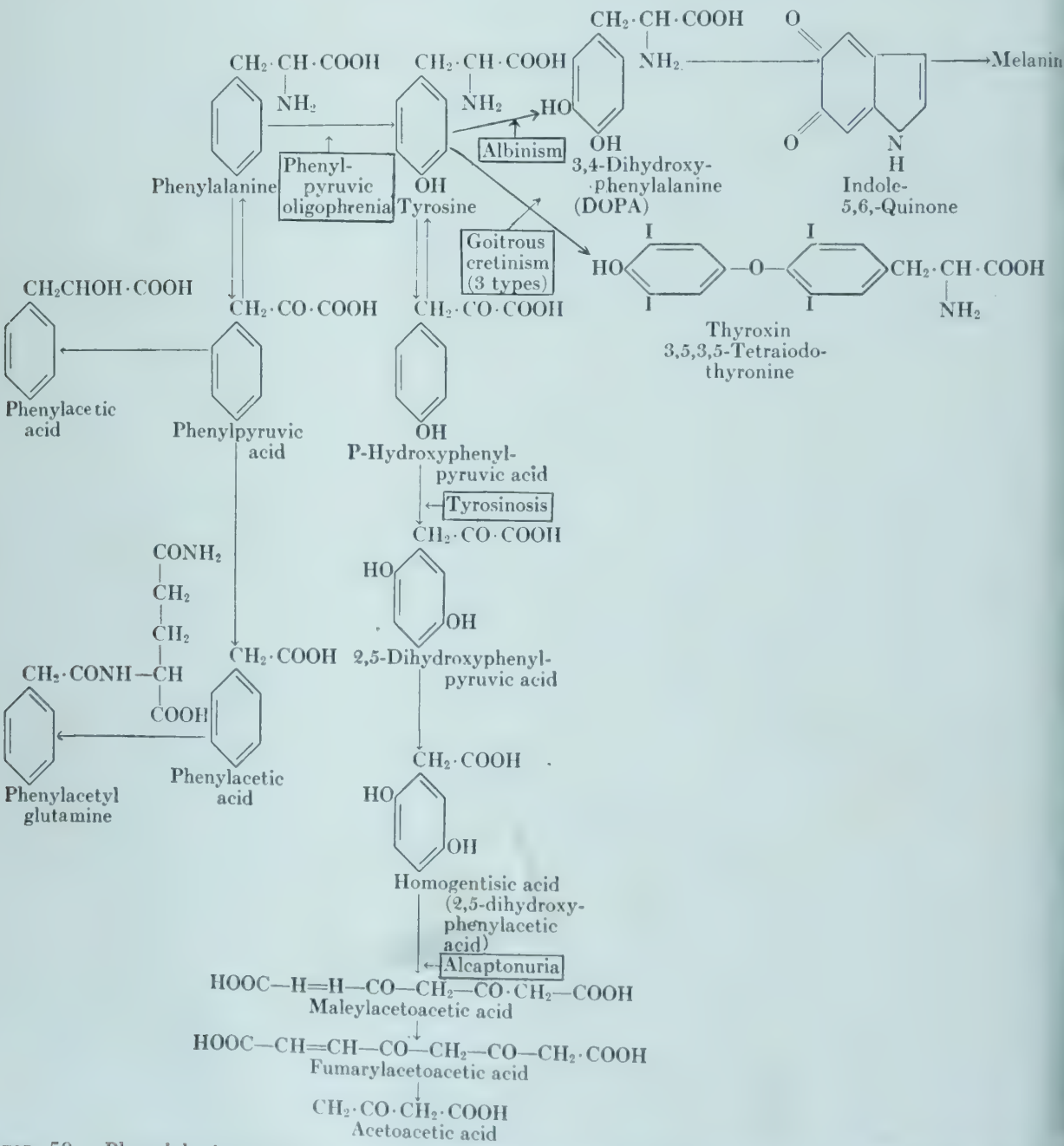


FIG. 59. Phenylalanine-tyrosine intermediary metabolism in man, indicating relation of inherited defects to specific chemical reactions.



fects associated with the inherited errors of phenylalanine-tyrosine metabolism is indicated in Figure 59.

### ALCAPTONURIA

Alcaptonuria is a rare disorder of phenylalanine-tyrosine metabolism characterized by the urinary excretion of homogentisic acid (also known as alcapton or 2,5-dihydroxyphenylacetic acid). More than 200 cases have been recorded. In the great majority of patients the disorder is transmitted by a single autosomal recessive gene. It is estimated that there are five alcaptonurics per million persons, and that one in 200 people is a heterozygous carrier of the recessive gene. It occurs in both white and Negro races.

Urine containing homogentisic acid becomes dark on standing, owing to oxidation and polymerization. In infants the diaper may be stained, leading to detection of the defect, which is otherwise asymptomatic. The darkness of the stain increases with continued exposure to air, and a dried diaper will show a pitch-black stain. The slow accumulation of a black polymer of homogentisic acid in the cartilage and other mesenchymal tissues produces a black discoloration of the cheeks, nose, sclerae and ears in middle-aged patients. This is termed *alcaptonuric ochronosis*. Degeneration of cartilage in which the pigment is concentrated leads to arthritis in about half of the older alcaptonurics.

The metabolic block in alcaptonuria is due to hereditary absence from the body tissues of homogentisate oxidase (see Fig. 59). As a consequence of the enzymatic deficit, the catabolism of tyrosine is arrested at the stage of homogentisic acid, which is rapidly excreted in the urine by the combined processes of glomerular filtration and renal tubular secretion. Alcaptonuria occurs in scorbutic guinea pigs, but, unlike the human disorder, this induced defect is abolished by administration of ascorbic acid.

The addition of alkali accelerates the spontaneous darkening of alcaptonuric urine. The urine has reducing properties, giving a positive reaction with Fehling's or Benedict's reagent and reducing an ammoniacal solution of silver nitrate in the cold. If a dilute solution of ferric chloride is allowed to drop into urine containing homogentisic acid, a fleeting deep blue color appears in the path of the drops. A rapid test for alcaptonuria is the blackening of sensitized photographic paper by a drop of strongly alkaline alcaptonuric urine. A positive Millon test occurs with

alcaptonuric urine. The failure of alcaptonuric urine to ferment yeast, to form osazones, to react with the specific glucose enzyme test papers or to rotate polarized light differentiates it from urine containing glucose. The dark urine of phenol poisoning and the melanuria associated with melanotic tumors have no reducing properties.

There is no treatment which will correct the enzymatic block. The fact that urinary excretion of homogentisic acid varies directly with protein intake, disappearing during starvation, is no indication for rigid dietary restriction of protein in view of the relative harmlessness of alcaptonuria in children. Corticosteroid therapy has a beneficial effect on the arthritis of older alcaptonurics.

### PHENYLKETONURIA

Phenylketonuria (phenylpyruvic oligophrenia, Fölling's disease, phenylpyruvic amentia, imbecillitas phenylpyruvica) (p. 1131) is a rare disorder characterized by mental deficiency and the excretion of phenylketones. Its incidence is estimated to be about one in 40,000. Affecting both sexes equally, it is transmitted by a recessive gene. About one per hundred of the population is an asymptomatic (heterozygous) carrier of the mutant gene.

Deficiency of the hepatic enzyme phenylalanine hydroxylase, which normally transforms phenylalanine to tyrosine, is the primary biochemical defect in phenylketonuria. Normally the portion of dietary phenylalanine in excess of the organism's requirement for protein formation is converted to tyrosine and utilized or degraded to acetoacetate. Inability to form tyrosine leads to a piling up of phenylalanine in the body fluids; adaptive mechanisms of alternative metabolic pathways for the disposal of phenylalanine account for the formation of the phenylketone bodies (phenylpyruvate, phenyllactate, phenylacetate and phenylacetyl glutamine), which are excreted in the urine. The existence of a secondary metabolic channel which apparently transforms 10 per cent of excess phenylalanine to ortho-tyrosine was first indicated by the finding of the compound ortho-hydroxy-phenylpyruvic acid in phenylketonuric urine.

The abnormal biochemical environment of the brain, created by high concentrations of phenylalanine and its derivatives, is responsible for mental deficiency and other neurologic abnormalities. The precise mechanism by which the nervous system is injured is not clear. Cutaneous abnormalities, such as ex-

cessive oiliness, scaliness and eczematoid lesions, which occur in one third of phenylketonuric children may have a pathogenesis similar to that for brain damage, and the high concentrations of phenylalanine are responsible for the "mousey" odor of the urine and the musty body odor of the unwashed body.

Failure of formation of melanin pigments because of an inadequate supply of tyrosine may account for the finding that 90 per cent of phenylketonuric children are blue-eyed blondes with fair skins. The rapid darkening of the skin, hair and eyes, which often occurs after the institution of a phenylalanine-restricted diet containing added tyrosine, supports this view.

Infants with phenylketonuria appear to be normal at birth and during the neonatal period. Plasma phenylalanine levels are normal in newborns, and phenylpyruvic acid does not appear in the urine until plasma phenylalanine rises to the level of 15 mg. per 100 ml. This may occur as early as six days and as late as thirty-five days. At this time progressive brain damage begins, reaching a maximal upper limit at two to three years of age. Diets low in phenylalanine (Lofenalac and Ketonil) begun during the neonatal period can prevent the development of mental deficiency. Initiation of dietary treatment before the age of two to three years may arrest the progress of brain damage; it does not appear to reverse the process. In older phenylketonuric children there is no apparent improvement of mental deficiency on such diets. However, improved attention spans, calmer behavior, subsidence of neurologic signs and improvement in previously abnormal electroencephalograms indicate the salutary effect of the avoidance of exposure of the maximally damaged brains of these children to phenylalanine.

As an aid to premarital genetic counseling, it appears that it may be possible to detect the asymptomatic heterozygous carrier of phenylketonuria by laboratory means. The fasting plasma phenylalanine levels are higher than usual, and there is a higher and more sustained rise in the plasma level following a test dose of phenylalanine in heterozygous persons than in normal ones.

#### TYROSINOSIS

In 1927 Medes discovered the only known instance of this error in tyrosine metabolism in an adult believed to have myasthenia

gravis. The presence of parahydroxy-phenylpyruvic acid in the urine indicated that catabolism of tyrosine was blocked at the level of its deamination product. Progressive increases in protein or tyrosine intake resulted in the appearance in the urine of tyrosine initially, then parahydroxy-phenyl-lactate and finally 3:4 dihydroxyphenylalanine. There were no apparent symptoms related to the metabolic defect.

Premature infants (p. 310) receiving a high protein diet without vitamin C have tyrosyluria, in that they excrete parahydroxy-phenylpyruvate and parahydroxy-phenyl-lactate. Administration of vitamin C abolishes this metabolic impairment. Since the liver is the site for the metabolism of parahydroxy-phenylpyruvate, it is not surprising that patients with liver disease spontaneously excrete small amounts of this compound.

#### ALBINISM

Albinism, or absence of cutaneous pigments, exists in two forms. Total albinism (*albinismus totalis*) is characterized by unpigmented skin, hair, eyebrows, eyelashes and eyes. The less common partial albinism (*albinismus conscriptus*) has two features: the white forelock and piebaldness, i.e., irregular, well defined pigment-free areas of skin, usually of the extremities and anterior trunk and abdomen. Total albinism is most often a recessive trait, whereas the partial form is transmitted by a dominant gene, a finding which conforms to the general rule in human heredity that the more severe form of a mutation tends to be recessive and the milder form, dominant. A moderate preponderance of male albinos may be indicative of a partial sex-linked inheritance.

Total albinism occurs in all races, varying in incidence from 0.7 per cent in the San Blas Indians of Darien to one in 100,000 in France. In the United States the rate is approximately one in 20,000; one in seventy is the estimated asymptomatic (heterozygous) carrier rate.

In addition to the extremely white skin and fine silky hair, albinos have numerous ocular abnormalities. Although traces of pigment may occur on the uveal borders, it is absent from the iris, sclera and fundus, and the eye appears pink and translucent. Refractive errors, strabismus, nystagmus and photophobia are common findings. In general, albinos do not differ in range of intelligence and mentality from the rest of the popula-



tion, even though there appears to be a slightly higher incidence of mental deficiency among them. The white forelock of hair may be the sole manifestation of the defect in some families; it is more frequent than piebaldness alone.

The albino has the normal number of pigment-forming cells (melanocytes) in the basal layer of the skin. Owing to the inherited deficit of the copper-containing enzyme tyrosinase, the cells do not form melanin. The pigmented skin areas of piebald human beings and animals contain tyrosinase.

There is no treatment for albinism. Preventive measures may be necessary against the harmful effects of sunlight on the unpigmented skin and eyes. Unable to tan, the skin is constantly vulnerable to the "burning" rays of the sun. Tinted glasses are required for relief of photophobia.

## HEREDITARY CLINICAL SYNDROMES OF TUBULAR INSUFFICIENCY

The concept of hereditary molecular disease extends the meaning of Garrod's term, the inborn error of metabolism. Pauling's conceptual designation now encompasses hereditary control of specific functional substances and mechanisms other than enzymes. For example, in cystinuria the genetically determined enzyme-like factor controlling renal tubular transport of certain amino acids is thought to be in the molecular category. In this sense, cystinuria and a number of other inherited renal tubular dysfunctions

Table 47. Hereditary Defects of Renal Tubular Function

- |  |
|--|
| I. Defects of a Single Tubular Function  |
| A. Glucose reabsorption  |
| 1. Renal glycosuria  |
| B. Water reabsorption  |
| 1. Nephrogenic diabetes insipidus  |
| C. Inorganic phosphate reabsorption  |
| 1. Pseudohypoparathyroidism (Seabright bantam syndrome)                          |
| 2. Vitamin D-resistant rickets (renal hypophosphatemia, renal hyperphosphaturia) |
| D. Acidification of urine  |
| 1. Renal tubular acidosis (hereditary type)                                      |
| E. Purine reabsorption   |
| 1. Simple xanthuria  |
| 2. Gout—hereditary hyperuricemia   |
| F. Amino acid reabsorption (the amino-acidurias)                                 |
| 1. Cystinuria  |
| 2. Simple glycinuria   |
| 3. Beta-aminoisobutyric aciduria   |
| II. Defects of 2 Tubular Functions   |
| A. Glucose and phosphate reabsorption  |
| 1. Renal rickets with renal glycosuria   |
| B. Glucose and amino acid reabsorption   |
| 1. Renal glycosuria with amino-aciduria  |

- C. Phosphate and amino acid reabsorption
1. Renal rickets with amino-aciduria

### III. Defects of Multiple Tubular Function

- A. Glucose, phosphate and amino acids
  1. De Toni-Debré-Fanconi syndrome
- B. Glucose, phosphate, amino acids with impaired urinary acid base regulation and/or impaired water reabsorption
  1. Severe instances of de Toni-Debré-Fanconi syndrome
- C. De Toni-Debré-Fanconi syndrome with cystinosis
- D. Glucose, phosphate, amino acids (mild), impaired urinary acid-base regulation and organic aciduria
  1. Syndrome of buphthalmos, cataracts, mental retardation, resistant rickets, hyperchloremic acidosis and organic aciduria

may be considered molecular diseases. A convenient grouping of the recognized clinical syndromes of tubular dysfunction is given in Table 47.

**Hereditary Defects of the Renal Tubules Involving a Single Function.** *Defective reabsorption of glucose.* *Renal glycosuria* is an uncommon benign disorder, usually inherited as a dominant trait (p. 1020).

*Defective reabsorption of water.* *Nephrogenic diabetes insipidus* (p. 1156) is distinguished from the type due to hormonal deficiency of pituitary origin by its lack of response to injected vasopressin because of the refractoriness of the renal tubules to the action of the antidiuretic hormone. In one family the disorder was inherited in a recessive sex-linked fashion, and only males were affected. In another lineage an affected female indicated that the gene was an autosomal recessive, and in a third family, heterozygous female carriers had mild diabetes insipidus.

*Defective reabsorption of inorganic phosphate.* *Pseudohypoparathyroidism (the Seabright bantam syndrome)* is due to hereditary failure of the renal tubules to respond to parathyroid hormone, an end-organ failure. The increased tubular reabsorption of phosphate which occurs in the absence of hormonal inhibition leads first to hyperphosphatemia and ultimately to hypocalcemic tetany (p. 1176).

*Renal hypophosphatemia or vitamin D-resistant rickets* is a relatively common congenital hereditary disease, transmitted by a sex-linked dominant gene (p. 1221).

*Defective acidification of the urine.* *Renal tubular acidosis* is a clinical syndrome due to impairment of the renal tubular mechanism for acidifying the urine (p. 1223).

*Defective reabsorption of purines (xanthine, uric acid).* *Simple xanthuria* is apparently due to deficient reabsorption from the glomerular filtrate, but the possibility of a metabolic defect involving xanthine has not been eliminated. Xanthine, a precursor of uric acid, is excreted in the urine in abnormal amounts, and uric acid is virtually absent from the plasma and urine.

*Hereditary hyperuricemia* is transmitted by a dominant autosomal gene with different degrees of penetrance in the two sexes. Elevated plasma uric acid levels occur in 84 per cent of males with the abnormal gene, but in only 12 per cent of the females. Gout also occurs earlier and about twenty times

more frequently in hyperuricemic men than in similarly affected women. Primarily an adult disorder, gout rarely occurs in children.

*Defective reabsorption of amino acids (amino-acidurias).* Cystinuria is discussed later.

*Simple glycinuria* is a unique amino-aciduria in that there is resorptive deficiency of only one amino acid, glycine. The defect is transmitted by a dominant gene. In a family of four affected persons, three formed calcium oxalate stones which contained 0.5 per cent of glycine. All showed glycinuria. They were otherwise asymptomatic and normal in growth.

*Beta-aminoisobutyric aciduria* is present in 5 to 10 per cent of the population in certain areas of England and Italy which have been studied. Affected persons are asymptomatic, but have a daily excretion of 100 to 300 mg. of beta-aminoisobutyric acid in contrast to 10 to 40 mg. in other members of the population. The defect is transmitted by a single recessive gene.

*Hereditary Double Functional Defects of the Renal Tubules. Combined glycosuria and phosphaturia.* This is a type of vitamin D-resistant rickets in which hypophosphatemia and rickets exist in combination with renal glycosuria. Dent has described four instances of this syndrome.

*Combined glycosuria and amino-aciduria.* This syndrome has been recorded in three generations of one family, including a pair of twins. Although the affected subjects were asymptomatic, generalized massive amino-aciduria and moderate glycosuria were present.

*Combined phosphaturia and amino-aciduria.* This is a variant of hypophosphatemic vitamin D-resistant rickets. Effective treatment of the rickets with massive doses of vitamin D also causes suppression of the amino-aciduria. This factor has been interpreted as evidence for a common tubular reabsorptive pathway for phosphates and amino acids. However, the demonstration of depressed glomerular filtration during such therapy may be the explanation for the decrease in amino-aciduria.

*Hereditary Multiple Functional Defects of the Renal Tubules. Glycosuria, phosphaturia, amino-aciduria, the de Toni-Debré-Fanconi syndrome.* De Toni first suggested that this triple defect, observed by him in a child, might be due to tubular dysfunction. The disorder, cystinosis, for which the names of Abderhalden, Kaufmann and Lignac are used in Europe, is included by many in this syndrome and will be so considered here under the term "de Toni-Fanconi syndrome with cystinosis."

*Glycosuria, phosphaturia, amino-aciduria, impaired acidification of urine and organic aciduria.* In a small number of patients with a syndrome of buphthalmos, cataracts, congenital rickets, hyperchloremic acidosis and mental deficiency in addition to many of the urinary findings of the de Toni-Fanconi syndrome, an appreciable excretion of organic acids is encountered (p. 1222).

## MOLECULAR DISEASES INVOLVING CYSTINE AND GLUTATHIONE

The sulfur-containing amino acid cystine is identified with the molecular diseases cysti-

nuria and cystinosis. These are entirely unrelated disturbances, due to different genetic defects, and are not the phenotypic variants of a single genic mutation they were once thought to be. Hereditary alteration in the metabolism of the tripeptide glutathione (glutamyl-cysteinyl-glycine) in the erythrocytes is responsible for certain drug- and toxin-induced hemolytic anemias.

### CYSTINURIA

Cystinuria is an inherited anomaly of renal function with massive urinary excretion of cystine, lysine, arginine and ornithine due to defective tubular reabsorption of these amino acids from the glomerular filtrate. Average daily excretions of 0.73 gm. of cystine, 1.8 gm. of lysine, 0.83 gm. of arginine and 0.37 gm. of ornithine reported in five patients are representative of the daily urinary losses. Cystine, because it is the least soluble and forms conspicuous crystals and calculi, was the only one of the four amino acids recognized until recently. Failure to appreciate the presence of the other three amino acids was responsible not only for the name of the disorder, i.e., cystinuria, but also for the erroneous assumption that it was a block in the intermediary metabolism of the sulfur-containing amino acids, cystine, cysteine and methionine. Two types of cystinuria have been differentiated genetically. In two thirds of the families the defect is transmitted as a recessive trait. The abnormal homozygotes excrete abnormal amounts of all four amino acids and form cystine stones at some time during their lives. No abnormality is discernible in the heterozygous "carriers." This condition has been termed *recessive cystinuria*.

In the second and smaller group of families the abnormal genes for cystinuria are only partially recessive. Here also the abnormal homozygotes excrete large amounts of the four amino acids and form renal stones. Clinically, they are indistinguishable from the genotypically similar members of families with recessive cystinuria. Heterozygous persons in this group, however, are not normal, for they excrete moderate quantities of cystine and lysine, and little or no arginine and ornithine. They do not form calculi except in the rare instance when the level of cystine excretion is high. The milder tubular reabsorptive defect in this second type of family is designated "*incompletely recessive cystinuria*."

The estimated incidence of cystinuria with



renal stone formation varies from 1:40,000 to 1:200,000. Nonstone-forming heterozygous excretors of cystine and lysine are more numerous (1:600).

Cystine crystals are clear colorless hexagons with somewhat unequal sides and are characteristically different from any other urinary deposit. Urine containing cystine liberates hydrogen sulfide on decomposition. Stasis and infection in the urinary tract predispose the cystinuric patient to calculus formation. Acidity and concentration of the urine may precipitate crystals of sparingly soluble cystine (1:9000 in water). The elaboration of more concentrated urine during sleep at night may initiate stone formation. Cystine calculi are usually white, but occasionally are yellow. When kept for years, the color changes to green. The stones cast dense roentgenographic shadows.

Responsible for less than 1 per cent of all adult urinary calculi, cystine stones account for a larger proportion of those encountered in infants and children. The diagnosis is established by detection of cystine crystals in acidified urine and the demonstration of abnormal quantities of cystine, lysine, arginine and ornithine by paper chromatography. Siblings of a cystinuric patient should be screened for the defect, since there is a one-in-four probability that any one of them may be affected.

Maintenance of a liberal fluid intake to ensure a constant and copious flow of dilute urine (above 2 cc. per minute) may minimize the tendency to stone formation. Eradication of urinary tract infection and stasis is important. At pH values above 7.6 the solubility of cystine in urine increases significantly. Whether the constant intake of the large doses of alkali needed to maintain such high pH values is practical appears doubtful. Of even more dubious value are attempts to dissolve cystine stones by such therapy. Cystine excretion increases on a high protein diet, but severe restriction of protein intake is inadvisable as a therapeutic measure in infants and children. The excretion of lysine, which is lost in larger quantities than cystine, may produce a negative balance for this essential amino acid with deleterious effects on growth.

**CYSTINOSIS (DE TONI-FANCONI SYNDROME WITH CYSTINOSIS, ABDERHALDEN-KAUFMANN-LIGNAC DISEASE)**

Cystinosis, which was first recognized at autopsy by Abderhalden and Kaufmann in 1903,

was established as a clinical entity by Lignac in 1924. It is characterized by the clinical pattern of the de Toni-Fanconi syndrome, i.e., stunted growth, resistant hypophosphatemic rickets, glycosuria, acidosis, generalized amino-aciduria, organic aciduria, combined with the presence of cystine crystals in various tissues of the body. With one possible exception, in which the inheritance appeared to be dominant, the disorder seems to be transmitted by a recessive gene. The adult variety of the de Toni-Fanconi syndrome is inherited as a dominant character.

The pathogenesis of the major abnormalities of the de Toni-Fanconi syndrome with cystinosis is not readily explained. The tubular dysfunctions characteristic of the de Toni-Fanconi syndrome by itself may occur in a number of known intoxications (lead poisoning) and can also be produced in rats by injection of maleic acid. Accordingly, it has been proposed that the renal defects in patients with cystinosis may be due to obscure cystine intoxication, especially since it has nephrotoxic activity. Another theory assumes a metabolic abnormality which prevents utilization of cystine by the cells, so that it is deposited as crystals. Before entering the metabolic pathway of the sulfur-containing amino acids, cystine normally undergoes reduction to cysteine. A deficiency of the specific enzyme, cystine reductase, is postulated to be the basic hereditary molecular defect in this hypothesis.

The characteristic pathologic finding in patients with cystine disease is the deposition of cystine in the reticuloendothelial system, especially apparent in the liver, spleen, lymph nodes and bone marrow. In the liver small foci of proliferated Kupffer cells containing cystine are conspicuous. Cystine deposits have been noted in the renal tubular cells. Vacuolization of tubular cells, probably due to potassium depletion, may be seen. Darmady has demonstrated a striking lesion in the most proximal portion of the tubule; narrowing due to atrophy produces a "swan's neck" appearance at this site. There is no evidence that this is a genetic defect. In cases of longer duration extensive glomerular changes and arteriolar lesions resembling chronic glomerulonephritis are seen.

Clinically, these infants usually appear normal at birth and during the early months of life. In the latter part of the first year or during the second year, growth becomes retarded. Anorexia, vomiting and constipation are conspicuous early manifestations. A

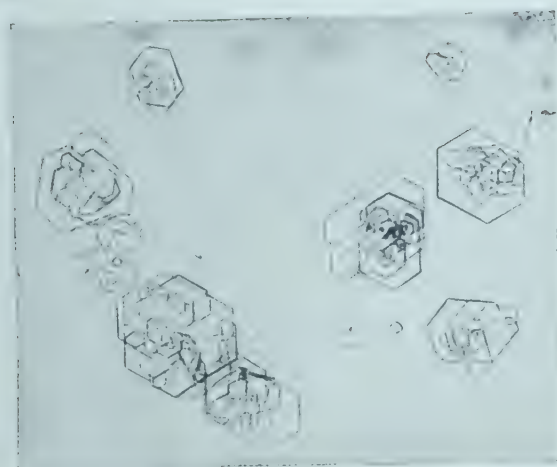


FIG. 60. Cystine crystals of ammoniacal spleen extract.  $\times 180$ . (Looser in *Ann. paediat.*, Vols. 162, 163.)

preference or even craving for meat and other protein foods is often noted. Polyuria, polydipsia and nycturia are frequent. Extreme thermolability with a tendency to high fever without apparent cause is present as the disease progresses. Dehydration and intoxication develop in response to mild infections. Intense photophobia may be a troublesome complaint. The bones at first show osteoporotic changes, upon which the changes of infantile rickets responding to vitamin D may become superimposed. With the gradual development of renal failure the bones show the changes of renal rickets (i.e., osteitis fibrosa cystica or renal hyperparathyroidism). Terminally there may be elevation of the blood pressure, but eyeground changes are usually absent. Enlargement of the liver, but not of the spleen, is seen in the final stages of the disease. The stunting of growth may be so extreme as to be classed as dwarfing.

The duration of the illness varies. It may progress rapidly, and death may occur as early as five months of age. Few children live beyond eight years of age.

The urine may be acid or alkaline. Early in the illness, polyuria and dilute urine are the result of deficient tubular reabsorption of water; later, as glomerular failure occurs, the specific gravity becomes low and fixed. Mild albuminuria and pyuria may occur. Glycosuria varies; slight or absent at first, it may rise to a level of 20 gm. per day. Phosphaturia is marked. Impaired tubular capacity to exchange intracellular hydrogen ions for urinary base causes loss of bicarbonate. Accordingly, the ammonia content of the urine may seem high, but is actually low when judged

by the severity of the acidosis. Considerable amounts of potassium are lost in the urine, in part by excretion with bicarbonate, but in larger measure through distal tubular secretion of potassium as an exchange for urinary sodium.

Paper chromatographic studies show a generalized amino-aciduria which varies in different patients, but has a constant pattern in the individual patient. Glycine is excreted in largest amount. Smaller, but as much as twenty times normal, amounts of threonine, serine, alanine, tyrosine and lysine are lost, as are also such essential amino acids as phenylalanine, valine, methionine, leucine and isoleucine. The amounts of cystine lost are far below those which occur in cystinuria. Amino-aciduria and glycosuria may disappear when renal failure occurs. Increased amounts of urinary organic acids occur and seem to be due to the same tubular reabsorptive defect which causes amino-aciduria.

The inorganic phosphate level of the blood is low during the early stages of the disease, but increases along with the nonprotein nitrogen as renal function fails. Concomitantly, serum calcium levels decrease and may reach tetanic levels. Phosphatase values may be low if active rickets is present; otherwise they tend to be normal. Serum protein concentration is usually not greatly altered. During illness the often low serum potassium level may decrease rapidly to still lower levels productive of clinical hypokalemia. Hyperchloremic acidosis is typically present. There are no characteristic hematologic changes, but anemia and bleeding phenomena occur with renal failure.

Cystine crystals, if present, are demonstrable in the cornea by slit lamp microscopy or in conjunctival scrapings. Bone marrow examination and lymph node biopsy are valuable diagnostic procedures in the search for crystals of cystine.

Therapy is unsatisfactory; death is characteristically due to uremia. Temporary amelioration is possible by the use of a basic ash diet supplemented with moderately high doses of vitamin D. Administration of a citrate solution (p. 1224) such as that of Shohl or Albright with added potassium chloride is advisable for control of the acidosis and hypokalemia.

#### DISORDERED GLUTATHIONE METABOLISM

Ingestion of primaquine, sulfanilamide, acetanilid, nitrofurantoin, naphthalene and fava



beans, in amounts nontoxic for most persons, causes hemolytic anemia in certain persons who are otherwise normal. Such persons have a genetically determined defect in the metabolism of glutathione in their erythrocytes. The specific molecular defect is a deficiency of the enzyme glucose-6-phosphate dehydrogenase, which is normally involved in the maintenance of glutathione in a reduced state. Reduced glutathione is an important source of free sulfhydryl groups (-SH), which are required by a large number of cellular enzymes and coenzymes.

This hereditary biochemical deficit has been found in 4.6 per cent of a random sample of 305 subjects; it was more than five times as common among healthy American Negroes as among healthy whites. It is transmitted as a recessive trait, which is apparently sex-linked and sex-modified.

Another genetic biochemical defect has been shown to be the basis for hypersusceptibility to the action of succinylcholine, a drug used as a muscle relaxant during anesthesia.

## INHERITED DISORDERS INVOLVING TRYPTOPHANE

**Metabolism of Tryptophane.** The essential amino acid tryptophane and a number of its derived compounds have important biologic activities. Skatole and indole, two foul-smelling substances, are products of bacterial putrefaction of tryptophane in the large intestine. The participation of pyridoxine in the metabolism of tryptophane was first indicated by the finding of xanthurenic acid, an unusual tryptophane metabolite, in the urine of rats with deficiency of vitamin B<sub>6</sub>. The discovery that pyridoxine deficiency was the cause of a convulsive disorder in infants was prompted by this observation in rats. Xanthurenic acid has been demonstrated in the urine of affected infants, and the convulsions are believed to be a result of disordered cerebral tryptophane metabolism. The detection of a disturbance in tryptophane metabolism in association with a hereditary anemia in infants has an analogue in the anemia exhibited by pyridoxine-deficient dogs. Unlike the deficient rat, the anemic dog does not excrete xanthurenic acid.

Serotonin (5-hydroxytryptamine or 5-HT) is an amine derived from a tryptophane metabolite, 5-hydroxytryptophane. It has potent pharmacologic actions, and as a central neurohumoral agent it is apparently involved

in cerebral function. First isolated from platelets in 1951, it was identified as a vasoconstrictive compound. The chromaffin ganglionic cells of the gastrointestinal tract and cerebral cells, acting as endocrine organs, are believed to secrete it. Serotonin-secreting carcinoid tumors in adults arise from the argentaffin cells of the gastrointestinal tract and cause a pattern of clinical findings which indicate the diverse activities of 5-HT, i.e., connective tissue damage evident as arthritis and endocardial sclerosis, intestinal hypermotility causing diarrhea, vasomotor disturbances such as flushing and hypotensive episodes, acute dyspnea due to bronchoconstriction, and azotemia from reduced glomerular filtration caused by constriction of renal arterioles. The resemblance of the cardiac lesion in these patients to endocardial sclerosis in infants has suggested a similar etiology for it. Increased urinary excretion of a catabolite of 5-HT (5-hydroxyindole acetic acid, 5-HIAA) has also been observed in adults with the celiac syndrome. A simple chemical test for detection of the compound is available.

Serotonin and the enzymes which form and degrade it are most highly concentrated in the hypothalamus. A current concept of its functional role in the brain is that it acts as a chemical mediator at the synaptic junctions in the parasympathetic centers. A similar action is proposed for norepinephrine in the sympathetic centers. The autonomic, motor and psychic responses to drugs such as reserpine and chlorpromazine are attributed to their effect on these two chemical mediators.

### DISORDERED TRYPTOPHANE METABOLISM IN CONGENITAL HYPOPLASTIC ANEMIA

Congenital hypoplastic anemia is a rare chronic anemia due to faulty formation or maturation of erythrocytes by an otherwise normally functioning bone marrow (p. 934). Anthranilic acid has been identified in the urine of ten patients. The nature of the disturbance in tryptophane intermediary metabolism and its relationship to the anemia are obscure, especially since there is no demonstrable deficiency of nicotinic acid in these patients (Fig. 61, pathway B).

### MENTAL DEFECT (AUTISM) AND DISORDERED TRYPTOPHANE METABOLISM

A defect in tryptophane metabolism has been observed in a child with autistic behavior and in a normal younger sibling; the possi-

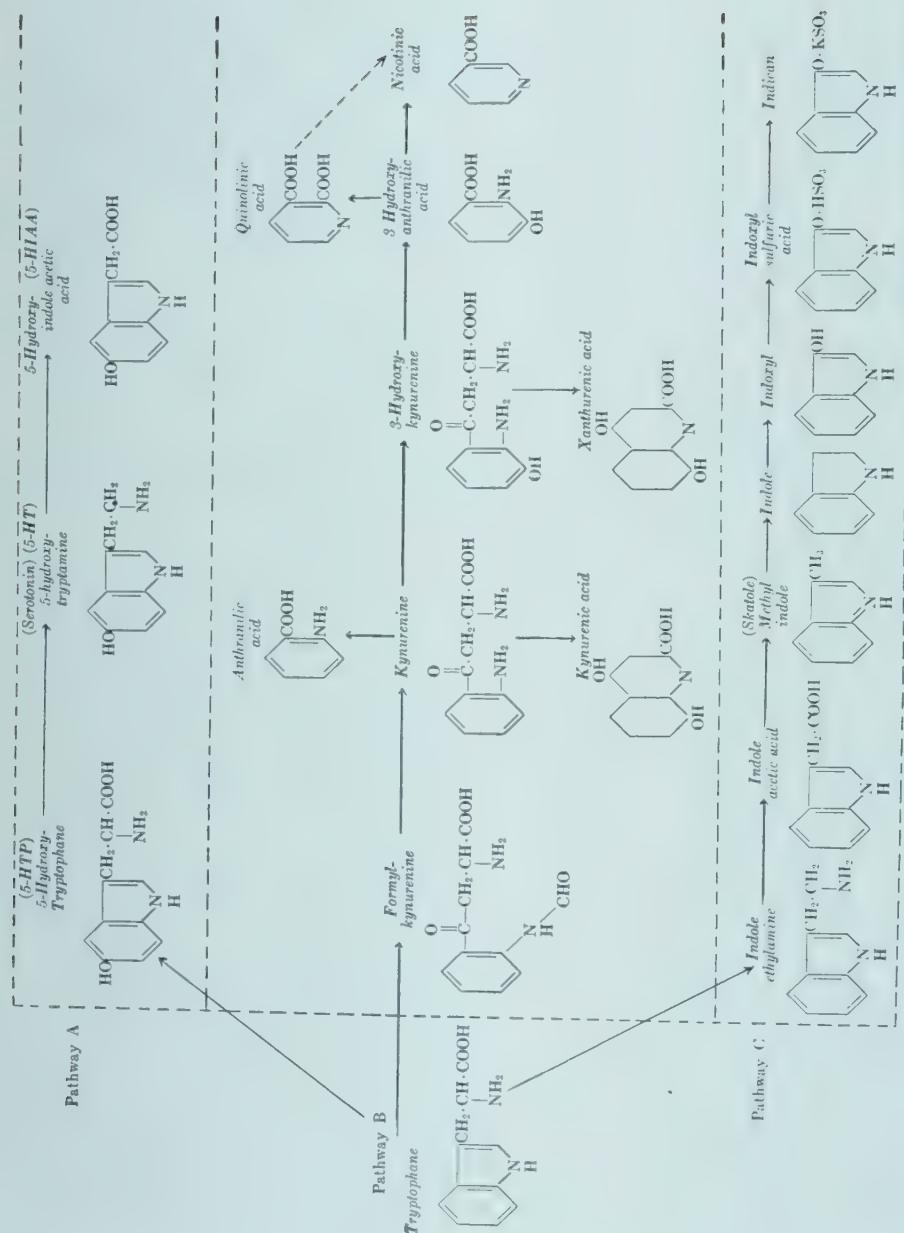


FIG. 61. Intermediary metabolic pathways for tryptophane. A, Serotonin formation and degradation (oxidative). Since the brain cannot utilize tryptophan directly, it uses the oxidation product 5-hydroxytryptophane. The brain enzyme 5-hydroxytryptophan decarboxylase converts 5-HTP to serotonin, which is metabolized by the enzyme monamine oxidase to 5-HIAA. Excessive formation of 5-HIAA results in excretion in the urine, where it may be detected chemically as an evidence of increased serotonin turnover.

B, Conversion of the indole ring of tryptophane to the pyridine ring of nicotinic acid. The first step in this metabolic pathway is the formation of a pyridine ring by enzymatic splitting of the indole ring. Formyl kynurenine is then hydrolyzed to kynurenine, and in a straight course this is converted to nicotinic acid (the aromatic pathway of tryptophane metabolism). In the rat a second pathway, the quinoline channel, is present, and kynurenine acid is formed from kynurenine. Anthranilic acid is an intermediate metabolite in man and has been found in the urine of infants with congenital hypoplastic anemia. Pyridoxine deficiency causes the appearance of xanthurenic acid in the urine of the rat and man. Although quinolinic acid is not on the straight route to nicotinic acid synthesis, it can apparently be partially converted.

C, Formation of indole in the intestinal tract by bacterial putrefaction. After decarboxylation all the compounds up to indole may be absorbed from the intestinal tract and, after conjugation in the liver, Indican is produced by conjugation with sulfuric acid.



bility of defective serotonin formation has been postulated.

#### **HARTNUP DISEASE**

Hartnup disease, first termed H disease to keep anonymous the affected English family after whom the disease is named, is a recently discovered hereditary molecular disease in which there is a block in the intermediary metabolism of tryptophane.

Clinical manifestations of cutaneous photosensitivity are seen early in most affected children. Unprotected skin areas become rough and red after moderate exposure to the sun. With greater exposure a rash, identical with that of pellagra, develops, together with a neurologic syndrome which is unlike the peripheral neuritis of pellagra. The neurologic findings consist of signs of cerebellar ataxia with traces of involvement of the pyramidal tracts. During the course of a febrile illness, ataxia may develop without a rash. The clinical course is variable; severe cutaneous and nervous disturbances may alternate with periods of complete remission over many years. Mental deficiency is a late occurrence and progresses slowly. Remission of the disorder occurs spontaneously in most patients, usually in adult life. However, administration of large doses of nicotinamide appears to facilitate regression of symptoms.

Massive amino-aciduria is present during the entire lifetime of patients; the pattern of excretion of individual amino acids is characteristic in that proline metabolism is not disturbed in contrast to the urinary excretion of it in the generalized amino-acidurias, such as the de Toni-Fanconi syndrome. Furthermore, there are no alterations in the excretion of hydroxyproline, methionine, arginine and taurine. There is excessive urinary loss of alanine, serine, asparagin, glutamine, valine, leucine, isoleucine, phenylalanine and tryptophane, and moderate losses of cystine, lysine and glycine. Plasma amino acid concentrations are normal, so that the amino-aciduria must be due to faulty tubular reabsorption of amino acids.

In addition to amino acids, large amounts (50 to 200 mg. daily) of indican, indole-3-acetic acid and indole-3-acetyl-glutamine, derivatives of tryptophane, are present in the urine.

The parents of the family in which this disorder was first found were first cousins and were unaffected. Four of the eight siblings had the urinary findings of the disorder,

and two of these had the complete syndrome. The disease is apparently transmitted by an autosomal recessive gene. Several other instances of Hartnup disease have been detected in persons of English origin with disorders diagnosed initially as pellagra.

Large doses of nicotinamide cause a sustained remission of the disorder. However, amino-aciduria and urinary loss of indole compounds are not suppressed by such therapy.

#### **DISORDERS INVOLVING LEUCINE,**

##### **ISOLEUCINE AND VALINE (BRANCHED-CHAIN AMINO ACIDS)**

The essential branched-chain amino acids leucine, isoleucine and valine have conspicuous but as yet undetermined roles in two different hereditary metabolic diseases. In one disorder increased levels of all three amino acids are present in the blood and urine. In the second disturbance a deleterious effect of dietary protein has been identified specifically with leucine and one of its metabolites.

##### **INFANTILE IDIOPATHIC HYPOGLYCEMOSIS AND LEUCINE**

Marked lowering of the blood sugar level with convulsions has occurred in some patients with idiopathic hypoglycemia after the feeding of protein (p. 1218). A study of this phenomenon, produced by dietary casein but not by gelatin or tyrosine, in three members of one family and in another unrelated child showed that administration of leucine and its degradation product, iso-valeric acid, caused a fall in the true blood sugar level. The non-sugar-reducing substances of the blood, believed to be mainly glutathione and ergothioneine, also drop sharply after ingestion of leucine. Unlike the true blood sugar, the depressed levels of nonsugar-reducing substances do not rise when glucose is given. The mechanism and site of this action of leucine are unknown. However, demonstration of this etiologic factor in otherwise idiopathic hypoglycemia suggests the probability of other genetically determined causes for this metabolic disorder.

##### **MAPLE SUGAR URINE DISEASE**

This rare familial syndrome is a recently recognized molecular disease characterized by

the excretion of urine with an odor of maple sugar and evidences of cerebral damage appearing early in life. In the neonatal period there is difficulty in feeding, and the Moro reflex is absent. Progressive spasticity is followed by coma and early death.

The blood and urine of one recorded patient contained elevated levels of the three branched-chain amino acids, valine, leucine and isoleucine. The infant also had low blood

levels of threonine, serine, alanine and cystine and an increased concentration of methionine, but these were considered secondary changes. The nature of the primary defect is unknown, but a single enzymatic deficit could be the basis for involvement of all three acids, e.g., a lack of an aminopeptidase which normally incorporated these essential amino acids into protein. Valine deficiency in the rat causes severe neurologic disturbances.

## INBORN ERRORS IN CARBOHYDRATE METABOLISM

### *Defective Mucopolysaccharide Metabolism*

#### HURLER'S SYNDROME

The stored material, apparent as large vacuoles in the cells of many tissues of patients with the Hurler syndrome or gargoylism, has recently been identified as an acid mucopolysaccharide. The complex carbohydrates which are included in this chemical species are fundamental building units for connective

tissue. Two mucopolysaccharides isolated from the urine of patients with gargoylism are similar to the stored material in the cells. It is suggested that Hurler's syndrome is an inborn error of metabolism which is characterized by an overproduction of certain acid mucopolysaccharides, with abnormal storage in cells and with renal excretion of them.

### *Defective Glycogen Metabolism*

#### GLYCOGEN DISEASE

Glycogen disease is the generic term applied to a group of disorders of carbohydrate metabolism characterized by storage of abnormally large amounts of glycogen in various body tissues. The biochemical common denominator of the five clinically recognized types of glycogen disease is an inability of varying severity to break down glycogen. The complex structure of glycogen and the multiple enzymes involved in its degradation make it obvious that any one of several biochemical and enzymatic aberrations may be responsible for the abnormal stability of glycogen. In three of the clinical varieties of this disorder a deficiency of a single and different enzyme is associated with each type. The enzymatic deficit in the other two clinical variants is unknown. As yet there is no recorded instance of more than one type of disturbance in a single family tree.

#### HEPATORENAL GLYCOGEN STORAGE DISEASE

(VON GIERKE'S DISEASE, HEPATONEPHROMEGALIA)

The disorder is apparently transmitted on a recessive basis. The studies of the Coris have

clarified a number of the biochemical defects in the disorder. Glycogen is a polydisperse polysaccharide of high molecular weight (mean range, 3 to 6 million). It is composed entirely of glucose units linked together. The nature of these linkages is shown in Figure 62.

Although other tissues, such as skeletal muscle, utilize the Embden-Meyerhof carbohydrate glycolytic pathway (Fig. 63) for the production of energy by degrading their stored glycogen to lactic acid (glycogenolysis), the liver uses this metabolic pathway chiefly to synthesize glycogen and glucose from lactate and other precursors (glycogenesis and gluconeogenesis). The enzyme glucose-6-phosphatase, present in hepatic but not in muscle cells, enables the liver to supply the blood with free glucose from glucose-6-phosphate, a function which muscle is unable to perform.

Glucose-6-phosphatase activity is deficient in the hepatic and renal cells in patients with von Gierke's disease. Blocked metabolism in the glycolytic pathway at glucose-6-phosphate causes retrograde accumulation of glycogen. The inefficiency or failure in forming glucose from hepatic glycogen or from other precursors which enter the Embden-Meyerhof pathway results in instability of the blood



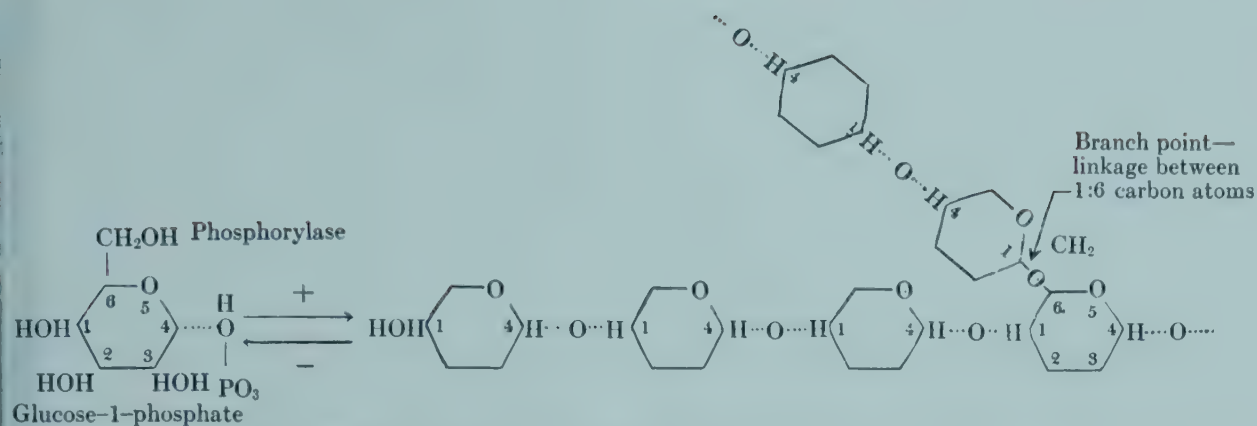


FIG. 62. The nature of the linkages of the glucose units in glycogen. The phosphorylase reaction forms or breaks the 1:4 linkages of glucose-1-phosphate molecules, which unite the units of glucose into chains. The linkage of chains at the branching points is between the 1:6 carbon atoms of adjacent glucose molecules. The branching enzyme forms this 1:6 union, and the debranching enzyme disrupts it.

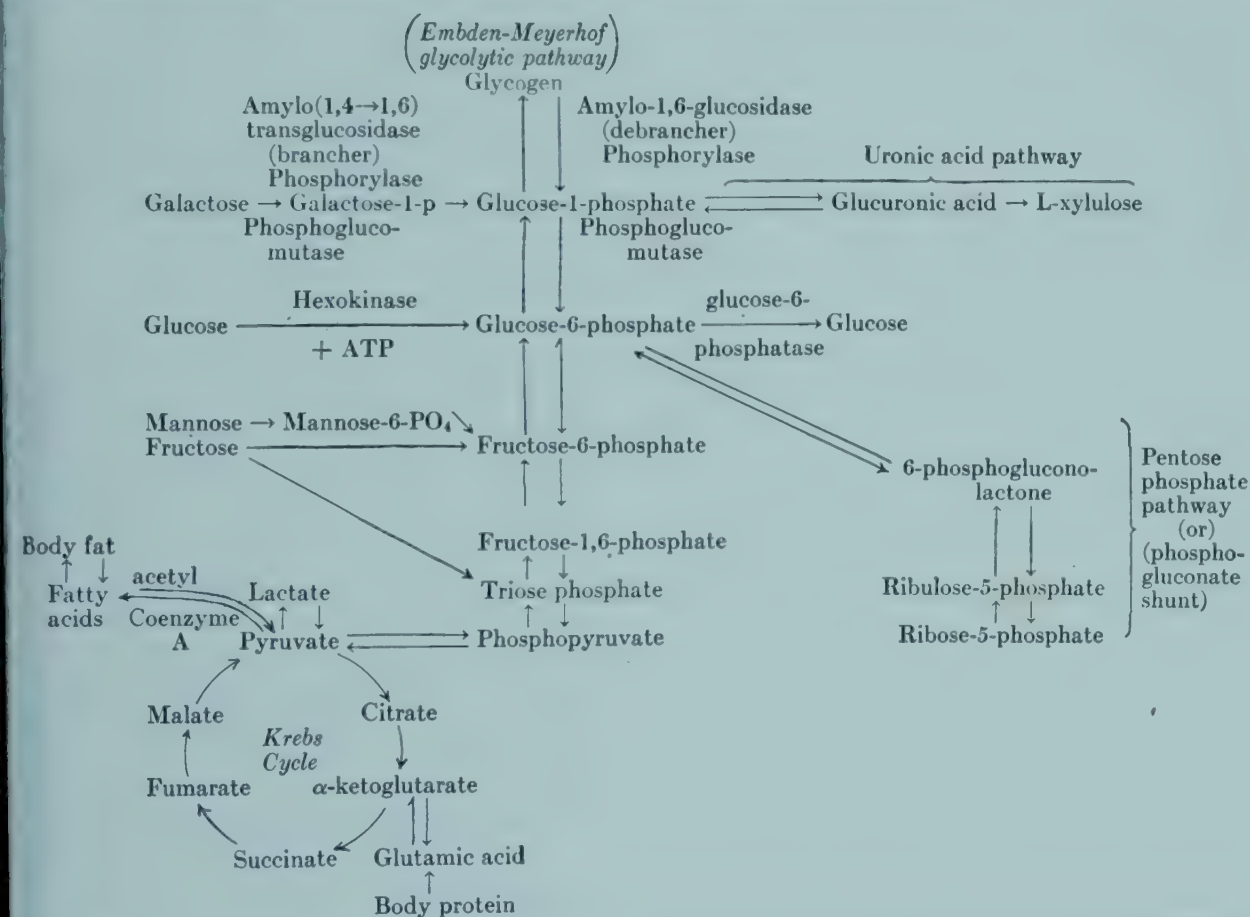


FIG. 63. Pathways of glucose metabolism in the cells, showing activation of inert glucose to glucose-6-PO<sub>4</sub> by hexokinase and ATP, and either storage as glycogen or glycolysis and degradation via the Embden-Meyerhof cycle and the Krebs cycle. Regeneration of glucose by the breakdown of glycogen (glycogenolysis) occurs only in the liver, since the enzyme glucose-6-phosphatase appears only there. Thus muscle can degrade glycogen to lactic acid, but it cannot liberate glucose.

The points at which the hexoses fructose, galactose and mannose enter the stream of glucose metabolism are indicated.

The reversibility of the metabolic pathway of glucose permits the formation of glucose and glycogen from tissue fat and protein by the utilization of fragments of glycerol, fatty acids and amino acids introduced into the Krebs tricarboxylic acid cycle. The oxidative processes in the Krebs cycle yield about 8 times more energy than the anaerobic glycolytic breakdown of glucose to lactate.

The phosphogluconate shunt is not only a pathway for the formation of pentose (ribose), but also is important in lipogenesis, in that 80 per cent of the carbohydrate metabolism of adipose tissue proceeds by this pathway.

sugar concentration and in hypoglycemia during periods of stress and fasting. The shift to fat metabolism is evidenced by hyperlipemia, fatty infiltration of the liver, ketosis and acetonuria. The accumulation of fat which gives many of the dwarfed children with this disorder a doll-like appearance is probably the result of conversion of unutilized glucose to fat. Impairment of protein synthesis is a likely cause of growth failure.

The enlarged smooth liver may contain 12 to 16 per cent of glycogen in contrast to an average normal content of 5 per cent (range, 3.2 to 7.6 per cent). The cytoplasm of the large hepatic cells, with small centrally placed nuclei, is filled with glycogen droplets, which would appear as empty spaces if the tissue had not been properly fixed after its removal. Intracellular fat is increased. Accumulation of glycogen in the renal convoluted tubules is responsible for the swollen kidneys. Slight increases are present in skeletal and cardiac muscle, and the smooth muscles may show moderate increases. White blood cells also contain glycogen globules. The presence of excess glycogen in the hepatic or renal cells is not conclusive evidence of the existence of von Gierke's disease; it must be demonstrated that spontaneous autolysis does not occur as an indirect proof of the enzymatic deficiency. In some instances fat deposition is so heavy that the excess of glycogen is obscured.

**Clinical Manifestations.** Variations in the severity of von Gierke's disease result in differences in the age at appearance of symptoms, in the intensity of the illness and in the prognosis. In the majority of patients the disorder has an insidious onset. Hepatomegaly is present at birth, but the abdominal enlargement may go unnoticed, since there are often no other symptoms during the first year of life. Gradually symptoms of hypoglycemia appear. Vomiting, more common at night, is frequent. Drowsiness, twitching and occasionally coma or convulsions may occur. Clinical manifestations of ketosis and acidosis are common complications of intercurrent infections. With advancing age the symptoms may become milder, and infrequently the hepatomegaly tends to regress in adulthood.

Occasionally, severe disturbances appear in the neonatal period, often within the first days of life, with tachypnea, dehydration and acidosis. Such infants are severely affected by the disorder and have fatty infiltration of the liver. Many die in early infancy.

Acetonuria is common and is increased during fasting. Ketonemia and elevated blood lactic acid levels lower the plasma carbon dioxide content. The fasting level of blood sugar is low, and the concentration is not increased by injection of epinephrine or glucagon in most patients. In mild cases of von Gierke's disease the hepatic glucose-6-phosphatase activity is only slightly depressed and there may be moderate elevation of the blood sugar after injection of epinephrine. The glucose tolerance curve is characterized by a high blood level after administration of glucose with a delayed return to normal range. Galactose tolerance is unimpaired. Hyperlipemia is common, especially early in the disease. The serum inorganic phosphate levels may be low, and elevation of the glycogen content of the blood has been observed. These laboratory findings are supportive but not diagnostic; demonstration of an increased amount of *stable* glycogen in hepatic or renal tissue constitutes proof.

**Treatment.** Though there is no corrective therapy for the biochemical defect in the liver, symptomatic measures can provide some relief by approximating physiologic levels of blood sugar. Protein aids in sustaining blood glucose levels and thus may prevent or minimize ketosis, acidosis, dehydration, hyperlipemia and perhaps the growth failure. Four or more meals, with protein constituting 25 per cent of the total calories, are advisable a day, the last being given at midnight. In one infant with severe early morning manifestations of hypoglycemia a formula containing 40 per cent protein given in three bottle feedings a day produced complete symptomatic relief. Corticosteroids may be helpful in controlling hypoglycemia during critical periods.

Prolonged withholding of food for diagnostic procedures should be avoided. The ease with which acidosis and hypoglycemia develop in the course of an infection should be anticipated and prevented by provision of adequate amounts of fluid containing glucose and sodium lactate or bicarbonate.

#### **DIFFUSE GLYCOGENOSIS WITH HEPATIC CIRRHOSIS**

(FAMILIAL CIRRHOSIS OF THE LIVER WITH STORAGE OF ABNORMAL GLYCOGEN)

This variety of hepatic glycogen disease, in which there is cirrhosis, splenomegaly, ascites and widespread accumulation of a chemi-



cally abnormal glycogen in various tissues, was identified by Anderson from autopsy findings in two siblings. The same disorder was apparently present in a number of cases previously reported as familial cirrhosis or hepatic glycogen disease with cirrhosis. Unlike von Gierke's disease, the fasting blood sugar and the glucose tolerance curve in the single patient studied were normal. The response to epinephrine, however, was poor, and hypoglycemic crises, acidosis and ketosis were absent. Impaired hepatic functions were manifest by abnormal thymol turbidity and cephalin flocculation tests, by low serum albumin and elevated serum globulin levels, by brom-sulfalein retention and by increased serum bilirubin concentration. All known patients have died at ages ranging from seven months to ten years. Treatment is entirely symptomatic.

Large amounts of glycogen were present in the diffusely nodular cirrhotic liver, smaller amounts in the spleen and none in the kidneys. The reticuloendothelial cells contained excessive glycogen and reacted to it as if it were a foreign material. Chemical studies of the glycogen by Cori revealed an abnormal molecule resembling that of amylopectin of maize starch. On the basis of these observations a hepatic deficiency of the enzyme amylo (1:4  $\rightarrow$  1:6) transglucosidase has been postulated. It is suggested that the hepatic and splenic fibrosis is a foreign body reaction to the abnormal starchlike glycogen.

#### GLYCOGEN STORAGE DISEASE OF LIVER AND MUSCLE

##### (LIMIT DEXTRINOSIS)

There are nine recorded cases of this rare familial disorder, which is characterized by large accumulations of chemically abnormal glycogen in the liver and voluntary muscles, with lesser amounts in the heart, and with little if any in the kidneys. The clinical and anatomic findings resemble those of mild cases of von Gierke's disease. Aside from abdominal enlargement due to hepatomegaly, which appears in infancy, and a craving for sweets, these patients appear well and may grow in fairly normal fashion. Fasting blood sugar levels are low and respond with slight rises to injection of epinephrine. Acetonuria occurs with fasting. The oral glucose tolerance curve rises to a high level and falls slowly. In later childhood there may be such evidences of portal hypertension and disturbed liver function as prominent abdominal veins, hy-

percholesterolemia and retention of brom-sulfalein. Sections of the liver reveal excessive deposition of glycogen and mild cirrhosis.

Cori has demonstrated an abnormal glycogen, a deficit or complete absence of the hepatic debrancher enzyme amylo-1:6-glucosidase, and suggested the name *limit dextrinosis* for this disorder.

Although two patients have died in infancy, one apparently normal woman of thirty-two years of age has been observed.

#### CARDIAC GLYCOGEN DISEASE

Cardiac glycogen disease is a rare familial condition which differs not only clinically, but also pathologically and chemically, from the hepatic type. About twenty-five cases are recorded. Though the heart is the most prominent site of glycogen accumulation, there is equally striking deposition in the voluntary muscles. Massive glycogen deposition in the cardiac muscle produces a "lacework" appearance of the fibers in microscopic sections and is responsible for the enlargement of the heart to as much as five times its normal size. Accumulated vacuoles of glycogen increase the diameters of voluntary muscle fibers from two to five times. The degree of vacuolization varies from muscle to muscle, but is always great in the tongue. Smooth muscle cells and reticuloendothelial cells show considerable glycogen infiltration. Smaller amounts are found in almost all other organs and tissues, including the central nervous system (p. 1095).

The glycogen of the cardiac variety, in contradistinction to that of the hepatic type, is unstable post mortem and undergoes autolysis at rates which are usually within normal limits. Chemical analysis has failed to uncover an enzymatic defect or any abnormality of the glycogen. There are no detectable derangements of carbohydrate metabolism, and the elevated serum lipid and cholesterol levels seen in von Gierke's disease are not encountered.

Symptoms related to impaired cardiac function may be manifest at birth and in most instances become evident within the neonatal period. Cyanosis, dyspnea, tachypnea and restlessness are common. With advancing cardiac embarrassment, anorexia, listlessness and cough may appear. The heavy glycogen infiltration of other tissues may produce clinical manifestations which are confusing. Mistaken diagnoses of mongolism, cretinism and amyotonia congenita have been

made on the basis of thickening of the tongue and extreme muscular hypotonicity. Neurologic abnormalities may be prominent when there is massive infiltration of the central nervous system with glycogen (p. 1095). The heart is greatly enlarged and has a circular appearance in roentgenograms. Murmurs are usually absent. Electrocardiographic tracings may show such changes as pronounced left axis deviation, inverted T waves and widened QRS complexes. Death usually occurs between one and eight months of age.

Though this disorder is rarely diagnosed before death, it should be considered a possibility in all infants under eight months of age with cardiac enlargement and failure not otherwise readily explained. Demonstration of increased glycogen content in muscle tissue supports the diagnosis, but does not confirm it, since other conditions may cause similar deposition. Aberrant origin of a coronary artery from the pulmonary artery, transposition of the great vessels, cor pulmonale in cystic fibrosis of the pancreas, acute inter-

stitial myocarditis and endocardial sclerosis, in particular, must be considered in the differential diagnosis.

Other than symptomatic therapy, no treatment is available.

GLYCOGEN DISEASE OF SKELETAL MUSCLE

(NEUROMUSCULAR GLYCOGEN DISEASE)

This rare familial disorder, of which there are ten recorded cases, is characterized by clinical manifestations resembling Werdnig-Hoffmann syndrome (p. 1100) and excessive storage of glycogen in the striated muscles. It is apparently transmitted by a recessive gene. Progressive muscular weakness, present at birth or appearing in the early months of infancy, is the most conspicuous finding. Intention tremor and spasticity may appear initially. Bulbar symptoms, especially dysphagia necessitating tube feeding, are prominent. The muscles are often enlarged, resembling those of pseudohypertrophic muscular dystrophy. About half of the patients

Table 48. Characteristics of the Various Glycogen Disorders

Type of Glycogen Disease	Relative Incidence	Organs Most Conspicuously Involved	Age		Clinical Findings				Enzymatic Defect
			At Onset of Recognition	At Death	Characteristic Appearance	Hypoglycemia, Hyperlipemia, Ketosis	Blood Sugar Elevation after Epinephrine	Structure of Glycogen	
Von Gierke's hepatorenal glycogen disease	Commonest variety; more than 100 recorded cases	Liver, kidney	Neonatal period (severe) to 2 years (mild)	Varies with severity; may live to adulthood	Dwarfism with hepatomegaly	++++	0 to ++	Normal	Glucose-6-phosphatase; degree of deficiency varies
Glycogen disease of liver (cirrhosis) and reticuloendothelial system	Very rare; one recorded family	Liver, including cirrhosis, reticuloendothelial system	Late infancy	Infancy to prepubertal period	Resembles von Gierke's disease with findings of severe hepatic cirrhosis	0	++	Long outer chains like amyloextrin (starch); fewer branch points	Brancher enzyme (amylol-1:4→1:6 transglucosidase)
Glycogen disease of liver and muscles with mild cirrhosis (limit dextrinosis)	Rare; 6 reported cases	Liver, including mild cirrhosis; skeletal muscles; cardiac	Late infancy	Varies with severity; may live to adulthood	Resembles von Gierke's disease with findings of mild hepatic cirrhosis	++	+	Short outer chains; numerous branch points	Debrancher enzyme (amylol-1:6 glucosidase)
Glycogen disease of the heart with generalized glycogenosis	Second most common; about 20 reported cases	Cardiac muscle; skeletal muscles (tongue); smooth muscle; reticuloendothelial system	Neonatal period	Usually within first year	Cardiac findings; may have mongoloid expression	0	Normal	Normal; muscle cells contain vacuoles of acid mucopolysaccharide	Unknown
Glycogen disease of the skeletal muscles with cardiomegaly and C.N.S. changes	Rare; 8 recorded cases	Skeletal muscle; central nervous system, heart, and others	Neonatal or early infancy	From 5 to 46 months; most under 1 year	Resembles amyotonia congenita; bulbar signs	0	Normal	Abnormal in 1 case; (short outer chains), vacuoles in muscle cells containing acid mucopolysaccharide	Unknown; presumably 1 case of debrancher enzyme



have macroglossia and are easily confused with cretins. Occasionally the facies may have a mongolian appearance. There is cardiac enlargement of moderate degree, but cardiac symptoms are usually absent. Hepatomegaly without splenic enlargement is common.

There are no characteristic abnormal chemical changes in the urine and blood, and the mechanisms for maintenance of physiologic blood sugar levels are intact.

The massive glycogen deposition in the muscle fibers and the presence of numerous vacuoles containing large amounts of acid mucopolysaccharide resemble the changes in the myocardial fibers in cardiac glycogen disease. There is also excessive glycogen in cardiac muscle and in hepatic cells, and considerable accumulations in nervous tissue in

about one third of the cases. Generalized glycogenesis involving all tissues studied has also been observed. Studies by Zellweger suggest a deficiency of the debrancher enzyme. Overlapping clinical and laboratory findings of the muscle and cardiac glycogen diseases suggest that they may be variants of a single genetic defect. However, the clinical pattern of progressive muscular weakness, bulbar symptoms, absence of cardiac symptoms and the high incidence of glycogen accumulation and degenerative changes in nervous tissue delineates glycogen disease of skeletal muscle as a clinical entity.

Most patients with this disorder die in infancy, usually during the first year; the longest known survival period has been forty-six months.

## *Defective Disaccharide Metabolism*

### **SUCROSURIA**

(SACCHAROSURIA)

This rare hereditary defect is a failure of hydrolysis of sucrose in the intestinal tract, so that it is absorbed intact and excreted in the urine. In one infant the urinary excretion of sucrose was increased by ingested fructose

or sucrose, suggesting an anomalous enzymatic synthesis of cane sugar in the body from fructose and glucose. Cane sugar does not reduce copper solutions. Patients with sucrosuria may have symptoms resembling those of diabetes, such as polyuria, polydipsia and loss of weight, without a reducing substance in the urine.

## *Defective Hexose Metabolism*

### **ESSENTIAL FRUCTOSURIA**

(LEVULOSURIA)

This rare and benign congenital abnormality of carbohydrate metabolism is characterized by the presence of fructose (levulose) in the urine. It results from an inability to metabolize fructose, so that it accumulates in the blood. The resultant high concentration of fructose in the glomerular filtrate exceeds the normally low tubular reabsorptive capacity for this sugar, and it is lost in the urine. Fructose occurs as a monosaccharide in many fruits and vegetables and in honey. It is also derived from the intestinal hydrolysis of sucrose and of the complex polysaccharides in onions, garlic, sugar beets and Jerusalem artichokes.

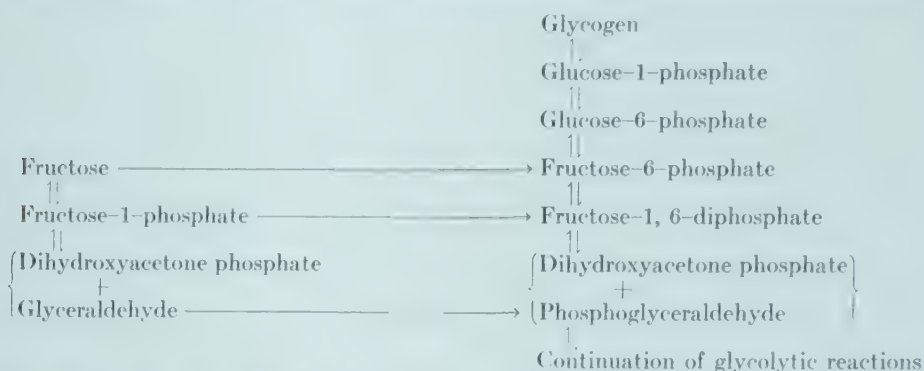
From 10 to 20 per cent of ingested fructose is excreted in the urine of patients with the defect. Inherited as a recessive trait, essential fructosuria occurs in less than one in

100,000 persons; all known patients have been white. The lifelong urinary loss of ingested fructose is without serious consequence.

Fructose reduces Benedict's or Fehling's solutions and is fermented by yeast. It may be differentiated from glucose by polariscopic examination; it has a specific optical rotation of  $-90^\circ$  (levorotatory) compared to glucose, which is  $+52^\circ$  (dextrorotatory). It also forms characteristic crystals of methylphenylhydrazine and osazone.

Other causes of fructosuria must be eliminated before it can be designated as essential. In acquired hepatic disorders such as infectious hepatitis, cirrhosis and syphilitic hepatitis, fructose is occasionally found in the urine if the hepatocellular damage is severe. As an extreme rarity, fructosuria has been encountered in association with severe diabetes mellitus. In an alkaline urine, glucose may be converted to fructose.

The metabolism of fructose in normal tissues proceeds according to the following scheme:



Fructose enters the major glycolytic pathway by three channels. Phosphorylated to fructose-6-phosphate, it is introduced directly into the main stream of carbohydrate metabolism. After conversion to fructose-1-phosphate it joins the glycolytic pathway by additional phosphorylation to fructose-1, 6-phosphate and by splitting into two fragments. One of these, glyceraldehyde, joins the glycolytic pathway as phosphoglyceraldehyde. From this point glucose and fructose follow the same metabolic pathways in both directions of the chain of glycolytic reactions.

Since the loss of dietary fructose in the urine is apparently harmless, no treatment or dietary restriction is indicated.

### HEREDITARY FRUCTOSE INTOLERANCE WITH HYPOGLYCEMIA

An inborn error of fructose metabolism with serious clinical disturbances has been observed in four members of a single family, two children and two adults in different generations. Hypoglycemia with severe symptoms occurred after ingestion of fructose. Administration of an oral test dose of this sugar (20 to 50 gm. per square meter of body surface) to an affected person was followed by a steep and prolonged rise in the blood level of fructose, with a simultaneous fall in the blood level of glucose to 10 mg. per 100 ml. The severe hypoglycemia persisted for several hours and was accompanied by nausea, vomiting, sweating, tremor and drowsiness. After the cessation of acute symptoms slight transient icterus was noted.

The disorder appears to be transmitted by an autosomal recessive gene.

### GALACTOSEMIA

Galactosemia, a congenital error in the metabolism of galactose, is responsible for retardation of growth and development and widespread tissue injury. It is inherited as a recessive trait, and is not as rare as the small number of recorded patients would indicate.

The severity of the tissue changes associated with galactosemia is directly propor-

tionate to the quantity and duration of galactose ingestion. Galactose does not occur in free form in foods; intestinal hydrolysis of the lactose of milk and milk products yields glucose and galactose. Less important food sources are the glycogen-like compound galactogen in snails and the polysaccharide raffinose in sugar beets, which yields glucose, fructose and galactose. Galactose cannot be utilized directly by cells as a source of energy, but must first be converted to a glucose compound. The transformation of galactose to glucose occurs chiefly in the liver. However, most, if not all, normal tissues, including the erythrocytes, can effect this conversion to some extent. Deficiency of the enzyme phosphogalactose uridyl transferase, which catalyzes the first of the three metabolic steps, is the inborn error in galactosemia (Fig. 64). The resultant metabolic block leads to an accumulation of galactose-1-phosphate in the tissue cells. The enzymatic deficit persists throughout life in hereditary galactosemia; temporary galactose intolerance occurs normally and in various disease states.

Galactose, unlike glucose, is not fermented by yeast. By determining the blood sugar before and after yeast fermentation the amounts which each of the sugars contributes to the total blood sugar can be separated. Identification of the nonfermentable sugar as galactose may be established by the phenylhydrazine test, which yields typical galactosazone crystals. The mucin test with nitric acid results in crystals characteristic of either galactose or lactose. Lactose may be ruled out by a yellow reaction with the Rubner test. Galactose



is also readily determined by paper chromatography. By individually determining blood glucose and galactose levels, Hartmann has shown that as much as 40 per cent of the blood sugar in normal infants on a milk diet may be galactose. This limited capacity for converting galactose to glucose in normal infants is greatly exaggerated in infants recovering from severe diarrhea when fed milk after a period of nonmilk feeding or starvation. Such infants frequently have high blood galactose levels, with those of glucose depressed to hypoglycemic levels. The abnormal galactose tolerance tests in patients with liver disease or hyperthyroidism indicate similar depression of the hepatic enzymatic conversion mechanism. When the blood galactose is elevated to a level which exceeds the capacity of the renal tubules to reabsorb it from the glomerular filtrate, galactose appears in the urine.

The clinical findings in galactosemia are apparently due to the deleterious effect of galactose-1-phosphate on cellular metabolism. The observation that enzyme deficient galactosemic erythrocytes have impaired oxygen utilization, while normal red cells are unaffected when exposed to galactose, indicates that a metabolite of galactose rather than the sugar itself is the injurious agent.

Proteinuria, amino-aciduria and occasionally hyperchloremic acidosis are evidences of renal cellular injury expressed as glomerular

and tubular dysfunctions. These are reversible phenomena, appearing some days after galactosuria begins, and disappearing slowly when lactose is excluded from the diet. Demonstrable pathologic changes predominate in the liver, beginning as fatty infiltration and progressing to cirrhosis. The brain and kidneys show minor and nonspecific changes.

Infants with galactosemia appear normal at birth. Galactosuria is present as soon as milk or lactose water is fed. The severe form of the disease may begin during the first or second week. Listlessness, feeding difficulties, vomiting and weight loss may be the first manifestations. Subclinical early hepatic damage may be responsible for jaundice, which may seem to be a continuation of the neonatal physiologic jaundice. Hepatomegaly and splenomegaly are evident quickly as early signs of portal obstruction, and nuclear cataracts appear about the same time. Galactosuria fluctuates in a degree with the lactose intake and is more severe in breast-fed infants because of the high lactose content of breast milk. Protein, casts and amino acids are present in the urine as signs of renal damage. With the onset of hepatic failure, hemorrhages, due to prothrombin deficiency, occur in the skin and mucous membranes, and generalized edema and ascites develop. At this stage the infant is usually emaciated, lethargic and hypotonic; death may occur from infection or severe hepatic failure.

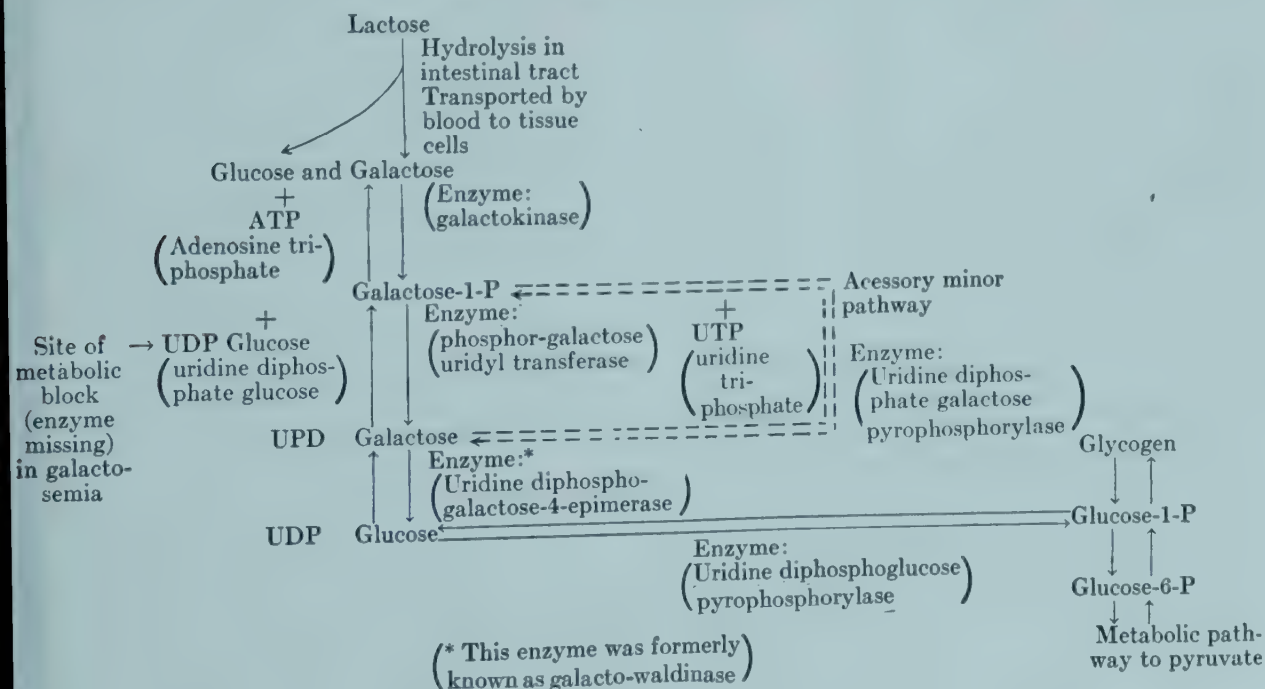


FIG. 64. Pathways of lactose and galactose metabolism.

In some infants the manifestations of galactosemia evolve more slowly and are milder. The discovery of hepatomegaly and cataracts in an underweight, but not acutely ill, three- or four-month-old infant may be the first indication. A significant degree of mental retardation occurs in most infants, and cirrhosis of the liver, cataracts and mental deficiency may remain as permanent sequels.

Examination of the relatives of galactosemic infants, with the galactose tolerance test, reveals a number with galactose intolerance as the only evidence of a subclinical form of galactosemia. Such persons often have a history of gastrointestinal milk intolerance during infancy, and some have a lifelong aversion to milk. The recent discovery of an alternate metabolic pathway for galactose may explain the variations in the clinical severity of galactosemia and account for the acquisition of tolerance for galactose with advancing age. The capacity for expansion of this minor enzymatic pathway (Fig. 64) should determine the amount of galactose-1-phosphate which bypasses the primary metabolic block and re-enters the pathway to glucose formation.

The sudden depression of glucose concentration which follows the rapid influx of galactose into the blood during the performance of a galactose tolerance test may produce clinical manifestations of hypoglycemia. For this reason the test should be used only when it is difficult to diagnose galactosemia by other means.

Amino-aciduria is a feature of the severe form of galactosemia. More than twenty different amino acids have been identified, the pattern of excretion varying from patient to patient. Proteinuria is present in all untreated infants and may amount to 1 gm. daily.

Hyperchloremic acidosis due to renal tubular dysfunction and hypokalemia are not uncommon. Increased plasma levels of bilirubin and alkaline phosphatase, prolonged prothrombin times and positive cephalin flocculation tests may be found early in the clinical course. The specific enzyme deficiency in patients with this disorder can be easily demonstrated in the erythrocytes by a relatively simple spectrophotometric test with umbilical cord blood.

Withdrawal of milk from the diet and substitution of a lactose-free diet result in cessation of galactosemia and galactosuria and, early in the clinical course, in disappearance of the abnormal clinical findings. Cataracts which persist require surgical treatment. The small quantities of galactose (less than 0.1 per cent) present in milk substitutes made with casein hydrolysates may be toxic to the tissue cells of affected infants even though they do not raise the blood galactose level high enough to cause galactosuria. Similarly, soy bean preparations are unsatisfactory substitutes because they contain stachyose, a complex polysaccharide composed of two molecules of galactose and one each of fructose and glucose. Holzel has successfully used a feeding mixture composed of cereal, egg and vegetable margarine as a galactose-free substitute for milk.\* Strict avoidance of milk, milk products and such unsuspected sources as lactose-containing tablets for the first three years of life is recommended as the best guarantee for normal growth of the brain.

Dietary lapse should be suspected as a cause of an illness in a treated infant, especially if hepatomegaly or jaundice develops. In the absence of galactosuria, amino-aciduria is a sensitive indicator of the presence of galactose in the diet.

### *Defective Pentose Metabolism*

More slowly absorbed than hexoses, the pentoses enter the main glycolytic pathway of carbohydrate metabolism by a collateral chan-

\* Holzel's formula is an adaptation of a milk-free pudding devised by Moll and Stransky.

*The ingredients:* 2 eggs, 6 ounces of cereal (containing no milk powder), pinch of salt, pinch of bicarbonate of soda and oleomargarine (without added butter).

*Method of preparation:* The egg yolks and sugar are beaten together. The egg whites, to which the pinch of salt and sodium bicarbonate are added, are beaten until stiff. The cereal is mixed thoroughly

nel, the pentose phosphate pathway (Fig. 65). Pentoses such as D-ribose and desoxyribose which are part of the molecular structure with water. All ingredients are mixed and cooked in a double boiler for 20 to 30 minutes. The cooking pan is greased first with oleomargarine and dusted with dry cereal. The amount of oleomargarine is gradually increased to 1 ounce at 3 to 4 months of age.

One part of this pudding is added to 4 parts of boiled water or weak tea, mixed well and strained before being put into the nursing bottle.

Additional calcium must be given daily.



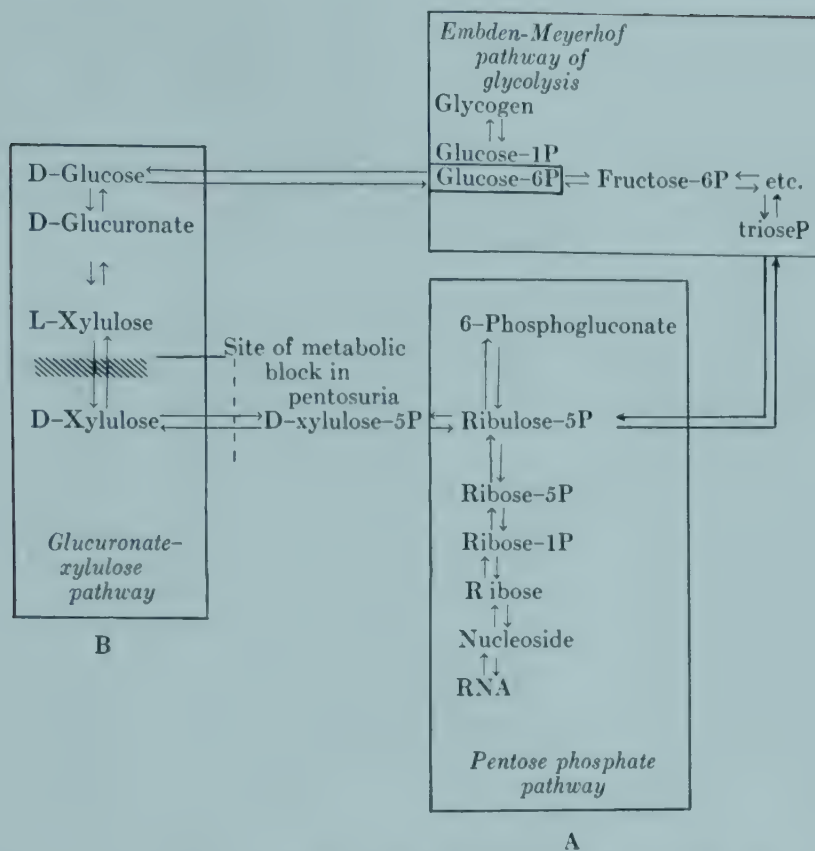


FIG. 65. Metabolic pathways for pentose. Two pentose-hexose cycles by which the metabolism of pentoses is integrated with the major pathway of glucose metabolism, the glycolytic pathway.

A, The pentose phosphate pathway is the metabolic sequence of reactions in which phosphate is used for energy. D-ribose is synthesized and incorporated into the various nucleosides, which in turn become part of the ribose nucleic acids (RNA) which characterize the nucleoproteins.

B, The glucuronate-xylulose pathway establishes the long obscure link between L-xylulose and the metabolism of glucose. The compound D-xylulose-5P is unique, in that it is a focal point in carbohydrate metabolism similar to glucose-6P. It links the 2 pentose pathways, and from it branches a pathway over which L-arabinose is metabolized.

ture of nucleoproteins are not derived directly from dietary sources; they are synthesized as needed from glucose by a sequence of metabolic reactions via the pentose phosphate pathway. Renal tubular reabsorption of filtered pentose is poor, so that a considerable portion of the pentose absorbed from the bowel may be lost in the urine. In such instances the urinary pentose is either xylose or arabinose. The presence of D-ribose has been noted in the urine of some patients with muscular dystrophy.

## ESSENTIAL PENTOSURIA

### (L-XYLULOSURIA)

This is a rare inherited anomaly characterized by excretion of L-xylulose regardless of diet. Found almost exclusively in Jewish families, it has an incidence of about one in 50,000. Most cases are not detected until adult life;

however, it has been encountered in a nineteen-month-old infant. The disorder is transmitted by an autosomal recessive gene.

Until recently the origin of the metabolic defect responsible for the presence of L-xylulose in pentosuria was unknown. It was recognized that feeding of D-glucuronic acid or of compounds which appear as D-glucuronides, such as menthol, borneol, amidopyrine and codeine, caused increased amounts of L-xylulose to appear in the urine of pentosurics. With the complete delineation of a second pentose-hexose cycle, in which many of the metabolic intermediate compounds are not phosphorylated, it is now clear that the precursor of L-xylulose, D-glucuronic acid, is derived from glucose. This metabolic chain connecting L-xylulose to the main stream of carbohydrate metabolism, the Embden-Meyerhof glycolysis schema, is called the glucuronate-xylulose pathway of pentose metabolism

(Fig. 65). A metabolic block beyond L-xylulose, preventing its re-entry into the pentose phosphate pathway, is one possible explanation for L-xylulosemia.

L-xylulosemia is usually harmless and symptomless; in some families an association with migraine has been noted. It is ordinarily

discovered by urinalysis; because it reduces Benedict's and Fehling's solutions it may be confused with glycosuria. L-xylulose is not fermented by yeast. With phenylhydrazine it forms an osazone which melts at 158° C. The reaction of orcin with Bial's reagent\* is positive.

## INBORN ERRORS OF LIPID METABOLISM

### IDIOPATHIC HYPERLIPEMIA

#### (FAMILIAL HYPERLIPEMIA)

Idiopathic hyperlipemia is a comparatively rare disorder of fat metabolism characterized by an increase in the neutral fat fraction of the blood. Of twenty-four reported cases, eleven were children and twenty-two were males. Both the white and Negro races are affected. The familial occurrence of hyperlipemia makes it likely that it is an inborn error of metabolism transmitted as a recessive trait.

The *pathogenesis* of idiopathic hyperlipemia is obscure. An unesterified fatty acid fraction, which is bound to protein, is the active transport form of blood fat. It is released from adipose tissue by the enzyme lipoprotein lipase. Whether this mechanism is disturbed in idiopathic hyperlipemia is unknown. The demonstrable pathologic changes, hepatosplenomegaly, lipemia retinalis, xanthomatous skin lesions and fat storage cells in sternal marrow result from storage of fat in the reticuloendothelial cells secondary to the excess blood lipids.

Clinically, the following triad of *symptoms* should suggest idiopathic hyperlipemia: (1) abdominal pain, usually recurrent and colicky and possibly related to meals. In the patient observed by Holt, such abdominal crises suggestive of a surgical condition took place when the blood fat rose to 8 per cent. Nausea and vomiting are not uncommon. (2) Hepatosplenomegaly, presumably due to deposition of fat; (3) xanthomatous skin lesions consisting of yellowish papules with an inflammatory halo.

In more than half of the patients lipemia retinalis was observed funduscopically. A level of blood fat of more than 3.5 per cent

gives the peripheral retinal vessels a pink appearance, so that it is difficult to distinguish veins and arteries. The parents and siblings of some reported cases had lesser degrees of hyperlipemia and were asymptomatic.

The excess neutral fat in the plasma produces a grossly chylous or milky white appearance. The other blood lipids, cholesterol, cholesterol esters and the phospholipids (sphingomyelin, cephalin and lecithin), are constantly but less markedly increased; they do not contribute to the chylous appearance of the serum. Hyperlipemia occurs physiologically after a meal of high fat content, reaching its peak in three hours. It is also seen in a variety of pathologic states, such as the nephrotic syndrome, renal vein thrombosis, poisoning with phosphorus, chloroform and carbon tetrachloride, starvation, anoxia, anemia, hypoproteinemia, leukemia, diabetes, hepatic glycogen disease, Niemann-Pick disease, hypothyroidism and pancreatic disease. There should be no difficulty in differentiating these disturbances from idiopathic hyperlipemia.

The clinical course of the disorder is relatively benign; thirteen of the reported patients were adults. However, sudden otherwise unexplained death has occurred.

There is no known cure. Low fat diets cause some decrease in blood fat, but not to normal levels. On such diets regression of many of the symptoms may occur.

\* *Bial's Reagent*: Dissolve 1 gm. of orcin in 50 ml. of hydrochloric acid (specific gravity, 1.51). Add 25 drops of 10 per cent aqueous ferric chloride. Keep in a dark bottle away from light.

*Orcin Test*: Overlay 5 ml. of Bial's reagent in a test tube with 5 drops of urine. A green ring appears at the junction of the 2 layers if xylulose is present.



## INBORN ERRORS OF PIGMENT METABOLISM

## THE PORPHYRIAS

The porphyrias are a group of hereditary metabolic errors involving the porphyrins, a class of pigments widely distributed in nature and occurring in plant and animal tissues. The porphyrins are derivatives of a parent substance, porphin, which consists of four pyrrole nuclei joined in an aromatic structure. Fischer showed that there were artificial isomeric porphyrins with methyl ( $\text{CH}_3$ ) and ethyl ( $\text{C}_2\text{H}_5$ ) groups in equal numbers as side chains. These he named the etioporphyrins I, II, III and IV. All the porphyrins occurring in nature are derivatives of either etioporphyrin I or III. Porphyrins of type I cannot be derived from type III. Thus the simultaneous occurrence of porphyrins of types I and III is interpreted as an independent synthesis of each type and is referred to as the "dualism" of the porphyrins. The respiratory pigments, hemoglobin, myoglobin, cytochrome, catalase, peroxidase and chlorophyll, are porphyrin derivatives. Free porphyrins occur in young cells of the erythrocyte series in the bone marrow.

Though porphyrins exist preformed in many food substances, including milk, bread, beer, fish, spinach, potatoes, rutabagas and green leaves, the porphyrins of the body are synthesized from simpler pyrroles. Porphyrins of types I and III are formed simultaneously in the body as products of the same chemical process from pyrrole precursors. Thus in the synthesis of hemoglobin and the other respiratory enzymes which contain protoporphyrin III in their molecules, one part of protoporphyrin I is formed as a by-product in the formation of 10,000 parts of the type III compound. The type III porphyrin combines with iron or specific protein to form the respiratory pigments, and the small amount of by-product coproporphyrin I is excreted.

In normal human adults (quantitative studies of porphyrin excretion in normal infants and children are lacking) from 14 to 100 micrograms of coproporphyrins are excreted in the urine daily. Approximately 80 per cent is the type I isomer (coproporphyrin I) and 20 per cent, type III (coproporphyrin III). In various pathologic conditions there is often a considerable alteration in the amount and ratio of the two types of porphyrin in the

urine. In certain hepatic diseases (obstructive jaundice, hepatitis with jaundice and cirrhosis) there is an increase in urinary coproporphyrin, usually of coproporphyrin I. In the febrile states associated with lung abscess and pneumonia and at times in rheumatic fever, increases in urinary coproporphyrin I also occur. In most cases of acute poliomyelitis there is an increased excretion of coproporphyrin III, which may be found in metallic and drug poisonings (lead, arsenic, sulfanilamide, chloral hydrate, Avertin, paraldehyde, ether, morphine, aspirin, phenacetin and acetanilid) and in various blood disorders (leukemia, aplastic anemia, pernicious anemia, hemolytic anemia and Hodgkin's disease).

In all the pathologic states mentioned the excretion of abnormally large amounts of porphyrin in the urine is referred to as *porphyria*, a term which must be distinguished from *porphyria*, which is the name applied to the congenital errors of metabolism of pyrrole pigments, in which there is also excretion of large amounts of porphyrins. It is convenient to divide the hereditary porphyrias into three clinical types, i.e., congenital porphyria, acute intermittent porphyria (hereditary) and the cutanea tarda type.

## "CONGENITAL" PORPHYRIA

## (ERYTHROPOIETIC PORPHYRIA)

Congenital porphyria is a rare metabolic error inherited as a recessive character. It may be present at birth and has been described in the fetus. The classic clinical manifestations of this disorder are excretion of a Burgundy red urine, discoloration of the bones and teeth, extreme sensitivity of the skin to light, and hirsutism. Hepatic and splenic enlargement is common. Not all these symptoms may be evidenced at one time or in one patient.

The biochemical defect in congenital porphyria may be a failure of conversion of uroporphyrin I, which is formed in excessive amounts, to coproporphyrin I. It is assumed that uroporphyrin is formed in postnatal life, but is ordinarily converted by decarboxylation of four  $-\text{COOH}$  groups to coproporphyrin I. The red color of the urine in congenital porphyria, which is due to the presence of excessive amounts of uroporphyrin I



FIG. 66. Porphyria showing (1) discoloration of the teeth; (2) pigmented scars of hydroa vacciniforme prominent on the forehead; and (3) hypertrichosis, manifested by the thick eyebrows joining in the midline, the long eyelashes and the low frontal hair line. (Dunskey, Freeman and Gibson: Am. J. Dis. Child., Vol. 74.)

and coproporphyrin I, has been noted at birth. In alkaline solutions porphyrins are reddish-brown; in mineral acid solutions they are purple or reddish-violet, and in organic acid solutions, a dull red. In many instances light-colored urine is passed which darkens after exposure to light, owing to photo-oxidation of leuco-porphyrins. In some patients with porphyria the urine becomes darker when the patient is exposed to sunlight. Once red urine is excreted, the passage of colored urine usually persists year after year. Conditions other than porphyrinuria may cause a reddish urine, so that hemoglobinuria, myoglobinuria and hematuria must be differentiated. The ingestion of beets or pyramidon may also color the urine red. A pink color is often seen in alkaline urines after ingestion of phenolphthalein, senna, cascara, rhubarb or santonin. In newborn and young infants precipitated amorphous urates frequently have a pink tinge. In congenital porphyria the passage of red urine usually precedes the appearance of cutaneous light sensitivity.

The presence of porphyrins in the tissues is responsible for the cutaneous sensitivity to sunlight. Like many other fluorescent com-

pounds, the porphyrins are sensitized by light and become powerful proteolytic agents. The porphyrins vary in their ability to sensitize tissues to light, the type I porphyrins, especially uroporphyrin I, being the most photodynamic. After exposure to sunlight the unprotected skin surfaces develop *hydroa aestivale*, a symptom complex which begins with itching and erythema and is followed by a vesiculobullous eruption that forms crusts and leaves pigmented scars. The tissue scarring is disfiguring and, when deep, may involve cartilage, ligaments and bones, resulting in mutilation or loss of parts of the nose, ears or fingers. Severe involvement of the conjunctiva and cornea may cause blindness. In some patients pigmentation and hirsutism develop in the skin surfaces exposed to sunlight. There are many cases of hydroa aestivale or vacciniforme not associated with congenital porphyria. *Hydroa is a symptom complex, but congenital porphyria with similar cutaneous lesions is a clinical entity due to a disorder of porphyrin metabolism.*

Continuous deposition of uroporphyrin I is responsible for the pigmentation of bones and teeth. Dark brown stained bones are in sharp contrast to the unstained cartilage. In about 10 per cent of patients the temporary and permanent teeth have a pink or purplish-brown discoloration (*erythrodontia*). Occasionally the fingernails are reddish-purple and may be shed during the summer after an episode of hydroa.

Splenomegaly due to increased hemolysis of erythrocytes is a regular occurrence, and the resultant increased bone marrow activity stimulates excessive formation and excretion of porphyrins. Clinical and chemical improvement may follow splenectomy.

Patients should be protected from sunlight with suitable clothing combined with application of "sun-tan" ointments or lotions capable of filtering out ultraviolet rays.

#### ACUTE INTERMITTENT PORPHYRIA (HEREDITARY)

Acute porphyria is a hereditary disorder of porphyrin metabolism in which there is urinary excretion of excessive quantities of type III porphyrin isomers. It is inherited as a dominant characteristic. Though a few children have had acute porphyria, it is usually manifest clinically between thirty and fifty years of age and is more common than congenital porphyria. There are no known cases of congenital porphyria in families with acute



porphyria. The precipitating factor of an attack is usually unknown, but attacks may be induced by ingestion of barbiturates and related compounds such as Sulfonal, Trional and Sedormid.

Patients with acute porphyria do not have unusual sensitivity to light or discoloration of the bones and teeth, but jaundice and a peculiar brownish pigmentation of the skin have been observed. Though there is great variation in the clinical picture, the symptoms are of three general types and appear intermittently and acutely: (1) abdominal symptoms, consisting in severe colicky pain, constipation and vomiting, often accompanied by fever, hypertension and tachycardia; (2) nervous symptoms, characterized by a symmetric progressive paralysis, at times accompanied by polyneuritis; and (3) psychotic disorders.

During an attack the urine is usually red, but in some instances it is yellow when excreted, becoming dark after exposure to light. In addition to the type III uroporphyrin, smaller amounts of uroporphyrin I and coproporphyrin I have been isolated from the urine of patients with acute porphyria. Various chromogens, responsible for some of the dark color, such as porphobilinogen and porphobilin, are also present in the urine. The porphyrin can be demonstrated in the urine by pink fluorescence in ultraviolet light, especially the Wood light. The simple test for porphobilinogen devised by Watson is pathognomonic for acute porphyria and may be used to differentiate the two types of porphyria. The determination of the type of porphyrin excreted is an elaborate procedure involving separation of the porphyrins chemically, and the identification by determination of melting points or by spectroscopy.

There is no effective treatment. Barbiturates must be rigidly avoided.

## CUTANEA TARDA TYPE OF PORPHYRIA

This chronic type of hereditary porphyria is characterized by photosensitivity which appears late in life (forty to fifty years of age). Brownish or violaceous skin pigmentation and bullae occur after exposure to sunlight. Abdominal and neurologic manifestations are absent. Hepatic dysfunction is common, and liver failure is often a cause of death. The urine may appear red and contains uroporphyrins of types I and III, but porphobilinogen is absent.

## HEREDITARY DEFECTS INVOLVING BILIRUBIN

Many of the obscurities surrounding the nature and origin of different types of jaundice have been resolved by the recent discovery that direct-reacting bilirubin is a glucuronide of bilirubin. The hepatic cell converts water-insoluble indirect-reacting bilirubin to the more soluble direct-reacting bilirubin by conjugating it with glucuronic acid (Fig. 67).

Two hereditary disorders associated with jaundice are due to metabolic defects in conjugation of bilirubin (see also p. 702):

1. *Congenital familial nonhemolytic jaundice with kernicterus*: a serious, rare hereditary condition in which the conjugating mechanism is deficient in the enzyme, uridyl transferase.

2. *Gilbert's disease*: a benign type of hereditary jaundice due to a deficit of the same enzyme.

## HEREDITARY METHEMOGLOBINEMIAS

### CONGENITAL METHEMOGLOBINEMIA

(IDIOPATHIC METHEMOGLOBINEMIA)

Congenital methemoglobinemia is a hereditary biochemical recessive defect of the eryth-

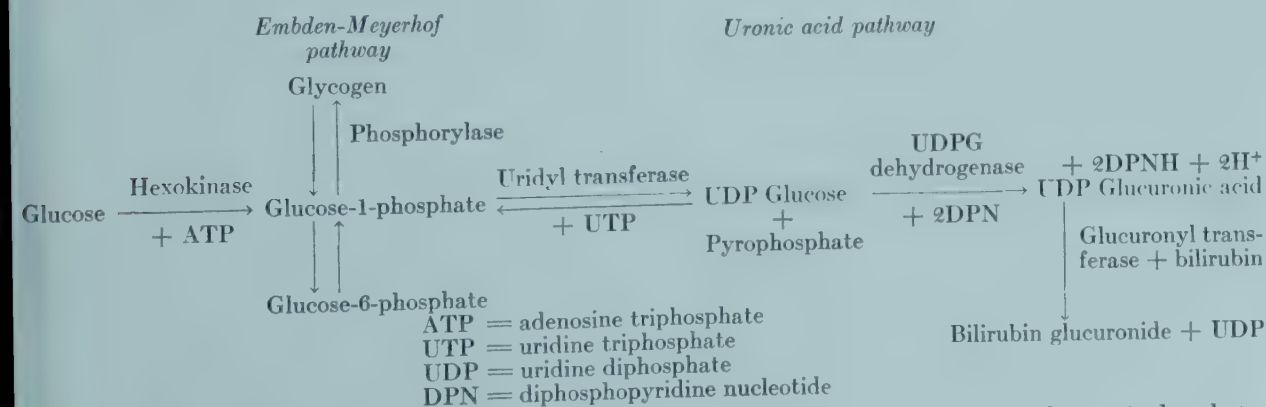


FIG. 67. Enzymatic steps in glucuronide synthesis along uronic acid pathway from glucose-1-phosphate.

rocyte characterized clinically by cyanosis resulting from the large amount of the intracellular hemoglobin which exists as methemoglobin. Hemoglobin iron functioning as a carrier of oxygen is always in the reduced or ferrous state ( $\text{Fe}^{++}$ ) in both oxygenated and deoxygenated hemoglobin. Methemoglobin iron is in the oxidized or ferric state ( $\text{Fe}^{+++}$ ) and is totally incapable of transporting oxygen. Methemoglobin is formed from deoxygenated hemoglobin by oxidation. Under aerobic conditions hemoglobin in aqueous solution is slowly and completely oxidized to methemoglobin. In intact normal erythrocytes methemoglobin is similarly and constantly formed. However, methemoglobin does not accumulate to more than 0.4 per cent of total hemoglobin in normal red blood cells, because it is reduced back to hemoglobin by a complex chain of enzymatic reactions almost as rapidly as it is formed.

The reduction of methemoglobin to hemoglobin in the intact erythrocyte is coupled with the oxidation of glucose or lactate. In the process of oxidizing glucose or lactate to pyruvate, coenzyme I (diphosphopyridine nucleotide) is reduced and is made available for the reduction of methemoglobin. A flavoprotein, the coenzyme factor, accelerates the reduction of methemoglobin by coenzyme I. In idiopathic methemoglobinemia there is a deficiency of the coenzyme factor, so that the accumulated methemoglobin comprises up to 40 per cent of the total erythrocyte pigment. In the absence of the coenzyme factor other reducing substances in plasma and red cells, e.g., ascorbic acid and glutathione, act as a secondary defense and reduce methemoglobin to a limited extent. In these patients methemoglobin shifts the oxygen dissociation curve of the blood to the left, an indication that the methemoglobin is present in all the erythrocytes.

Severe, persistent, diffuse cyanosis, most marked on the fingers, toes, lips, oral mucous membranes, conjunctiva and retinas, is the main clinical finding and is usually manifest at birth. The symptoms of respiratory or cardiac distress are mild in comparison to the intensity of the cyanosis. Dyspnea, tachycardia and palpitation may occur. Administration of oxygen does not relieve the cyanosis or other symptoms. In older persons fatigue, headache and poor tolerance to exercise are manifestations, but patients may be asymptomatic even after strenuous activity. Clubbing of the fingers does not occur. To compensate for the inert methemoglobin, sec-

ondary polycythemia with an accompanying reticulocytosis develops.

Freshly drawn blood has a chocolate color and does not regain its red color when oxygenated by shaking in air. The plasma is clear. Examined in a hand spectroscope after dilution with water (10 to 100 times), the characteristic dark absorption band of methemoglobin at 630 millimicrons is seen. Addition of 2 to 3 drops of 5 per cent potassium cyanide causes disappearance of the band. Sulfhemoglobin has an absorption band of 618 millimicrons, which is not abolished by potassium cyanide. Examination of the transilluminated ear lobe with the spectroscope may also reveal the characteristic absorption band. Despite adequate dietary intake the serum ascorbic acid content is low, as is the glutathione content.

Acquired methemoglobin may be caused by a variety of chemicals (p. 1379).

The capacity of ascorbic acid or methylene blue to reduce methemoglobin to hemoglobin is used both as a diagnostic test and as therapy. Large doses (200 to 500 mg.) of ascorbic acid taken daily in divided doses will reduce the methemoglobin content from 40 to about 10 per cent of the total pigment. Intravenous injection of methylene blue in a dose of 1 to 2 mg. per kilogram of body weight will cause prompt disappearance of both methemoglobin and cyanosis. From 3 to 5 mg. per kilogram of body weight daily in divided oral doses will keep a patient free from cyanosis. Ascorbic acid acts directly as a reducing agent, whereas methylene blue produces reduction of methemoglobin by acting in an enzyme system.

#### BIOCHEMICAL VARIANT OF IDIOPATHIC METHHEMOGLOBINEMIA

One patient has been observed who, though clinically indistinguishable from other patients with congenital methemoglobinemia, had no shift in the oxygen dissociation curve of his blood (Eder). However, there was good response to methylene blue and ascorbic acid.

#### HEMOGLOBIN M-METHEMOGLOBINEMIA

Persons with a genetically and chemically different type of methemoglobinemia have been identified in four generations of two different German families. "Cyanotic" persons with this trait appear well and are not inconvenienced physically, even though 15 to 25 per cent of their red blood cell pigment is methemoglobin. The biochemical abnor-



malinity resides in the globin fraction of the hemoglobin molecule. It is transmitted by an autosomal dominant gene, designated hemoglobin M. Hemoglobin M has a different spectral absorption curve from ordinary methemoglobin, and it does not cause a shift in the oxygen dissociation curve of blood. Ascorbic acid and methylene blue have no effect on hemoglobin M.

## CONGENITAL SULFHEMOGLOBINEMIA

Hereditary sulfhemoglobinemia is one of the rarest inborn errors of metabolism. A recent report of the disorder in a female infant is perhaps the first authenticated instance. Spectroscopic examination of the blood performed in the neonatal period because of persistent unexplained cyanosis revealed a sulfhemoglobin content of 1.0 gm. per 100 ml. (normal is less than 0.2 gm.). The infant's father, paternal grandfather, uncle and two cousins had similar values. At six months of age the infant was still cyanotic, but had grown and developed normally. The disorder was transmitted as a dominant characteristic.

Sulfhemoglobin is an inert pigment and does not transport oxygen. Hydrogen sulfide inhalation, ingestion of large amounts of sulfur and production of hydrogen sulfide in the bowel by bacterial action may cause sulfhemoglobinemia.

MILTON RAPOPORT

## REFERENCES

### General

- Childs, B., and Sidbury, J. B.: A Survey of Genetics as It Applies to Pediatrics. *Pediatrics* (Supp.), 20: 178, 1957.
- Garrod, A. E.: *Inborn Errors of Metabolism*. London, Oxford, 1923.
- Haldane, J. B. S.: *The Biochemistry of Genetics*. London, George Allen and Unwin, Ltd., 1954.
- Harris, H.: *An Introduction to Human Biochemical Genetics*. London, Cambridge University Press, 1953.
- Hottinger, A., Hauser, F., and Berger, H.: *Modern Problems in Pediatrics. Congenital and Familial Metabolic Disturbances*. Basel, S. Karger, 1958, Vol. 3.
- McKusick, V. A.: *Heritable Disorders of Connective Tissue*. St. Louis, C. V. Mosby Company, 1956.

### Errors in Protein Metabolism

- Aggeler, P. M., Hoag, M. S., and Wallerstein, R. O.: Plasma Thromboplastin Component (PTC) Deficiency. *J. Am. M. Women's A.*, 12:280, 1957.
- Alexander, B., Goldstein, R., Landwehr, G., and Cook, C. D.: Congenital SPCA Deficiency, a Hitherto Unrecognized Coagulation Defect with Hemorrhage, Rectified by Serum and Serum Fractions. *J. Clin. Invest.*, 30:596, 1951.

- Allison, A. C., and ap Rees, W.: The Binding of Haemoglobin by Plasma Proteins (Haptoglobins). Its Bearing on the Renal Threshold for Haemoglobin and the Etiology of Haemoglobinuria. *Brit. M. J.*, 2:1137, 1957.
- Bearn, A. G.: Wilson's Disease—An Inborn Error of Metabolism with Multiple Manifestations. *Am. J. Med.*, 22:747, 1957.
- Bennhold, H.: in *Verh. Dtsch. Ges. Inn. Med.*, Wiesbaden, 1956.
- Brinkhous, K. M., Langdell, R. D., and Wagner, R. H.: Hemostatic Disorders: Hemophilia and the Hemophiloid Diseases. *Ann. Rev. Med.*, 9:159, 1958.
- Bruton, O. C.: Agammaglobulinemia. *Pediatrics*, 9: 722, 1952.
- Cochrane, W. A., Payne, W. W., Simpkins, M. J., and Woolf, L. I.: Familial Hypoglycemia Precipitated by Amino Acids. *J. Clin. Invest.*, 35:411, 1956.
- Cooke, J. V.: Familial White Skin Spotting (Piebaldness) ("Partial Albinism") with White Forelock. *J. Pediat.*, 41:1, 1952.
- Dent, C. E., Harris, H., Baron, D. N., Hart, E. W., and Jepson, J. B.: Hereditary Pellagra-Like Skin Rash with Temporary Cerebellar Ataxia, Constant Renal Amino-aciduria and Other Bizarre Biochemical Features. *Lancet*, 2:421, 1956.
- de Toni, G.: Renal Rickets with Phospho-glucosaminic Renal Diabetes (de Toni-Debré-Fanconi Syndrome). *Ann. paediat.*, 187:42, 1956.
- Deutsch, S., and Mescon, H.: Melanin Pigmentation and Its Endocrine Control. *New England J. Med.*, 257:222, 257, 268, 1957.
- Frick, P. G., and McQuarrie, I.: Congenital Afibrinogenemia. *Pediatrics*, 13:144, 1954.
- Giedion, A., and Scheidegger, J. J.: Kongenitale-immunparese bei fehlen spezifischer B<sub>2</sub> Globuline und quantitativ normalen  $\alpha$ -Globulinen. *Helv. paediat. Act.*, 12:241, 1957.
- Graham, J. B., Barrow, E. M., and Hougie, C.: Stuart Clotting Defect. II. Genetic Aspects of a New Hemorrhagic State. *J. Clin. Invest.*, 36:497, 1957.
- Gross, R. T., Hurwitz, R. E., and Marks, P. A.: An Hereditary Enzymatic Defect in Erythrocyte Metabolism: Glucose-6-Phosphate Dehydrogenase Deficiency. *J. Clin. Invest.*, 37:1176, 1958.
- Harris, H., and Robson, E. B.: Cystinuria. *Am. J. Med.*, 22:774, 1957.
- Harrison, H. E., and Harrison, H. C.: Amino-aciduria in Relation to Deficiency Diseases and Kidney Function. *J.A.M.A.*, 164:1571, 1957.
- Henderson, W.: A Case of Hartnup Disease. *Arch. Dis. Childhood*, 33:114, 1958.
- Homburger, F., and Peterman, M. L.: Studies on Hypoproteinemia. II. Familial Idiopathic Dysproteinemia. *Blood*, 4:1085, 1949.
- Ingram, V. M.: Gene Mutations in Human Hemoglobin: The Chemical Difference between Normal and Sick Cell Hemoglobin. *Nature*, 180:326, 1957.
- Janeway, C. A., and Gitlin, D.: *The Gamma Globulins*; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1957, Vol. 9.
- Jim, R. T. S., and Goldstein, S.: Hageman Trait (Hageman Factor Deficiency). *Am. J. Med.*, 23: 824, 1957.
- Kingsley, C. S.: Familial Factor V Deficiency: The

- Pattern of Heredity. *Quart. J. Med.*, 23:232, 1954.
- Knox, W. E.: Sir Archibald Garrod's "Inborn Errors of Metabolism." *Am. J. Human Genet.*, 10:3, 95, 1958.
- Knox, W. E., and Hsia, D. Y.-Y.: Pathogenetic Problems in Phenylketonuria. *Am. J. Med.*, 22:687, 1957.
- Kretchmer, N., and Etzwiler, D. D.: Disorders Associated with the Metabolism of Phenylalanine and Tyrosine. *Pediatrics*, 21:445, 1958.
- McCune, D. J., Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (the Fanconi Syndrome). *Am. J. Dis. Child.*, 65:81, 1943.
- Medes, G.: A New Error of Tyrosine Metabolism: Tyrosinosis. *Biochem. J.*, 26:912, 1932.
- Mudge, C. H.: Clinical Patterns of Tubular Dysfunction. *Am. J. Med.*, 24:785, 1958.
- Pearson, H. A., and Cone, T. E., Jr.: Congenital Hypoplastic Anemia. *Pediatrics*, 19:192, 1957.
- Piel, C. F.: Diseases of the Renal Tubules in Childhood. *Pediatrics*, 20:337, 1957.
- Quick, A. J., Pisciotto, A. V., and Hussey, C. J.: Congenital Hypoprothrombinemic States. *A.M.A. Arch. Int. Med.*, 95:2, 1955.
- Rosenthal, R. L., Dreskin, O. H., and Rosenthal, N.: Plasma Thromboplastin Antecedent (PTA) Deficiency: Clinical, Coagulation, Therapeutic and Hereditary Aspects of a New Hemophilia-Like Disease. *Blood*, 10:120, 1955.
- Schulman, I., and Smith, C. H.: Coagulation Disorders in Infancy and Childhood; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1957, Vol. 9.
- Sjoerdsma, A., Weissbach, H., and Udenfriend, S.: A Clinical and Biochemical Study of Patients with Malignant Carcinoid (Argentaffinoma). *Am. J. Med.*, 20:520, 1956.
- Sutton, H. E., and Read, J. H.: Abnormal Amino Acid Metabolism in a Case Suggesting Autism. *A.M.A. Am. J. Dis. Child.*, 96:23, 1958.
- Thompson, W. H., McQuarrie, I., and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in Liver, with Studies of Water and Mineral Exchanges. *J. Pediat.*, 9: 604, 1936.
- Uhlstrom, R. A., Smith, N. J., and Heimlich, E. M.: Transient Dysproteinemia in Infants, a New Syndrome. *A.M.A. Am. J. Dis. Child.*, 92:219, 1956.
- Watson, J.: Hemoglobins and Disease; in *Advances in Internal Medicine*. Chicago, Year Book Publishers, Inc., 1956, Vol. 8.
- Westall, R. G., Dancis, J., and Miller, S.: Maple Sugar Urine Disease, a New Molecular Disease. *Proc. Soc. Pediatric Research*, 27th Annual Meeting, Carmel, Calif., June, 1957, p. 110.
- Wilkinson, J. F., Israëls, M. C. G., and Nour-Eldin, F.: Unusual Transmission of the Haemophilic Gene. *Brit. M. J.*, 2:1528, 1957.
- Worthen, H. G., and Good, R. A.: The de Toni-Fanconi Syndrome with Cystinosis. *A.M.A. Am. J. Dis. Child.*, 95:653, 1957.
- Brante, G.: Gargoylism—A Mucopolysaccharidosis. *Scandinav. J. Clin. & Lab. Invest.*, 4:43, 1952.
- Bridge, E. M., and Holt, L. E., Jr.: Glycogen Storage Disease: Observations on Pathologic Physiology of Two Cases of Hepatic Form of the Disease. *J. Pediat.*, 27:299, 1945.
- Cori, G. T.: Glycogen Structure and Enzyme Deficiencies in Glycogen Storage Disease. *Harvey Lectures*, series 48:145. New York, Academic Press 1952-53.
- Di Sant'Agnese, P. A., Andersen, D. H., and Mason, H. H.: Glycogen Storage Disease of the Heart. II. Critical Review of the Literature. *Pediatrics*, 6: 607, 1950.
- Dorfman, A.: Studies on the Biochemistry of Connective Tissue. *Pediatrics*, 22:576, 1958.
- Elmer, A. W., Krasowska, M., and Ptaszek, L.: Sucro-suria: A Rare Metabolic Error. *Acta med. Scandinav.*, 101:596, 1939.
- Forbes, G. B.: Glycogen Storage Disease. Report of a Case with Abnormal Glycogen Structure in Liver and Skeletal Muscle. *J. Pediat.*, 42:645, 1953.
- Froesch, E. R., Prader, A., Labhart, A., and others: Hereditary Fructose Intolerance, a Previously Unknown Congenital Disturbance of Metabolism. *Schweiz. med. Wchnschr.*, 87:1168, 1957.
- Hartmann, A. F., Grunwald, F., and James, D. H., Jr.: Blood Galactose in Infants and Children. *J. Pediat.*, 43:1, 1953.
- Holzel, A., Komrower, G. M., and Schwartz, U.: Galactosemia. *Am. J. Med.*, 22:703, 1957.
- Isselbacher, K. J.: Evidence for an Accessory Pathway of Galactose Metabolism in Mammalian Liver. *Science*, 126:652, 1957.
- Koulischer, N., and Pickering, D. E.: Glycogen Storage Disease. *A.M.A. Am. J. Dis. Child.*, 91:103, 1956.
- Lasker, M., Enklewitz, M., and Lasker, G. W.: The Inheritance of I-Xyloseketosuria (Essential Pentosuria). *Human Biol.*, 8:243, 1936.
- Mason, H. H., and Turner, M. E.: Chronic Galactosemia. *Am. J. Dis. Child.*, 50:359, 1935.
- Recant, L.: Recent Developments in the Field of Glycogen Metabolism and Glycogen Storage. *Am. J. Med.*, 18:160, 1955.
- Reiner, M., and Weiner, S. B.: Saccharosuria in an Infant. *Am. J. Dis. Child.*, 57:590, 1939.
- Trivette, D., and Anderson, K.: Essential Fructosuria in Siblings. *Am. J. Dis. Child.*, 75:88, 1948.
- Ullter, F. M.: Carbohydrate Metabolism. *Ann. Rev. Biochem.*, 27:245, 1958.
- von Gierke, E.: Hepatonephromegalia Glycogenica (Glycogen Speicher Krankheit der Leber und der Nieren.). *Beitr. path. Anat.*, 82:497, 1929.
- Zellweger, H., Dark, A., and Abu Haidar, G. A.: Glycogen Storage Disease of Skeletal Muscle. *Pediatrics*, 15:715, 1955.

#### *Errors in Lipid Metabolism*

#### *Errors in Carbohydrate Metabolism*

Andersen, D. H.: Familial Cirrhosis of the Liver with Storage of Abnormal Glycogen. *Laboratory Invest.* 5:11, 1956.

Boggs, J. D., Hsia, D. Y., Mais, R. F., and Bigler, J. A.: The Genetic Mechanism of Idiopathic Hyperlipemia. *New England J. Med.*, 257:1101, 1957.

Holt, L. E., Jr., Aylward, F. X., and Timbres, H. G.: Idiopathic Familial Lipemia. *Bull. Johns Hopkins Hosp.*, 64:279, 1939.



*Errors in Pigment Metabolism*

- Arias, I. M., and London, I. M.: Bilirubin Glucuronide Formation in Vitro: Demonstration of a Defect in Gilbert's Disease. *Science*, 126:563, 1957.
- Billing, B. H., and Lathe, G. H.: Bilirubin Metabolism in Jaundice. *Am. J. Med.*, 24:111, 1958.
- Breakey, V. K. St. G., Gibson, Q. H., and Harrison, D. C.: Familial Idiopathic Methaemoglobinemia. *Lancet*, 1:935, 1951.
- Crigler, J. F., and Najjar, V. A.: Congenital Familial Nonhemolytic Jaundice with Kernicterus. *Pediatrics*, 10:169, 1952.
- Dunsky, I., Freeman, S., and Gibson, S.: Porphyria and Porphyrinuria. *Am. J. Dis. Child.*, 74:305, 1947.
- Gerald, P. S., Cook, C. D., and Diamond, L. K.: Hemoglobin M. *Science*, 126:300, 1957.
- Miller, A. A.: Congenital Sulfhemoglobinemia. *J. Pediat.*, 51:233, 1957.
- Schmid, R.: Congenital Defects in Bilirubin Metabolism. *J. Clin. Invest.*, 36:977, 1957.
- Waldenstrom, J.: The Porphyrins as Inborn Errors of Metabolism. *Am. J. Med.*, 22:758, 1957.
- Watson, C. J., and Larsen, E. A.: The Porphyrins and Their Relation to Porphyria Disease. *Oxford Medicine*, 4:228, 1951.

# The Newborn Infant

The duration of the newborn or neonatal period has been variously defined as the first two to four weeks after birth. The period is essentially that during which the organism is physiologically adjusted from an intrauterine to an extrauterine environment. Although the greatest changes and the largest incidence of morbidity and mortality occur in the first forty-eight hours of life (Fig. 68) and most

infants have begun to grow satisfactorily in their new environment by the fourteenth day, some of the adjustments are not complete by a month or more of age. Since most official morbidity and mortality statistics define the newborn period as the first month, it will be so considered in this section.

Directly or indirectly, much of the morbidity and mortality of the first forty-eight hours is related to factors arising before or during delivery. This is implicit in the term "obstetric death," used in some maternity clinics to include all stillbirths and all infant deaths within a week after delivery. This term, even more explicit than the more common one of "perinatal mortality," indicates the obstetrician's contribution to the condition of the infant during his early postnatal life. The joint activity of obstetricians and pediatricians in conferences on fetal and neonatal deaths and in preparation and analyses of statistics is especially fruitful.

Newborn premature infants are usually considered to have problems distinct from those of infants of full gestation, requiring nurseries where they can be given specialized care. Although the details of such care merit the section devoted to prematurity on page 306, it should be clearly understood that the prematurely born infant can be affected by any of the disease processes common to full term newborn infants. Because of this, no attempt has been made to describe separately all disturbances which may occur in premature infants.

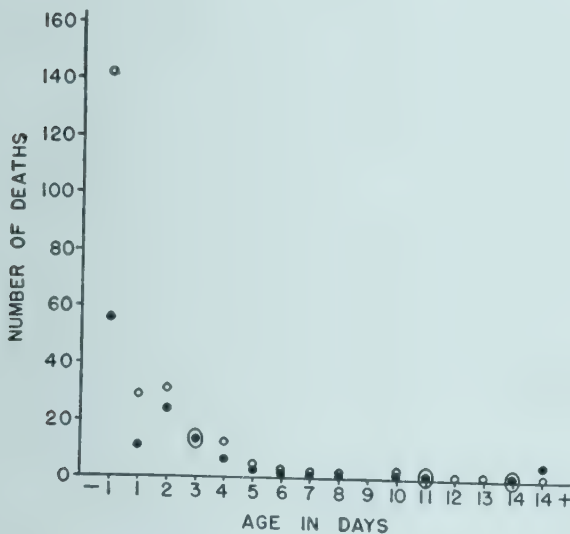


FIG. 68. Distribution by fetal maturity and by postnatal age of all neonatal deaths in the Boston Lying-in Hospital during the 5 years 1945-1949, inclusive:

- ° 249 deaths among premature infants.
- 128 deaths among full term infants.
- 377 neonatal deaths

## PHYSIOLOGY OF THE NEWBORN INFANT

**Respiration. Tissue respiration.** Most evidence indicates that fetal blood has differences in oxygen affinity from maternal blood. These would allow fetal blood to become somewhat more saturated with oxygen than maternal blood at any given tension, and to release its oxygen to the fetal tissues with relatively little loss of tension. If these char-

acteristics are effects of fetal hemoglobin, they should persist in the infant's blood during and after the neonatal period. Most fetal hemoglobin is naturally replaced by adult hemoglobin by three to six months after birth. Since the artificial replacement of hemoglobin by transfusion immediately after birth does not obviously affect the infant's respiration,



fetal blood or fetal hemoglobin does not appear to offer significant advantages to the infant after birth.

The carbonic anhydrase activity of the erythrocytes is reduced in newborn and especially in premature infants. Such a deficiency must reduce the rate of carbon dioxide release and oxygen uptake in the lungs, but the clinical significance of this factor is also in doubt.

The young of all mammals seem able to withstand reduction or absence of atmospheric oxygen longer than adults of the same species. This feature appears related to the brief persistence after fetal life of an anaerobic type of carbohydrate metabolism and perhaps to a reduction of energy metabolism in general when oxygen supply is reduced. The human infant may thus survive anoxic episodes which would be lethal for the adult, but survival entails the risk of permanent damage to the central nervous system.

**Pulmonary respiration.** Although mammalian fetuses often exhibit rhythmic respiration-like movements in utero, this is apparently not a constant phenomenon. Therefore extrauterine respiration probably does not represent the simple continuation of an established process.

Some infants may begin breathing after birth as a result of exposure alone, just as they breathe more deeply, or cry, when further sensory stimuli are applied. Others, whose sensation or responsiveness is dulled by anesthesia, trauma or previous anoxia, may begin breathing only when chemical changes resulting from separation from the placenta reach a certain necessary level. Breathing under these circumstances is often irregular, gasping and of primitive character, but usually becomes more regular, rhythmical and effective as a result of improved oxygenation of the brain.

The first breaths require extra force to

overcome the cohesive state of the moist alveolar surfaces normal in uterine life, so that a negative pressure of 15 to 25 cm. of water may be needed for primary expansion. Since the newborn infant's thorax and diaphragm are capable of producing negative pressures of 40 cm. or more of water, there seems to be a wide margin of safety under ordinary circumstances. Normally, the lungs expand rapidly and completely in the first hour, sometimes with the first few breaths. Although the arterial blood is only about 50 per cent saturated with oxygen at the moment of birth, the level may exceed 90 per cent in most infants within thirty minutes; in almost all infants these higher saturations are attained within three hours.

Respiration in the neonatal period is normally accomplished by the diaphragmatic and abdominal musculature, with little thoracic movement. It is characteristically irregular, in both depth and frequency, and in normal infants may assume "cogwheel" or periodic patterns suggestive of pathologic states. Table 49 gives certain approximately normal mean values by which the breathing of the newborn infant can be compared with that of the adult. It will be noted that vital capacity and tidal volumes are roughly similar per unit of body weight. Minute volume and work of respiration in the infant are much greater per kilogram than in the adult, but are in keeping with the metabolic needs of the infant. The infant's heat production of 46 calories per kilogram per twenty-four hours, in contrast to twenty-three in the adult, is largely an expression of surface area differences (p. 290).

In the premature infant, weakness of the thoracic cage and respiratory muscles, incomplete development of alveolar structures, as well as elastic tissue and capillaries in the lungs, and feeble gag and cough reflexes all introduce added difficulties in the onset and

**Table 49. Adult and Neonatal Respiration**  
(Compared with Reference to Weight and Normal Heat Production)

	Actual (Mean)		Per Kilogram		Per 100 Cals.	
	Adult (70 kg.) (1600 Cals.)	Infant (2.5 kg.) (115 Cals.)	Adult	Infant	Adult	Infant
Vital capacity in ml.	4,800	140	68	56	300	120
Minute volume in ml.	6,000	500	85	200	370	435
Tidal air in ml.	500	15	7.1	6	31	13
Rate/minute.	12	34	(12)	(34)	(12)	(34)
Work (gm. cm./min.)	17,000	1,500	240	600	1,060	1,300

maintenance of respiration. The oxygen saturation of the arterial blood tends to be slightly lower in premature than in full term infants, even under normal circumstances. At usual saturations of 89 to 94 per cent, periodic breathing is more common than regular breathing. The momentary apnea associated with such periods may produce intermittent cyanosis. If the atmospheric oxygen is increased, there is usually increased ventilation and conversion of periodic to regular breathing. The explanation of this change is not known, nor is this regularization of breathing in itself an indication for oxygen administration if apneic spells can be terminated by gentle physical stimuli. It may be wiser to use oxygen only when nothing else will relieve cyanosis, and then only in the least effective concentration.

**Circulation.** The mechanics and timing of alterations in the human fetal circulation at birth are matters of dispute, although studies with roentgen cinematography have shown how these adjustments occur in other mammals.

In the fetal sheep oxygenated blood entering the right atrium from the inferior vena cava crosses through the foramen ovale into the left atrium with little admixture of venous blood from the superior vena cava. This oxygenated stream goes from the left ventricle into the ascending aorta and thus to the head and upper extremities. The larger part of the blood leaving the right ventricle appears to enter the descending aorta through the ductus arteriosus.

The major peripheral changes at birth are (1) the increased resistance beyond the descending aorta, (2) the decreased return through the inferior vena cava to the right atrium (both resulting from the removal of the placental circuit), and (3) the sudden decrease in resistance beyond the pulmonary artery as the lungs expand in breathing. The resultant relatively increased pressure in the left side of the heart tends to cause closure of the valve covering the foramen ovale. The muscular wall of the ductus arteriosus apparently constricts promptly (perhaps because of a local sensitivity to increased oxygenation of its blood), but the constriction may be incomplete for hours or days. Flow of blood through the temporarily persisting ductus may occur in either direction, depending upon changing pressure relationships. Murmurs are said to be absent in such infants even though the oxygen saturation and pressures measured at cardiac catheterization indicate considerable flow through the ductus. Exactly when and why complete constriction

occurs is not known; the anatomic closure of the ductus does not take place till the second or third month after birth.

Separation from the cord and placenta at birth removes about 100 cm. of vascular channels from the circulatory system. As a result, the heart has less work to do after than before birth, so that it does not grow so fast as the body in the first months of life. Thus standard relationships of cardiothoracic diameters cannot be applied to roentgenograms of the newborn infant. The fetal circulation involves at least as much work by the right ventricle as by the left, so that a right ventricular preponderance is a normal electrocardiographic finding.

Variability of the *pulse rate* is a characteristic of the newborn infant. For a few minutes after birth the average rate may be 150 to 180 per minute, but within an hour falls to 130 to 140, which remains the average for several weeks. During minimal activity the heart may beat as slowly as 80 per minute; during crying and exercise, more rapidly than 180 per minute.

Measurements of the *blood pressure* (see p. 822 for technique) differ with the method of registration. By auscultation mean systolic/diastolic readings at birth are 80/46 mm. of mercury; at one day, 85/40; and at ten days, 100/50. The mean systolic pressures measured by palpation are 10 to 15 mm. of mercury less, and by the "flush" method the readings are still lower.

Acceptable data regarding *circulation time* are still lacking. The *blood volume*, usually between 7.5 and 8.5 per cent of body weight at birth, may be slightly higher if the cord was not clamped until pulsation ceased or if blood from the cord was stripped toward the infant before clamping. Apparently 75 to 100 ml. of blood may be conserved for the infant by this procedure. Since the blood volume is rapidly readjusted by extrusion of excess plasma after birth, the result is a higher hematocrit value rather than a blood volume appreciably greater than that of infants whose cords were tied at once. There is no clear evidence that the gain or loss of this placental blood is of benefit in the newborn period. Its greatest effect may be upon the infant's store of iron, and thus not demonstrable until two or three months after birth.

**Peripheral circulation and capillary resistance.** The peripheral circulation of normal newborn infants is sluggish. The hands and feet are often cyanotic from the local stagnant anoxia even when arterial oxygen content is



normal, and local stagnation with seepage of plasma through capillary walls may explain the concentration of cells in heel- or finger-prick blood. Such samples may contain 10 to 20 per cent more cells and hemoglobin than those simultaneously obtained by venipuncture.

The capillaries of the skin are more coarse and profuse than those of the adult until several weeks after term birth, yet their resistance is relatively high. Petechiae appear when the skin of a premature infant of 1 kilogram (2.2 pounds) is subjected to negative pressure of about 150 mm. of mercury. Premature infants of 2 to 2.5 kilograms (4.4 to 5.5 pounds) do not show evidence of capillary rupture at negative pressures below 400 mm. of mercury, and the capillaries of "mature" infants weighing 3 kilograms (6.6 pounds) withstand 500 mm. negative pressure. The resistance appears to decline after birth to a critical pressure between 250 and 400 mm.

The susceptibility of the premature infant to hemorrhage is presumably caused by the increased fragility just mentioned, by vascular permeability associated with occasional anoxia, and by impairment of the clotting mechanism, as from inadequate conversion of vitamin K to prothrombin by the immature liver.

**Blood Formation.** The morphology of the blood during neonatal life is described on page 922. The hemoglobin and erythrocyte values rise slightly during the first two days. Readjustment of blood volume is partly responsible for this increased concentration, but the reticulocytosis (3 to 6 per cent) and the occasional nucleated red blood cells normally present indicate that blood formation is active. After the second day, concentrations of hemoglobin and erythrocytes decrease, especially during the second and third weeks after birth. The hemoglobin falls more rapidly than does the erythrocyte count.

**Icterus Neonatorum and Hepatic Function.** About 50 per cent of all newborn infants become visibly jaundiced. This physiologic icterus usually appears on the second or third day of life, regresses by the seventh, and disappears by the fourteenth. The excess pigment responsible for such jaundice has not passed through the hepatic cells and gives the "indirect" or "delayed" reaction in quantitative measurement of serum bilirubin. Since its concentration is already slightly elevated in the cord blood and reaches its peak by the third to fifth day, before the erythrocyte

count has begun its most rapid fall, the hyperbilirubinemia of physiologic icterus apparently results from impairment of bilirubin removal rather than an increase in the amount to be removed.

It now appears that many instances of jaundice presumed to be physiologic are actually the result of pathologic hyperbilirubinemia. Data formerly accepted as indicating the range of serum bilirubin concentrations encountered in physiologic jaundice therefore require revision. Even the accepted concept that icterus neonatorum is especially common after premature birth and the inference of "physiologic hepatic immaturity" await such revision. Tests of hepatic function in newborn infants have not demonstrated much impairment, even after premature birth. There is a slower clearance of sulfobromophthalein by newborn premature than by newborn term infants, and the relative hypoproteinemia, hypoprothrombinemia and hypoglycemia of the premature infant all suggest imperfectly developed hepatic functions not otherwise demonstrable.

**Digestive Tract.** After delivery the digestive tract of the newborn infant is rapidly converted to an actively functioning system. This transition is enhanced by a relatively large absorptive surface, with numerous secretory glands, and a relatively thin and lax muscular coat. This latter feature favors distention, which may be induced by the swallowing of large quantities of air, which begins at birth. The usual advance of air to the descending colon within the next three hours makes its roentgen demonstration diagnostically useful in suspected intestinal obstruction. Food moves relatively slowly through the upper gastrointestinal tract, portions of a single feeding often remaining in the stomach as long as eight hours, but material may traverse the entire large bowel of the newborn in two to four hours.

With the exception of amylase, *enzymes* are present in the gastrointestinal canal early in fetal life. The pH of gastric contents at birth is in the range of neutrality, but between five and twenty-four hours after birth the reaction becomes remarkably acid, with an average pH of about 1.5. After this the acidity decreases to a temporary low level which is reached between the first and second weeks of life.

The intestinal tract at birth contains from 60 to 200 gm. of greenish-black viscid material known as meconium. It contains relatively little nitrogen, most of which is non-

Table 50. Approximate Caloric Requirements of Premature and Term Infants after the First Week of Life

Daily Caloric Requirements per Kg. of Body Wgt.		
Individual Factors	Premature Infants	Term Infants
Basal metabolism.....	60	50
Specific dynamic action and activity.....	10	20
Total catabolism.....	70	70
Fecal loss.....	20	10
Maintenance.....	90	80
Weight gain.....	30	20
Total.....	120 (55/lb.)	100 (45/lb.)

protein, some lipids and, as the largest component, a mucopolysaccharide. In infants who are secretors of the specific polysaccharides of the A and B blood groups, the meconium contains these substances in high concentration. Meconium is apparently largely composed of the residue of mucous secretions of the fetal digestive tract after their digestion by the proteolytic enzymes. Passage of meconium from the rectum usually begins during the first ten hours, and most meconial characteristics disappear from the stools by the fourth day after birth. There may then be a few greenish, moist, "transitional" stools before the defecations become characteristic of infancy.

The digestion and assimilation of proteins and simple sugars are efficiently performed by both term and premature infants. Higher carbohydrates such as starches are not well digested, owing to insufficient enzymes. Fats seem to be digested without difficulty, but absorption of split fats appears to be relatively inefficient. The premature infant may absorb a higher percentage of fat from human than from cow's milk. The nutrition of premature infants is hampered by some degree of impaired assimilation and by their relatively rapid growth.

**Metabolism.** The surface area of the newborn infant is large in comparison to his weight, so that the *basal metabolism* per kilogram is higher than that of the adult. By the more applicable standard of surface area, the average infant's heat production is about 25 calories per square meter per hour during the first week of life. Corresponding figures for the child of two years and for the adult are, respectively, about 48 and 38 calories. An

increase of 10 to 20 per cent in heat production occurs by the end of the first month as more calories are added to the basal requirements for the needs of growth. There are inadequate data concerning the metabolism of premature infants during the first week of life, but beyond that age their heat production is usually lower per unit of surface area than that of term infants.

The limited data available on measurements of the *respiratory quotient* provide only an indication of the pattern of caloric combustion. The higher respiratory quotients usually found immediately after birth suggest that the fetus obtains energy mainly, if not entirely, from carbohydrate. Within the first few hours the metabolic mixture appears to be about two-thirds carbohydrate and one-third fat, but by the second day it consists entirely of fat. Apparently the available glycogen is rapidly consumed. After maternal lactation has become sufficient for weight gain, or by the sixth or seventh day, fat becomes the source of about 60 per cent of energy, and carbohydrate of 40 per cent. This sudden utilization of fat in early postnatal life is accompanied by large increases in concentration of the blood lipids. The few data from premature infants suggest that after the first week or two, relatively more of their energy comes from carbohydrates than is the case with infants born at term.

The *caloric requirements* of premature and term infants in general are lower in the first week of life than after postnatal growth has been established (see Table 50).

The relatively large surface of premature infants, the low heat production, their inactivity and the lack of subcutaneous fat resulting in poor insulation contribute to a tendency toward hypothermia. Conversely, the immature sweating mechanisms of the premature infant favor hyperthermia in overheated environments or when the escape of body heat is prevented by too many wrappings. An unsettled question of importance is whether body temperature of 37° C. (98.6° F.) is of greater advantage than stabilization at a somewhat lower level. A lower requirement for oxygen at reduced body temperatures is a theoretic possibility, but has not been proved. Nevertheless the satisfactory clinical status of many small premature infants maintained with rectal temperatures of 35° C. (95° F.), or even lower, has been demonstrated repeatedly.

**Acid-Base Balance.** In both term and premature infants perhaps the outstanding char-



acteristics of acid-base balance are the wide ranges of blood hydrogen ion content and of concentrations of related plasma components, and the tendency toward a metabolic acidosis. These features are more pronounced and tend to persist longer in premature infants than in term ones. Concentrations of chloride ions and of other strong acid radicals may be increased in the plasma. Whether unusual accumulations of lactic and pyruvic acids resulting from incomplete glucose metabolism ("anaerobic metabolism") account for all the increase of strong acids remains to be established. If this were so, it would indicate that the metabolic pattern of the fetus persists for some time, particularly after premature birth. Whatever the explanation for the slightly lowered pH of the blood in infants born at term, the acquisition of a normal pH within twenty-four hours indicates that the initial metabolic acidosis is promptly compensated by adjustments which may be both renal and respiratory; this compensation does not occur so quickly in infants born prematurely. Since low pH levels are regularly observed in premature infants in apparently satisfactory clinical condition, there is no proof that this chemical status is harmful.

**Water balance and renal function.** The infant's body contains relatively more water at birth than in later infancy. Since the degree of hydration is still greater in earlier fetal life, many small premature infants are obviously edematous at birth. The relatively high content of sodium as compared to that of potassium in the body of the newborn and fetus suggests a large extracellular fluid space. The physiologic weight loss of 6 to 10 per cent of body weight during the three to five days after birth is accounted for in part by loss of vernix from the skin and of meconium from the bowel, and by metabolism of body stores of glycogen, fat and protein, but the largest factor is loss of body water. Infants who receive no fluid for three days after birth may lose more than 10 per cent of body weight. Loss of so much water may be accompanied by hemoconcentration, which may not be harmful and is promptly rectified by the administration of fluid on the fourth day.

Since adults similarly deprived of fluid conserve enough body water by secreting a urine of high concentration to prevent hemoconcentration, the larger water loss of the newborn infant is an example of one limitation in renal function. The maximum concentration of urine (about 700 milliosmols per liter) is apparently no greater in term than

in premature infants, and increase in this function is more closely related to postnatal than conceptional age. Since the food of infants is fluid, this limitation in renal concentration during the first two to four weeks after birth is not of critical significance under usual circumstances, though it assumes great importance in diseases accompanied by excessive loss of body water and in the application of therapy to their repair. Conversely, the kidney is able to excrete an excessive load of water by dilution of the urine.

The more specific tests of renal function measuring glomerular filtration rate, renal plasma flow and tubular excretion have provided data perhaps more interesting to the renal physiologist than applicable by the clinician. In general, these functions are all reduced in the term infant and somewhat further reduced in the premature one. Performance comparable to that of the adult kidney appears to be reached a year or two after birth. But the bases for comparison of data from infants and adults are undetermined; if referred to surface area, there is a wide scatter of the data obtained from normal infants at any age, many measurements being within the adult range. The responses of infants less than one month of age to such tests generally show further limitation of function, but with no less scatter, and there is considerable overlap of the results from premature and term infants. Hence the guidance of the laboratory in the diagnosis and therapy of newborn infants with suspected renal impairment is limited. Even the blood concentrations of nonprotein and urea nitrogen are difficult to evaluate in the first week or two after birth, since their levels normally vary with protein and water intake. During the "hydropenia" of the second or third day after birth, concentrations of 60 and 30 mg. per 100 ml., respectively, may be attained. The general belief that albumin is normally present in the urine of newborn infants is probably based on falsely interpreted tests. A relatively high percentage of nitrogen in the infant's urine is in the uric acid fraction; it may be deposited as "uric acid infarcts" in the kidneys and as pink urates on the diaper.

**Endocrine Glands.** Endocrinologic alterations accompany the transition from a dependent intrauterine status to an independent extrauterine one. Not only must the glands of the infant take over new responsibilities, but also there are actual and potential effects from *maternal hormones*. These may persist

after placental transmission (and production), or the infant may react to the sudden release from their influence. Most infants of both sexes have hypertrophy of the breasts during the first week of life, and many have some secretion of so-called witch's milk. These changes, observed less frequently in prematures, are apparently due to two hormones. The first appears to be an estrogenic substance of placental and ovarian origin, which produces the mammary hypertrophy and is also responsible for other changes such as hypertrophy of the vulvar tissues, vaginal discharge and desquamation, and occasional uterine bleeding in female newborn infants and transitory prostatic metaplasia in males. The second hormone, prolactin, comes from the anterior pituitary and is responsible for the temporary lactation in the infant, but whether its source is the mother's or the infant's pituitary is not known.

The *adrenal glands* are proportionately much larger at birth than at any time thereafter, representing 0.2 per cent of total body weight as compared to 0.01 per cent of adult body weight. The enlargement is almost entirely in the inner cortical zone. Involution of this tissue begins immediately after birth, reaching its height in the second week, but continuing for a period variously estimated to be two weeks to a year. This involution has been interpreted as a discarding of a "masculinizing" or androgenic tissue developed to protect the fetus against the rising tides of maternal and placental estrogens, but there is no elevation of 17-ketosteroid excretion in the urine of newborn infants to support this hypothesis.

Little is known about the various activities of the *pituitary gland* in the newborn infant, but less oxytocic and antidiuretic activity can be obtained from glands removed from newborns than from those of adults. The *thyroid gland* is well developed at birth, is normally somewhat hyperemic and contains adequate colloid. Its secretion is apparently provided to the fetus for several months before birth and perhaps may be available to the mother if her supply of thyroid hormone is deficient. Maternal thyroid hormone may also cross the placenta, since the clinical cretinism of athyrotic infants may be masked for some time after birth.

The *parathyroid glands* and the islet cells of the *pancreas* have received less attention in regard to their characteristics in neonatal life than in regard to the fetal-maternal in-

terchange of hormones in utero. Although there may be a transient hypoparathyroidism, the temporary increase of serum phosphate and decrease of serum calcium in newborn infants may be related to renal as well as to parathyroid factors. The islet tissue content of the pancreas of newborn infants is variable. Peculiarities of insulin secretion have not been discovered, although it has been supposed that an increased production occurs in the offspring of diabetic women as a result of fetal exposure to hyperglycemia. Passage of either parathyroid hormone or insulin between the human mother and her fetus has not been demonstrated, but from observations on other mammals may be presumed to occur.

**Immunity.** Although the newborn infant acquires certain antibodies by placental transfer, resistance to infection is generally weak and infectious processes are poorly localized. It is possible that the production of antibodies is less efficient than in the older person, although this apparent disability may be associated with the presence of transient passively acquired immunity rather than the immaturity of immunologic response mechanisms per se. In human beings the transplacental acquisition of antibodies is much greater than their ingestion in colostrum and mother's milk.

Present knowledge of specific infectious agents and of immunologic responses can be summarized as follows:

1. Antibodies to diphtheria, tetanus and the viruses of measles, mumps and smallpox, and probably those of poliomyelitis and the common cold, will, if present in the mother, pass the placenta in sufficient quantity to exert a passive protective effect of some degree but brief duration. In the prematurely born infant less reliance can be placed on the effectiveness of such protection.

2. To several common infectious agents the newborn infant appears to receive no transplacental immunity, and even to have a special susceptibility. These include *H. pertussis*, streptococci, staphylococci and such organisms as *E. coli* which do not ordinarily cause disease in older persons.

3. Certain viruses and bacteria which cause severe diarrheal disease among newborn infants apparently either are not pathogenic for older persons or produce in them different and relatively less severe manifestations.

4. The standard immunization procedures may result in slightly less rapid antibody pro-



duction if begun during the first two months after birth (see p. 141 for schedule for immunization).

5. Protection of newborn infants from contact with infection is a more reliable means for the prevention of disease than dependence upon transplacental immunity or upon antimicrobial prophylaxis. Since infec-

tion in newborn infants may not only be relatively inapparent, but also easily transmitted, such prevention of contact with infection must be directed against contact with other infants as well as adults.

CLEMENT A. SMITH  
R. J. MCKAY, JR.

## THE HISTORY IN NEONATAL PEDIATRICS

The medical history of the neonate should (1) be aimed at uncovering factors which may lead to early identification of diseases in which disability or mortality may be prevented by prompt treatment, (2) lead to the anticipation of conditions which may be of importance later to the infant, and (3) uncover possible etiologic factors which may help identify and explain to parents any pathologic condition regardless of its immediate or future significance. Parents are reassured as to the competence and interest of their child's physician when he diagnoses inapparent disease in the newborn period and when he offers explanation for apparent disease.

Although ideal, it is impossible under ordinary circumstances to take the time to record a detailed family history, including that of the pregnancy, on every newborn infant. It should be obtained, however, whenever there is any untoward circumstance in the newborn or any known familial disease, and it should be routine in all instances to inquire about the existence of genetically determined disease.

**Genetic Factors.** Congenital anomalies, inborn errors of metabolism, certain endocrinopathies and a variety of specific disease states identifiable in the newborn period are or may be genetically determined.

Their occurrence in siblings or direct ancestors should suggest the possibility of the same defect in the newborn infant. Since most of these conditions are not immediately obvious on physical examination, they may be missed unless a careful history is obtained. Because many parents are aware not of the name or existence of these genetically determined diseases, but only of one or more of their manifestations, specific inquiry should be made about any disease affecting more than one blood relative. (See Prenatal Factors in Disease, p. 234; Inborn Errors of

Metabolism, p. 250; Diseases of the Blood, p. 930; The Genitourinary System, p. 1005; Mental Deficiency, p. 1129; The Nervous System, p. 1063; The Endocrine System, p. 1150; Diabetes Mellitus, p. 1205; The Bones and Joints, p. 1226; The Muscles, p. 1264; The Skin, p. 1274; The Eye, p. 1329; and Allergy, p. 1304.

**Maternal Factors.** *Maternal age* is a factor in fetal and neonatal mortality. The lowest neonatal mortality rate (about 2 per cent) occurs in infants of mothers twenty to thirty years of age; it is almost doubled if the mother is forty to forty-five years, and quadrupled if she is forty-five and over. The neonatal mortality is also high if the mother is less than fifteen years of age.

*Maternal illness* early in pregnancy, while the embryo is undergoing organogenesis, can result in serious maldevelopment (see p. 242). Severe illness or trauma at any time during pregnancy may cause fetal death or premature onset of labor. Certain maternal infections, notably syphilis, toxoplasmosis and Coxsackie virus group B, may infect the fetus. Maternal diabetes (perhaps even in the prediabetic state), and possibly paternal diabetes, may affect the fetus and infant profoundly (p. 1214). The dangers of incompatibility between maternal and fetal blood groups are discussed on page 956. Platelet antibodies associated with maternal thrombocytopenic purpura may be transferred across the placental membrane to cause transient platelet deficiency in the infant. Likewise, transient neonatal myasthenia gravis may be seen in the infants of mothers with the disease without apparent relation to the severity or degree of control of the maternal myasthenia. Drug addiction by the mother may result in alarming withdrawal symptoms in the infant such as tremors and convulsions. Maternal hyperthyroidism may result in a transient hyperthyroid state of the

infant. The toxemias of pregnancy presumably disturb the infant directly and also indirectly by influencing obstetric management. The direct effects appear to be related to an intrauterine anoxia associated with placental infarction, separation and hemorrhage rather than to any toxic substance reaching the fetus. Lactation tends to be less successful after delivery in the toxemic woman. The incidence of prematurity, stillbirth and neonatal deaths is twice as great in infants from toxemic mothers as in those born to healthy ones.

*Obstetric factors* are of understandable importance when one considers that neonatal mortality is greatest during the first twenty-four hours after delivery. Rupture of membranes earlier than twenty-four hours before delivery carries a risk of infection of the intrauterine contents which may justify antibacterial treatment of the infant. Prolonged labor definitely increases the "risk of being born." The risk of neonatal death in uncomplicated labors lasting twenty-four hours or less is approximately 0.32 per cent; it increases sixfold in labors lasting over twenty-four hours, and twentyfold, to 6 per cent, in those over thirty hours. A tumultuous short labor, with a precipitate delivery, is also unfavorable for the infant. Placental separation, abnormal implantation or compression of the cord increases the possibility of fetal anoxia. Fused placentas in multiple pregnancies may considerably affect the circulation and general development of the fetus.

Some information of diagnostic value may be obtained from the type and amount of amniotic fluid. A brown or muddy fluid suggests that meconium has been passed during an episode of fetal anoxia. Polyhydramnios may occur with toxemia and maternal diabetes or for unexplained reasons; its presence should also suggest the possibility of interference with fetal swallowing, as by an esophageal atresia. Conversely, congenital aplasia or hypoplasia of the infant's kidneys is often accompanied by a reduced amount of amniotic fluid, presumably because fetal urine has not been formed.

Although the relative danger of any type of delivery, normal or operative, depends upon the skill of the obstetrician, statistics show that an increased hazard accompanies certain methods. Obviously, this results not only from the method, but also from the accompanying circumstances which dictated its use. The study from Chicago by Bundesen, Potter

**Table 51. Neonatal Mortality Rate per 1000 Live-born Infants by Various Methods of Delivery**

Spontaneous vertex delivery . . . . .	24.7
Low forceps . . . . .	7.9
Mid and high forceps . . . . .	29.7
Cesarean section . . . . .	35.7
Breech extraction . . . . .	39.6
Version and extraction . . . . .	118.2
Total mortality rate by all methods of delivery	21.5

and others showed a neonatal mortality rate per 1000 live-born infants as above.

Neonatal deaths following deliveries by mid and high forceps, breech extraction and version are likely to be related to intracranial injury; those following other forms of delivery are more apt to be due to anoxic disturbances.

Infants born by cesarean section present problems which may be related to the unfavorable obstetric circumstance which necessitated the operation or to prolonged maternal anesthesia. The impression prevails, however, that even in the absence of these factors, delivery through the abdomen carries a greater risk than delivery through the birth canal. Though the neonatal mortality from elective cesarean sections performed at term by a skilled obstetrician with an experienced anesthetist is extremely low, occasional deaths do occur. Hyaline membrane syndrome (p. 324) is the condition most frequently associated with an unfavorable outcome. Moreover, perhaps 5 per cent of infants so delivered have some degree of respiratory difficulty for a day or two after birth. The infant delivered by cesarean section should be kept under close observation during the first few days of life.

Anesthesia and analgesia affect the fetus as well as the mother. The skilled use of these agents consists in avoiding severe fetal narcosis while securing the benefits of gentle and unhurried delivery. Even skilled use often results in a mildly depressed infant whose crying and breathing may be delayed a minute or two and who may be somewhat inactive for several hours. Such infants are of less concern than those in whom an apparently similar status has been produced by central nervous system impairment from anoxia or trauma. When anesthesia and analgesia are carelessly used, or when their milder effects are added to already unfavorable fetal circumstances such as prematurity, anoxia or trauma, the consequences are clearly dangerous.



Finally, a vaguely understood but real factor in the maternal history is known under the loose term of "reproductive inefficiency." Some women do not easily become pregnant. They, and others, frequently abort spontaneously in early pregnancy or carry infants to a later unexplained intrauterine death, to pre-

mature or to postmature birth. Any newborn infant whose mother has such an unfavorable background should receive careful medical attention, since an increased likelihood of neonatal morbidity and mortality is one more evidence of what is termed reproductive inefficiency.

## THE PHYSICAL EXAMINATION IN NEONATAL PEDIATRICS

The purposes of the initial physical examination of the newborn as soon as possible after delivery are twofold: to detect abnormalities and to establish a baseline for subsequent examinations. Since examination in the mother's presence affords an ideal opportunity for initiating the anticipatory guidance which should be an integral part of all periodic health examinations, a second one should be performed twelve to twenty-four hours later when she has had a chance to rest from the rigors of her labor. At this time even minor anatomic variations which seem insignificant should be explained, because the mother may be disturbed if she has to point them out or if the physician does not appear to give them adequate consideration. This procedure carries the possibility of unduly alarming otherwise unworried parents unless it is carefully and skilfully done. No infant should be discharged from the hospital without a final examination, since certain abnormalities, particularly heart murmurs, frequently appear or disappear in the immediate neonatal period, or there may be evidence of acquired disease. Pulse and respiratory rates, weight, length, head circumference and dimensions of any visible or palpable structural abnormality should be recorded at these three examinations.

Many of the physical and behavior characteristics of the newborn infant are described on page 28 and many physiologic attributes on page 286. These sections should be consulted before reading this one, for repetition has been avoided so far as possible.

The examination of the newborn infant requires patience, gentleness and flexibility in standard routines of procedure. Thus, if the infant is quiet and relaxed when first approached, palpation of the abdomen or auscultation of the heart may best be introduced before other more disturbing manipulations.

The **general appearance** of the infant tells much. Physical activity may be absent in the relaxation of normal sleep or depressed by central disturbance; the infant may be lying with motionless extremities because all his energies are conserved for the effort of difficult breathing, or he may be vigorously crying with accompanying activity of arms and legs. Coarse, tremulous movements with ankle or jaw clonus are more common and of less significance in newborn infants than at any other age. Such movements tend to occur when the infant is active, whereas convulsive twitchings usually occur in an otherwise quiet state. Nutritional status is evidenced by weight and length and by wrinkling or plumpness of the body surfaces. An appearance superficially suggesting good nutrition may be produced by edema, frequently present in premature infants. There may or may not be pitting after pressure, but the fingers and toes will lack the normal fine wrinkles over the knuckles because they are puffed out with fluid. Edema of the eyelids is a common result of irritation from silver nitrate.

**Skin color** is important. Vasomotor instability and sluggishness of peripheral circulation are revealed by deep redness or purple lividity in the crying infant, whose color may darken profoundly with the closure of the glottis preceding a vigorous cry, and by the harmless cyanosis of the hands and feet, especially when these are at all cool. Mottling is another example of general circulatory instability. An extraordinary division of the body from forehead to pubis into a red half and a pale half has been aptly named a *harlequin color change*. This is transient, apparently harmless, and inadequately explained. Significant cyanosis may be masked by pallor in circulatory failure; on the other hand, the relatively high hemoglobin content of the first few days and the thin skin may combine to produce an appearance of cyanosis when the

arterial oxygen saturation is adequate. Localized cyanosis is differentiated from ecchymosis by the momentary pallor which follows pressure. The same maneuver is also helpful in demonstrating icterus, which may be of considerable degree, but pass unnoticed if the skin is suffused with blood.

The vernix and lanugo hair are described elsewhere (p. 29), as are the common transitory capillary hemangiomas of the eyelids and neck (p. 1274). Slate-blue, well demarcated areas of pigmentation are seen over the buttocks, back and sometimes other parts of the body in about half of all Negro infants and occasionally in white ones. These have no certain anthropologic significance in spite of their designation as mongolian spots; they tend to disappear within the first year. The vernix, skin and, especially, the cord may be stained a brownish-yellow if the amniotic fluid has been colored by passage of meconium during or before birth, usually because of intrauterine anoxia. The skin of the premature infant is thin and delicate and tends to be deep red; in extreme degrees of prematurity the appearance is almost gelatinous. The nails are rudimentary at very premature birth; conversely, they may protrude beyond the finger tips in infants born past term.

The skull may be molded, particularly if the infant is the first born and if the head has been engaged for a considerable time. The parietal bones tend to override the occipital and the frontal bones. The head of an infant born by cesarean section or from a breech presentation is identified by its characteristic roundness. The suture lines and the size and tension of the anterior and posterior fontanels should be determined digitally. There is much variation in the size of the fontanels at birth; if small, the anterior fontanel usually tends to increase during the first few months of life. Soft areas (craniotabes) which have the resilience of a ping-pong ball are occasionally found in the parietal bones at the vertex near the sagittal suture; they are usually inconsequential, but, if they persist, should be differentiated by roentgenographic examination from lacunar skull (p. 1230) and from other causes of craniotabes. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, cretinism and occasionally mongolism. Transillumination of the skull in a dark room will rule out hydranencephaly (p. 1093) or porencephaly (p. 1075).

The face may be asymmetric from fetal posture (p. 1250); when the jaw has been held against a shoulder or an extremity during the intrauterine period, the mandible may deviate strikingly from the midline. The skull of the premature infant may suggest hydrocephalus because of the relatively larger brain growth as compared to that of other organs. The eyes are often opened spontaneously if the infant is held up and tipped gently forward and backward. This is undoubtedly a result of labyrinthine and neck reflexes. This maneuver is more successful than that of forcing the lids apart to inspect the eyes. Focus and equality of pupils are normally established some weeks after birth. Conjunctival and retinal hemorrhages do not by themselves have serious significance. Deformities of the pinna of the ears are seen occasionally. Unilateral or bilateral preauricular papillomas occur fairly frequently; if pedunculated, they can be ligated tightly at the base, and dry gangrene and slough will result. The tympanic membrane is easily visualized otoscopically through the short, straight external auditory canal and is normally dull in appearance. There may be a slight obstruction of the nose from an accumulation of mucus in the narrow nostrils. The mouth may rarely show precocious dentition, with supernumerary teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt. Premature eruption of deciduous teeth is even more unusual. On the hard palate on either side of the raphe may be temporary accumulations of epithelial cells called Epstein's pearls. Retention cysts of similar appearance may also be seen on the gums. Both disappear spontaneously, usually within a few weeks of birth. Clusters of small white or yellow follicles or ulcers on an erythematous base may be found on the anterior tonsillar pillars, most frequently on the second or third day of life. Their cause is unknown, and they clear without treatment in two to four days. There is no active salivation. The throat of the newborn infant is hard to visualize because of the arch of the palate; this, however, should be clearly visualized because of the possibility of easily missed clefts of the posterior palate or uvula. The small tonsils give no clue to the size to be attained during later lymphoid tissue growth. The tongue appears relatively large; the frenulum may be short, but rarely, if ever, is this a reason for cutting it. Occasionally the sublingual mucous membrane forms a prominent fold. The cheeks have a fullness on both



the buccal and the external aspects due to the accumulation of fat which makes up the sucking pads. These pads, as well as the labial tubercle on the upper lip, disappear when the suckling days are over. The neck appears relatively short. Abnormalities are not common; they include goiter, cystic hygroma, branchial cleft rests and lesions of the sternocleidomastoid muscle, which are presumably traumatic (p. 1264).

Almost as much can be learned about the lungs by observation of breathing as by auscultation and percussion. Variations in rate and rhythm are characteristic. The rate may vary from 20 to 100 times a minute in normal infants, depending largely on their physical activity, state of wakefulness or presence of crying. However, the pattern of fluctuations of the rate measured while the infant is quiet carries prognostic significance. Miller divides newborn infants into three groups, depending on the trend of their resting respiratory rates (see Table 52). The premature infant may normally breathe with a Cheyne-Stokes rhythm or with complete irregularity, but, in any stage of maturity, irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, strongly indicates serious impairment of respiratory centers. The breathing of newborn infants is almost entirely diaphragmatic, with the result that the soft front of the thorax is commonly drawn inward during inspiration and the abdomen simultaneously protruded. If the baby is quiet, relaxed and of good color, this "paradoxical movement" is not necessarily a sign or a cause of insufficient ventilation. On the other hand, labored respiration is important evidence of abnormal pulmonary ventilation, pneumonia or other mechanical disturbance of the lungs. The interspaces usu-

ally draw in during inspiration when the mechanical difficulty is that of either too much or too little air in the lungs, so that the differentiation between atelectasis and emphysema must be made on the size and shape of the chest and on the percussion note. The weak groaning or whining cry which often accompanies expiration in severe disturbances of respiration is a most unfavorable prognostic sign. A method of "retraction scoring" which, along with the respiratory rate and the presence or absence of cyanosis, affords a convenient gauge of respiratory difficulty in newborn infants is illustrated in Figure 69.

Percussion may be more informative than auscultation, because in the small total area of the lungs breath sounds from an adjoining region may be heard as though directly under the stethoscope. Normally, the breath sounds are bronchovesicular. Suspicion of diminished breath sounds should always be verified by inducing deeper breathing and, if a local area is suspicious, altering the position of the infant's head and body before final decision. This latter maneuver also applies to suspected percussion dullness. The fine, crackling rales of early pneumonia in the newborn may be heard only at the end of the deep inspirations induced by crying.

The size of the heart is estimated with some difficulty, owing to normal variations in the size and shape of the chest. There may be transitory murmurs; conversely, congenital malformations may not at once produce the murmur which will be present later. According to Richards, there is only a 1:12 chance that a murmur heard at birth represents congenital heart disease. Evaluation of the heart by roentgenogram and electrocardiogram is desirable when the possibility of significant

Table 52. First-Week Deaths According to Birth Weight and Respiratory Group\*

Respiratory Group	1001-1500		Birth Weight—Gm.				Total	
	Born	Died	1501-2000		2001-2500		Born	Died
			Born	Died	Born	Died		
I.....	2	0	20	0	104	0	126	0
II.....	2	0	30	0	90	0	122	0
III.....	31	11	42	10	29	2	102	23

Group I: Infants who, while quiet, breathe approximately 40 times a minute from birth on without fluctuations greater than 15 per minute.

Group II: Infants whose respiratory rates are high (usually over 60 per minute) the first hour, show no significant increase after the first hour and subsequently decrease to normal levels, usually within 4 to 48 hours after birth.

Group III: Infants whose respiratory rates show a significant increase (15 per minute or more over the mean for the first hour) during the first 48 hours.

Infants with major anomalies or with hemolytic disease of the newborn were excluded.

\* Adapted from H. C. Miller: Studies of Respiratory Insufficiency in Newborn Infants. Pediatrics, 20:817-26, 1957.

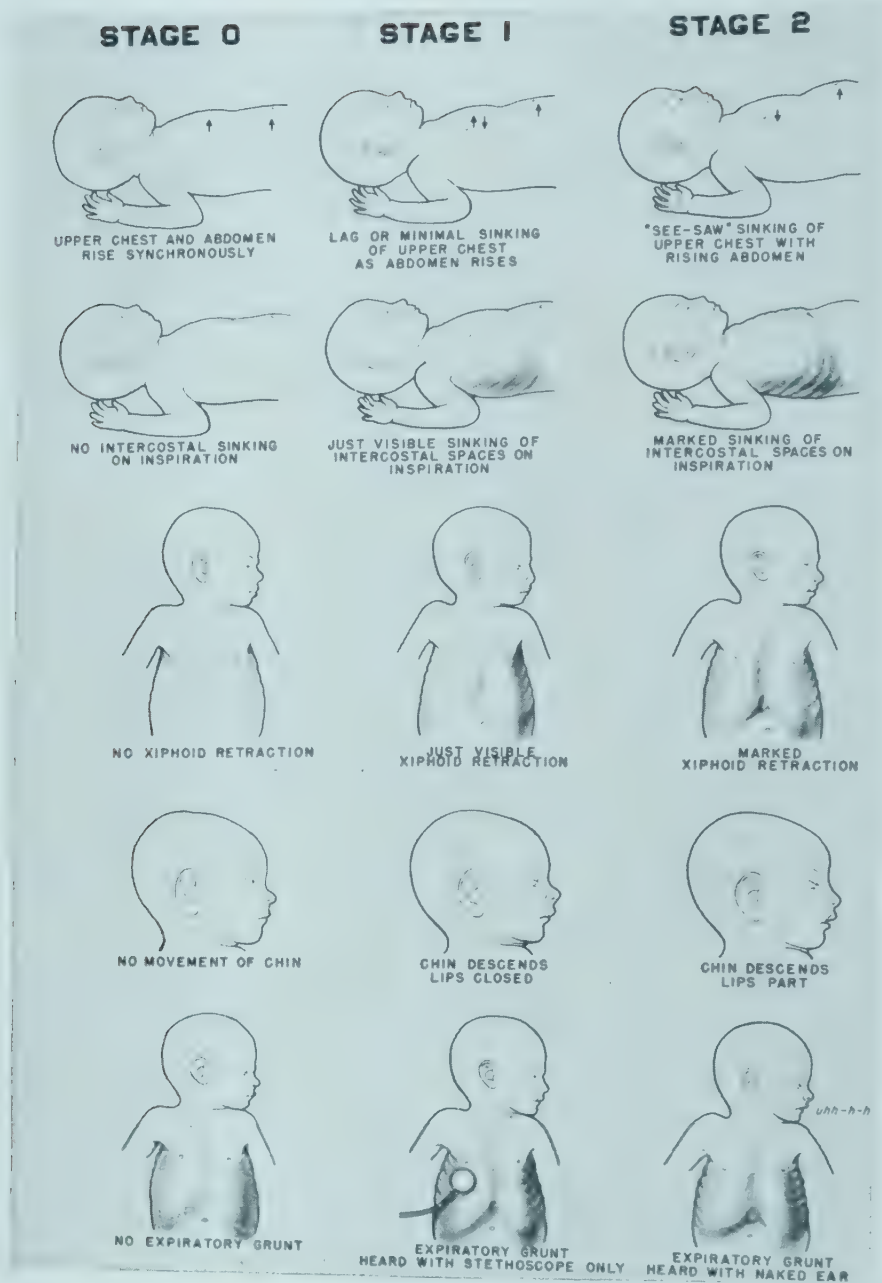


FIG. 69. Retraction scoring. The "retraction score" is computed by adding the values (0, 1 or 2) assigned to each criterion at the time of a single observation. A score of zero indicates no respiratory distress; a score of 10 indicates severe respiratory distress. (Modified from Silverman and Andersen: *Pediatrics*, 17: 1, 1956.)

lesions exists. The pulse may vary normally from 90 per minute in relaxed sleep to 180 during activity. The still higher rate of paroxysmal tachycardia may be counted better on an electrocardiogram than by ear. **Blood pressure** measurements (see p. 288), though technically difficult, are sometimes a valuable diagnostic aid. A cuff of 2.5-cm. (1 inch) breadth is needed for accurate measurement (see p. 822). The balloon should also be long enough to encircle the arm, or decep-

tively high pressures will be recorded. The *auscultatory method* can often be used satisfactorily, provided the stethoscope head is small enough. Currently popular methods are the *palpatory method*, in which the systolic blood pressure is taken to be the point at which the pulse distal to the cuff becomes palpable in the course of deflation, and the *flush method*, in which the extremity is firmly compressed to render it relatively bloodless below the cuff followed by deflation of the



cuff with the systolic pressure recorded at the point flushing appears in the arm and hand below the cuff. Each has the disadvantage that the pulse pressure is not obtained and that the systolic reading is generally less than obtained by the auscultatory method.

In the **abdomen** the liver is usually palpable, sometimes as much as 2 or 3 cm. below the rib margin. Less commonly, the spleen and kidneys may be felt. Unusual masses should be investigated immediately by "flat film" of the abdomen, followed by intravenous pyelography and exploratory laparotomy if their innocent nature cannot be established. Urinary tract anomalies, renal embryoma, ovarian cysts and intestinal duplications are the commonest masses encountered. Abdominal distention at birth suggests meconium ileus. Later it suggests intestinal obstruction due to lower bowel obstruction or peritonitis. Scaphoid abdomen in the newborn suggests diaphragmatic hernia. At no period of life is the air content of the gastrointestinal tract so varied in amount, nor may it be so relatively great under normal circumstances. The abdominal wall is normally weak (especially in premature infants), and diastasis recti and umbilical hernias are common, particularly among Negro infants.

The **genitals** and **mammary glands** normally respond to transplacentally obtained maternal hormones, as described on page 291. The enlargement and secretion of the breasts in both sexes and the prominence of the female genitals, often with considerable nonpurulent secretion, are transitory manifestations requiring observation but no interference. The scrotum is relatively large; its size may be increased by the necessary trauma of breech delivery and also by a transitory hydrocele, which is easily distinguished from a hernia by palpation and transillumination. The testes may be in the scrotum or palpable in the canals, or may not be felt until spontaneous descent, which may not occur until later infancy. The male Negro infant usually has dark pigmentation of the scrotum before the rest of the skin assumes its permanent color.

The prepuce of the newborn infant is normally so tight and adherent that no information can be obtained as to later need for circumcision. Apparent hypospadias or epispadias should always arouse suspicion that the infant is actually a masculinized female with enlarged clitoris, since this may be the

first evidence of the adrenogenital syndrome (p. 1185). Erection of the penis is common and has no significance. Urine is usually passed during or immediately after birth; there may then normally follow a period as long as twenty-four hours without voiding.

Some passage of **meconium** usually occurs within the first twelve hours after birth, but may be delayed until the third or fourth day. Imperforate **anus** is not always visible, and may require the evidence obtained by the examiner's little finger or a rectal thermometer. Inexperienced physicians may mistake the dimple or irregularity of skin-fold often normally present in the sacrococcygeal midline for an actual or potential pilonidal sinus.

In examining the **extremities** the effects of fetal posture (p. 1250) should be noted if for no other reason than that their cause and usual transitoriness can be explained to the mother. The suspicion of a fracture or nerve injury associated with delivery is more commonly aroused by observing the extremities in spontaneous or stimulated activity than by any other means.

Certain **reflexes** are normally observed only in newborn infants. The *Moro reflex* is a startle reaction elicited by jarring the blanket or table on which the infant lies or by clapping the hands loudly near him. There are movements of abduction and adduction; the infant draws up the legs, brings forth the arms as in an embrace, and often begins to cry. The normal infant will show a symmetric response (Fig. 70). In the *tonic neck reflex* the infant assumes a fencing position when the head is turned sharply to either side; the arm and the leg on the side toward which the head is facing are extended and the others flexed (the resting infant in the upper photograph of Figure 70 shows the position). Both these reflexes are indicative of the immaturity of the nervous system of the newborn infant; they disappear after the first few months of life if the mental development of the infant progresses normally. A *grasp reflex* can be elicited in the hands and feet. If the palm of the hand is stimulated by the examiner's finger, the infant's fingers will grasp his finger and hold on firmly. If the sole of the foot is stroked from the heel forward, the toes turn downward.

*Chvostek's sign* and *Babinski's sign* can often be elicited in the newborn infant and at this age are merely another indication of the immaturity of the nervous system. The sucking reflex is active, but the infant lacks



FIG. 70. Moro reflex.

the voluntary buccal phase of swallowing and has only the involuntary pharyngeal and esophageal phases. The *patellar reflex* is present, but the response is variable, owing to difficulty in obtaining relaxation; its apparent absence does not necessarily indicate a pathologic condition. The *abdominal reflexes* are also difficult to elicit; their absence is not necessarily significant. The *corneal* and *pharyngeal reflexes* are active. The *cremasteric reflex* is usually present. The *rooting reflex* is described on page 118.

The pupillary *light reflex* is present, although the response is usually not sustained. The infant can see, but does not have coordinated vision. The sense of taste is present at birth. The infant is able to hear as soon

as the eustachian tube is aerated and the external auditory canal is free from debris. He usually reacts to loud noises by blinking, or may move his eyes or head toward the source of the noise. The infant responds to contact stimuli and cries from pain, exposure or discomfort. The lips are most sensitive to touch; when stimulated, the infant purses his lips and begins to suck. He winks, sneezes, yawns, coughs and hiccups. He can raise his head from the prone position. His grasp may be strong enough to support himself when holding the examiner's thumbs. When placed on his abdomen, he demonstrates suggestive crawling movements and, in water, swimming behavior. When he is held erect, reflex stepping movements are elicited.



## CARE OF THE NEWBORN INFANT

The basic requirements of the newborn infant are immediate assistance at birth, when needed, for the establishment of respiration and subsequent assistance in obtaining adequate nutrition, in maintaining a normal body temperature and in avoiding contact with infection. These requirements should be met in an environment which not only provides constant nursing and medical alertness for any sign of specific illness, but also reduces separation of the infant from his mother to a necessary minimum. The care of full term and premature infants differs only in the degree of emphasis on each of the three general factors. (See page 306.)

**Immediate Care at Delivery.** The infant should be suspended head downward immediately after delivery until the mouth, pharynx and nose have been cleared of fluid, mucus, blood and amniotic debris by gravity and gentle suction with a bulb syringe or soft rubber catheter. Wiping the palate and pharynx with gauze may lead to abrasions and the development of thrush, pterygoid ulcers (Bednar's apthae) or, rarely, to tooth bud infection with maxillary osteomyelitis and retrobulbar abscess formation. The infant should then be placed on his side, head downward, in a bassinet tilted at an angle of about 30 degrees to promote drainage from the respiratory tract for four to eight hours. With possible intracranial hemorrhage following difficult delivery the reverse position may be indicated. As a guide to prognosis and the need for particularly close observation or care in the delivery room and nursery, Apgar has devised a method of scoring which is of practical value (Table 53; Fig. 71). For reasons not clear, the stomachs of infants delivered by cesarean section may contain more fluid than those of infants delivered normally. It has been postulated that regurgitation and aspiration of this fluid may contribute to hyaline membrane disease (p. 324). It is recommended that the stomach be aspirated, preferably before the first breath is taken. If this theory is correct, it would be logical to remove any gastric contents in premature infants by suction, since they have a high incidence of hyaline membrane disease. An additional advantage to this procedure would be the immediate discovery of esophageal atresia if present.

**Resuscitation.** Failure to breathe spontaneously within one minute of birth is an indication for some method of resuscitation. If the central mechanism can be revived, the infant will usually be more effective in ventilating his lungs than will any available machine. When the need for resuscitation results from failure of peripheral rather than of central mechanisms, as in "previable" premature infants, most of whom demonstrate adequate initial function of the respiratory center, presently available resuscitative measures are notably ineffective.

Resuscitation should start with some method of simple, gentle physical stimulation such as snapping the soles of the feet with a finger or repeatedly passing a nasal catheter. The upper respiratory passage should be suctioned again and a small plastic or metal airway inserted to lift the tongue off the posterior pharyngeal wall. If the infant has an Apgar score of 1 or less, or if the pulse rate is less than 80 beats a minute, some method of artificial respiration or pulmonary inflation is usually indicated, since the lungs offer the most suitable surfaces for oxygenating the blood and reducing the carbon dioxide tension or concentration of any volatile anesthetics in the medulla. If a gentle flow of oxygen at pressures up to 25 cm. of water, administered either steadily or in puffs through a small mask, does not produce improved color and tone followed by spontaneous respiratory movements, direct laryngoscopy or direct intratracheal intubation with suctioning of the lower respiratory passages and an attempt to inflate the lungs through the application of short bursts of oxygen at higher pressures is indicated. The latter procedures should be carried out by personnel skilled in the techniques, of whom there should be one (usually the anesthetist) in every delivery room. Positive pressures much lower than 20 cm. of water are unlikely to introduce oxygen into the lungs. Pressures of 25 cm. of water may rupture the lung if only a small area is being expanded. On the other hand, positive pressures of 40 cm. of water have been safely applied by using a resuscitator which automatically limits the inspiratory phase to 0.1 second and provides an expiratory phase of 5.9 seconds. A recently proposed theory that capillary erection

Table 53. Evaluation of the Newborn Infant

Sign	0	1	2
Heart rate.....	Absent	Below 100	Over 100
Respiratory effort.....	Absent	Slow, irregular	Good, crying
Muscle tone.....	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)....	No response	Grimace	Cough or sneeze
Color.....	Blue, pale	Body pink, extremities blue	Completely pink

Sixty seconds after the complete birth of the infant (disregarding the cord and placenta) the 5 objective signs above are evaluated, and each is given a score of 0, 1 or 2. A total score of 10 indicates an infant in the best possible condition. (Modified from Virginia Apgar: Current Researches in Anesth. & Analg., 32:260, 1953.)

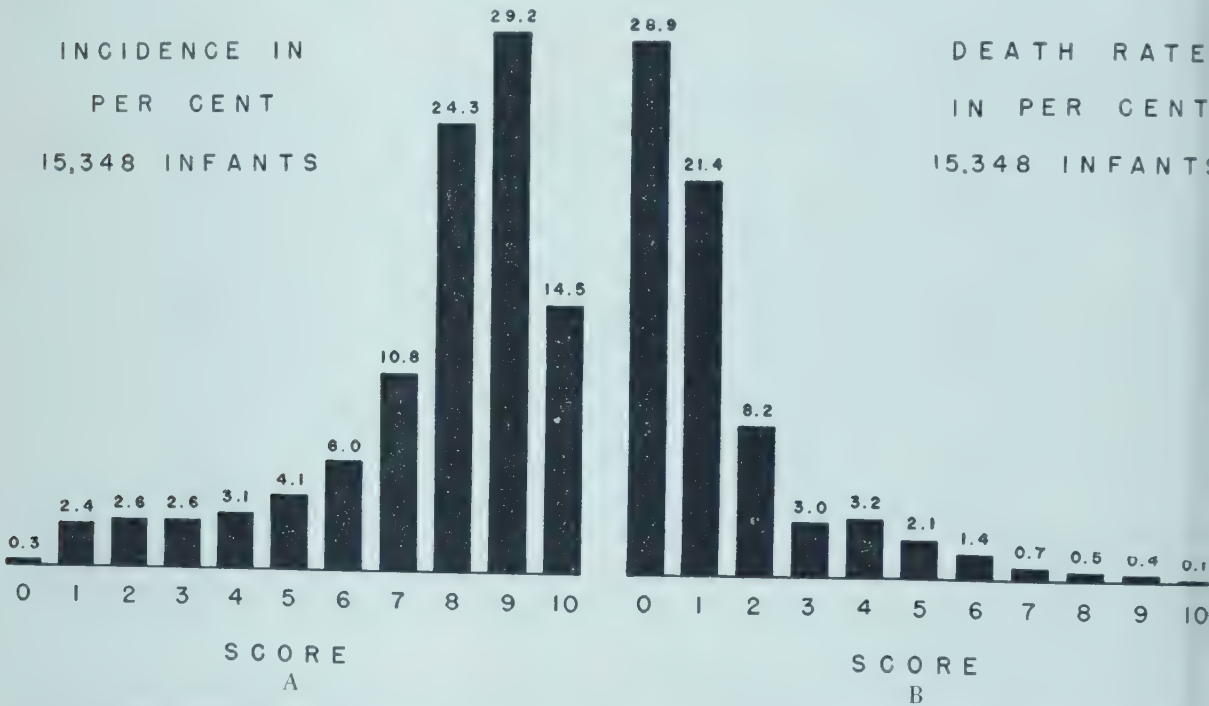


FIG. 71. Incidence and significance of Apgar scores (see Table 53) in newborn infants. (From data supplied by Dr. Virginia Apgar.)

is essential to initial alveolar expansion has not been confirmed by further experimental evidence, but its implications for presently used methods of resuscitation are of interest.

Several more elaborate devices for resuscitation are available. Among them are a "rocking-bed" type of respirator which rhythmically rocks the body so that the weight of the abdominal organs alternately presses against and falls away from the diaphragm, and the Bloxsum "air lock," which is an airtight tank incubator in which the pressure is rhythmically varied between 1.0 and 3.0 pounds per square inch above atmospheric pressure. The electrophrenic respirator of Sarnoff utilizes the infant's own musculature. Definite proof is lacking that any one of these devices is more effective than another, or that they are more effective than simple

physical stimulation plus the use of oxygen.

The elementary procedure of mouth-to-mouth breathing has presumably been successful in resuscitating some infants, but may well have been harmful to others by introducing infection or alveolar rupture from uncontrolled pressures. Even if safety devices are interposed, the gas thus supplied is less effective than oxygen. Manual compression of the soft thorax is unlikely to be followed by enough rebound expansion to produce air movement.

If the infant is making feeble but spontaneous respiratory movements, their effectiveness will be increased by raising the partial pressure of oxygen at the nose and mouth, even without any change in atmospheric pressure. Oxygen administration, particularly to premature infants, should always



be discontinued as soon as the baby can get along without it.

Warmth must be provided during any resuscitation requiring more than two or three minutes.

No drug advocated as a respiratory stimulant has proved to be of definite value; moreover, most of them may be convulsant if given in doses slightly greater than those supposed to stimulate breathing. For narcosis from maternally administered morphine derivatives, *n*-allyl normorphine (Nalline) in a dose of 2.1 mg. in 2 ml. of isotonic saline solution injected into the umbilical vein is indicated. This drug is a respiratory depressant and should not be used otherwise..

**Other measures.** The *umbilical cord*, after it has been cut and tied, requires no dressing. Initial and daily painting of the cord stump with a bactericidal dye while the infant is in the nursery results in a significant reduction in positive cultures for staphylococci from the nose and skin of newborns. Frozen sections of the cord at birth may expedite a diagnosis of neonatal sepsis through microscopic identification of perivascular leukocytic infiltrations. Likewise, the identification of a single umbilical artery through gross inspection of the cord at birth may lead to the early discovery of congenital anomalies.

The eyes of all infants must be protected against gonorrheal infection. Although numerous methods of ophthalmic prophylaxis with sulfonamide or antibiotic preparations have been advocated, the instillation of 1 per cent silver nitrate drops remains the best-proved and only universally lawful method. Prompt subsequent irrigation of the eyes with isotonic saline solution is said to reduce the incidence of chemical conjunctivitis without affecting the prophylactic efficacy.

Although hemorrhagic disease of the newborn (p. 336) may be due to factors other than vitamin K deficiency, the usual neonatal decrease in the plasma prothrombin level may be lessened by the intravenous administration of 10 mg. of vitamin K to the mother a few hours before delivery or by small doses to the infant immediately after birth. Since oral or intravenous administration is not always practical and since the duration of action of vitamin K, especially in the anoxic infant, is not known, an intramuscular injection of 2.5 mg. of a suitable preparation should be given in the delivery room and again on the third day of life to all infants. Larger amounts predispose to the development of hyperbilirubinemia and ker-

nicterus and should be avoided. Vitamin K<sub>1</sub> should be the preparation of choice, but is not at present available in a form suitable for intramuscular use.

**General Care. Nursery.** Routines for safeguarding the infant after he leaves the delivery room are modified by so many local circumstances that many important organizational and administrative aspects cannot be detailed in this brief section. Infants (1) born prematurely, (2) delivered operatively or with any unusual obstetric complication, (3) requiring resuscitation in the delivery room, (4) born to mothers with infections or premature rupture of the membranes, (5) born to toxemic or diabetic mothers, (6) born to mothers with a history of previous infants with death or serious illness during the newborn period, (7) with any important malformation or suspicion of such malformation, (8) under suspicion of blood incompatibility disease, or (9) delivered more than three weeks after expected confinement should be under close observation of the most interested and experienced nurses available and should be visited frequently by a physician until such time as complications of any of the foregoing circumstances may no longer reasonably be expected.

Infants not in the foregoing categories may be taken after examination in the delivery room to the "regular" newborn nursery, or may be placed in the mother's room if the hospital has a "rooming-in" arrangement.

The bassinet should be easily and frequently cleaned and preferably be of plastic material to allow easy visibility. All care should be given in the bassinet; this includes physical examination, change of clothing, temperature-taking, skin cleansing and other procedures which, if performed elsewhere, establish a common point of contact and thus provide a channel for cross infection. The clothing and bedding should be the minimum needed for the infant's comfort. Maintenance of a fairly constant temperature in the nursery at approximately 75° F. will simplify problems of clothing. The temperature of the infant may be taken by rectum or, if properly done, in the axilla. The interval depends on many circumstances, but need not be less than four hours during the first two or three days and eight hours thereafter. Axillary temperatures of 96° to 99° F. are considered within normal limits.

The *skin* requires little or no care beyond removal of blood and vernix from the face (largely for esthetic reasons) upon arrival in

the nursery. Clothing can be put on over the unbathed and unoiled body. Vernix is spontaneously shed within two to three days; much of it will adhere to the clothing, which should be completely changed daily. Daily baths with a soap or detergent containing hexachlorophene reduce the incidence of skin infection and should be instituted in any nursery where pustules are noted. As a permanent routine, bathing is probably not worth the nursing time required. The diaper should be checked before and after feeding and when the baby cries. When wet or soiled, it should be changed. Meconium or feces should be cleansed from the buttocks, and, if necessary, vernix from the body creases with sterile cotton moistened with sterile water. The foreskin of the male infant is normally tight and should not be retracted.

Little is gained by frequent *weighing* of the normal infant. A few accurate weights are of more use than numerous hurriedly taken ones. Weighing at birth and on alternate days thereafter is certainly sufficient, and even less frequent weighing is satisfactory for the majority of infants.

The problems of staphylococcal infections in the nursery are discussed on page 344.

**Feeding.** Only the initiation of feeding will be considered here (see p. 112 for other details). More mistakes are made by feeding the infant too much or too early than too little or too late. Both premature and term infants can, if necessary, tolerate a period as long as three days after birth without any

fluid intake. The one occasional but clear indication for prelacteal feeding is elevation of temperature not explained by other factors. Satisfactory progress is being made if the infant is no longer losing weight by the seventh day and gaining by the fourteenth. Many infants are unnecessarily fed artificially merely because the physician did not acquaint the mother with the delays normally encountered in establishing breast feeding.

If the principles of feeding are understood by the mother and the nursery staff, fixed routines for feeding will have little applicability. The schedule is less important than the principle of unhurried beginning and patient assistance and instruction by the nurse who takes the infant to the mother. But since some general plan may be useful from the standpoint of the hospital, the following is suggested: During the first twelve hours after birth no feeding is given. The infant is taken to the mother for his first feeding at 10 A.M. or 6 P.M., whichever is nearer the end of the twelve hour period of post-natal rest. Subsequent feedings are given every four hours day and night except for the first two nights, when no 2 A.M. feeding is given. Artificially fed infants should receive 5 per cent glucose in water for the first feeding, since regurgitation and aspiration of this solution are not likely to cause significant irritation of the respiratory tract. There is no clear need for complicating newborn care by the addition of any vitamins until the infant is at least two weeks of age.

## MULTIPLE PREGNANCIES

The reported incidence of twins varies; in general, it is highest among Negroes and East Indians, followed by whites of northern European extraction, and lowest among the Mongolian races. In the United States twins occur in approximately one of eighty-six pregnancies; other ratios are, Belgium, 1:56; United States Negroes, 1:70; United States whites, 1:88; Italy, 1:86; Greece, 1:130; Japan, 1:150; and China 1:300. Differences in the incidence of twins are due to differences in numbers of fraternal (polyovular) twins, the frequency of identical (monovular) twins being about the same in all racial and ethnic groups. It is roughly estimated that triplets occur in one of 86<sup>2</sup> pregnancies and quadruplets in one of 86<sup>3</sup> pregnancies

in the United States. Quintuplets and sextuplets are very rare, and it is questionable whether human septuplets have ever been born. The incidence of females increases with the number of fetal products of a multiple pregnancy, reaching approximately 53.5 per cent for quadruplets, as opposed to approximately 48.5 per cent among single births.

The occurrence of monovular twins appears to be independent of genetic or environmental influences. Such births constitute 25 to 33 per cent of twins. Polyovular pregnancies, on the other hand, are more frequent beyond the second pregnancy, in older women and in families with a history of polyovular twins. They may result from simultaneous maturation of multiple ovarian



ollicles, but follicles containing two ova have been described as a genetic trait leading to twin pregnancies. Monoovular twinning is believed to result from a retardation of growth in the early stages of development. When more than two fetuses coexist in the uterus, each may be derived from a separate ovum, all may come from the same ovum, or they may result from combined monoovular and polyovular twinning.

*Superfecundation*, the fertilization of an ovum by an insemination which takes place after one ovum has already been fertilized, has occasionally been advanced as the cause of differences in size and appearance of twins. *Superfetation*, the fertilization and subsequent development of an ovum when a fetus is already present in the uterus, has been proposed as a reason for differences in size of certain twins at birth, but objective evidence to support this theory is lacking. In fact, twins of unequal size at birth usually show the same degree of organ maturation.

Differentiation between monoovular and polyovular twins is usually made on the basis of the appearance of the placenta. An apparently single placenta may be present with either monoovular or polyovular twins. However, inspection of the polyovular placenta reveals for each fetus a separate chorion which crosses the placenta between the attachments of the cords. If the initiation of monoovular twinning occurs at the first cell division or during the morula stage, there may be two amnions and two chorions, and even two placentas, leading to an erroneous diagnosis of polyovular twins. For this reason, determination of whether twins of the same sex are monoovular or polyovular may have to be made on the basis of identical or non-identical physical characteristics. This is best done between the ages of two and four years, at which time differences caused by inequalities of intrauterine existence have been largely erased and differences created by external environmental factors have not yet become marked.

Physical criteria for determining monoovular twins are (1) that both be of the same sex; (2) that their features, including ears and teeth, be obviously alike (but they need not resemble one another more than the two lateral halves of one individual); (3) that their hair be identical in color, texture, natural curl and distribution; (4) that their eyes be of the same color and shade; (5) that their skin be of the same texture and color

(nevi may be differently apportioned and distributed); (6) that their hands and feet be of the same conformation and of similar size; (7) that their anthropometric values show close agreement; (8) that their finger, palm and sole prints be similar, the resemblance being either direct or mirror-imaged. Perhaps a more reliable method of determining zygosity of twins is through the use of detailed blood typing, including at least the ABO, Rh and MN systems. Monoovular twins should have identical blood types in all systems. Polyovular twins usually do not.

The identification of twins as monozygotic or dizygotic is of importance because the study of monozygotic twins is a useful scientific tool in determining the relative influence of heredity and environment on the etiology and course of many conditions.

One placenta may be markedly smaller than the other, or a dichorionic placenta may be divided disproportionately between the two fetuses. In either instance the fetus attached to the smaller placenta or smaller portion of placenta is usually smaller than its twin, or is malformed. With monoovular twins one umbilical cord may arise from the other after leaving the placenta. In such instances the twin attached to the secondary cord is usually malformed. Attachment of the cord to an inadequate portion of placenta or to the umbilical cord of the twin may also be responsible for fetal death, presumably as the result of an inadequate blood supply. Parabiosis of the placental circulations of monoovular twins, with arteriovenous shunts between the two circulations, may rarely result in the birth of twins, one of whom is large and polycythemic and the other small and anemic. Varying degrees of this condition may be responsible for apparent differences in size of monoovular twins.

Most twins are born prematurely, and maternal complications of pregnancy are more common than with single pregnancies. There is no significant difference between the neonatal mortalities of twin and single births in comparable weight groups. However, since most twins are premature by weight, their over-all mortality is higher than that of single births. The incidence of malformations incompatible with life is greater in multiple than in single pregnancies. In general, mortality rates of twins do not vary with order of birth if macerated fetuses are excluded. If one of the fetuses is macerated, the live twin is usually delivered first. Theoretically,

the second twin is more subject to anoxia than is the first because of the possibility that the placenta may separate after the birth of the first twin and before the birth of the second. For reasons which are not clear, premature infants born of multiple pregnancies appear to be more susceptible to retrolental fibroplasia than do premature infants born of single pregnancies. Notable differences in size at birth of monovular twins usually dis-

appear by the time the infants are six months of age.

*Conjoined twins* are probably the result of relatively late monovular twinning, as is the presence of two embryos in one amniotic sac. The latter condition has a high fatality rate, owing to obstruction of the circulation secondary to intertwining of the umbilical cords. The prognosis for conjoined twins depends on the possibility of surgical separation.

PERINATAL MORTALITY

The term "perinatal mortality" is applied to deaths of fetuses and infants weighing 1000 gm. or over which occur between twenty-eight weeks of gestational life and twenty-eight days of neonatal life. Emphasis on perinatal mortality, initiated by obstetricians, has been the greatest single factor in bringing about a team approach, involving obstetricians, pathologists, pediatricians, public health officials and nurses, to the problems of fetal and neonatal life. Table 54 illustrates the type of data obtained from studies of perinatal mortality, delineating the relative importance of principal causes of fetal and neonatal deaths. The reader will note that prematurity alone is not considered a cause of death, although the majority of fetal and neonatal deaths listed in the category "no abnormal state" occur among infants who are premature by weight at the time of delivery. It is also apparent that fetal and neonatal deaths contribute equally to perinatal mortality; the key position of the obstetrician in the reduction of perinatal mortality is obvious.

Table 54. Relative Importance of Causes of Fetal and Neonatal Deaths (Infants 1000 Gm. and Over)

Cause	Fetal	Neonatal	Total Perinatal
Anoxia*	25%	9%	34%
No abnormal state†	23%	9%	32%
Birth injury	2%	8%	10%
Malformations	4%	5%	9%
Abnormal pulmonary ventilation‡	0%	7%	7%
Infection	1%	4.5%	5.5%
Erythroblastosis	0.6%	1.1%	1.7%
Other	0.7%	0.1%	0.8%
Total	56.3%	43.7%	100.0%

Adapted from R. E. L. Nesbitt, Jr., and G. W. Anderson: Perinatal Mortality: Clinical and Pathologic Aspects. Obst. & Gynec., 8:50, 1956.

\* Defined as any interference in the supply of oxygen from mother to fetus producing visible structural changes in the fetus or infant at autopsy.

† Defined as lack of adequate lethal factors demonstrable at autopsy to explain the death.

‡ This category includes so-called pulmonary hyaline membrane disease.

PREMATURITY

**Definition.** A premature infant is a live-born\* infant weighing 2500 gm. (5 pounds 8 ounces) or less at birth. This definition, although in common use, is admittedly un-

\* Live birth is defined by the World Health Assembly (1950) as "the complete expulsion or extraction from its mother of a product of conception . . . which, after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached." This definition is approved by the American Public Health Association.

satisfactory, since it includes infants of low birth weight resulting from factors other than prematurity and excludes those actually premature who would have been of large size if carried to term. The additional qualification of a crown-heel length of 47 cm. (18½ inches) or less has been little used. The prognosis for survival of premature infants (less than thirty-seven weeks' gestation) in any weight group is directly related to gestational age. For example, in one analysis the neonatal mortality of a group of seventy-nine infants between 1000 and 1499 gm. birth weight



was 46 per cent; when the group was divided by recorded gestational age, the infants of less than thirty weeks had a mortality rate of 63 per cent, compared to 21 per cent for those in the same weight range, but with gestational ages of thirty-four to thirty-seven weeks (Steiner and Pomerance).

**Mortality and Incidence of Prematurity.** About two thirds of all mortality among newborn infants occurs in the relatively small percentage born prematurely (see Table 55). In a few instances no cause of death other than prematurity can be demonstrated; in the majority the cause of death, such as infection or hemorrhage, can be identified if careful postmortem study is made. From Figure 68 (p. 286) it is apparent that the mortality for both premature and term infants follows the same numerical relationship on successive days after birth, so that the basic problem of the premature, like that of the term infant, is to survive the first few days.

Table 55 presents the approximate distribution of live-born premature infants in the United States in 1950 by birth weight and the mortality rate for each group in comparison with those from a hospital which devotes special attention to research in problems of newborn infants, in order to emphasize that such attention does result in lowering of neonatal mortality rates. It is also apparent how greatly deferment of premature birth could affect absolute mortality.

Since nonwhite infants tend to weigh less at birth than white infants of the same gestational age, the incidence of prematurity based on a birth weight of 2500 gm. or less is greater among nonwhite infants, but the expected mortality rate is lower.

In the United States the incidence of premature birth is approximately 7 per cent of all live births in population groups of reasonably favorable socio-economic circumstances, although rates from 6 to 16 per cent are reported from various sections.

**Causes of Prematurity.** The cause of premature birth is not known in most instances. The relationship between multiple pregnancy and prematurity is clear. Maternal toxemia and infections increase the likelihood of premature delivery; congenital syphilis was formerly a frequent cause. In some instances premature labor may be initiated or its induction may be required because of factors such as placenta previa, premature separation of the placenta, toxemia, diabetes mellitus or severe sensitization to the Rh blood factor. Premature rupture of the membranes and

other obstetric disturbances may be considered manifestations of premature delivery almost as properly as causes. Chronic maternal malnutrition is undoubtedly an important factor in premature birth. Malnutrition tends to be associated with poor general hygiene, fatigue, increased frequency of infection, inadequate prenatal care, and other factors which contribute to increased fetal and neonatal loss. However, the majority of premature births are not satisfactorily explained.

**Prevention.** The higher the rate of premature births in any locality, the more obvious should be the steps which could result in its reduction. Usually these are in the areas of health education and better medical services. Preliminary studies suggest that "relaxin," an extract from the ovaries of pregnant sows, may have some value in the prevention of premature labor.

**Pathology.** Neonatal deaths among premature and term infants result from the same general group of pathologic disturbances (Table 54), the principal differences being in the distribution of the causes of death. When the cause of death is sought by careful macroscopic and microscopic postmortem examination, it is found in a high percentage of instances. Prematurity itself should not be considered a cause of death in an infant born alive. The principal causes of death among premature as well as term infants are anoxia,

**Table 55. Approximate or Predictable Average Distribution of 100 Live-Born Premature Infants on the Basis of Birth Weight and Approximate Expected Mortality Rate for Each Weight Group**

<i>Birth Weight</i>	<i>Percentage and Number of Infants</i>	<i>Approximate Mortality Rate (U.S. Average)*</i>	<i>Approximate Mortality Rate (Research Hospital)†</i>
1000 gm. or less . . . . .	6	87%	90%
1001-1500 gm. . . . .	8	55%	40%
1501-2000 gm. . . . .	19	21%	11%
2001-2500 gm. . . . .	67	5%	4%
All under 2500 gm. . . . .	100	17%	14%
All over 2500 gm. . . . .	100	0.8%	0.4%

\* U.S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics: *Weight at Birth and Its Effect on Survival of the Newborn: United States by Geographic Divisions and by Urban and Rural Areas, Early 1950. Vital Statistics—Special Reports, Selected Studies Volume 45, No. 10, 1957.*

† Boston Lying-In Hospital.

birth injuries (principally cerebral), malformations, pulmonary "hyaline membrane syndrome," bronchopneumonia, septicemia and other infections.

*Pulmonary hyaline membranes* associated with "resorption atelectasis" are found at autopsy in approximately 50 per cent of premature infants dying one hour to four days after birth and are seen with any frequency in full term infants only in those born by cesarean section or of diabetic mothers.

*Hemorrhage*, whether associated with trauma, anoxia, infection, or defect of clotting mechanism, is frequent and often severe. Subcutaneous ecchymoses, bleeding into the choroid plexus, subependymal and intraventricular hemorrhages are all frequently found in premature infants and are presumably due to "increased capillary fragility." Sudden shock and collapse during the first few days of life are usually due to intraventricular hemorrhage. Fatal hemorrhage into the lungs may also occur without clear cause.

*Retrolental fibroplasia* (see p. 1343) is a retinopathy of premature infants which results from too great an exposure to atmospheres with increased oxygen content. Before this effect of oxygen administration was appreciated partial or complete blindness was reported in 5 to 25 per cent of surviving infants whose birth weights were below 4 pounds (1800 gm.); the condition had replaced gonococcal ophthalmia as the commonest cause of blindness in children. Adoption of the practice of administering oxygen only in such amounts and at such times as are absolutely necessary for respiratory distress has practically eradicated the disease.

*Kernicterus* associated with hyperbilirubinemia (see p. 1077) is seen in 2 to 20 per cent of autopsies of premature infants. Incidences of kernicterus approaching the latter figure are probably the result of procedures used locally in the care of premature infants, such as administration of large amounts of vitamin K analogues to mothers in labor or to newborn infants, and use of sulfisoxazole as chemoprophylaxis (see p. 334).

**Care.** At birth the same measures for clearing of airway, initiation of breathing, care of the cord and of the eyes are required as for full term infants. The next considerations are (1) need for incubator care, (2) need for increased oxygen, and (3) details of feeding. Safeguards against infection and against careless or inefficient nursing can never be relaxed. Finally, the need of instructing the mother for the care at home

and the question of prognosis for later growth and development require special consideration.

**Incubator Care.** The original purpose of the incubator was the efficient conservation of body heat; to this have been added regulated humidity and oxygen supply and reduced atmospheric contamination. No rigid rule can be used to decide which premature infants should have incubator care, but, in general, the smaller the infant, the more helpful is such care. Many relatively large premature infants can be maintained satisfactorily in bassinets in a room of suitable temperature. On the other hand, for some term infants presenting special problems, incubator care is advantageous. The incubator is best prewarmed to 85° F. for infants above 3½ pounds, and to 90° F. or more for smaller infants. If the infant's temperature taken thirty minutes after placement in the incubator has risen by more than 2 degrees and/or reached 98° F., the temperature of the incubator may be slightly reduced. Simultaneous recordings of infant and incubator temperatures at thirty minute intervals for a few hours will usually be adequate for adjustment to a routine of four-hourly temperature readings. Stability of the infant's temperature should be obtained rather than any exact temperature level. A temperature varying in a range of 2 degrees, the low point of which is 94° F. (axillary) is probably more satisfactory than one which oscillates in a wider range about a mean of 98.6° F. If the infant is weakened, as by trauma or infection, the aim should be to keep his temperature somewhat nearer the 98° F. mean; such infants do not stabilize well at any temperature.

Though constancy of relative humidity within the incubator is, in general, more important than any fixed level, a relative humidity of 60 per cent or higher is more desirable than a lower one. If an incubator is not available, the general conditions of temperature and humidity control can be attained by the intelligent use of blankets and warm water bottles and by control of the temperature and humidity of the room. The infant should be removed from the incubator only when the gradual change to the atmosphere of the nursery is not accompanied by a significant change of his temperature, color or activity. The removal may be only a day or two after birth for some infants, or at more than a month of age for other and less mature ones.

Since disturbed pulmonary ventilation is responsible for a large portion of the deaths



of premature infants, it seems logical to increase atmospheric oxygen during the first hours or days following birth when there are such definite indications as cyanosis or dyspnea. Owing to the risk of retrolental fibroplasia, its use as a general measure should be avoided. When oxygen is administered in a closed incubator, its atmospheric concentration should be kept at the lowest level providing adequate relief for the infant, and administration of it should be discontinued just as soon as possible. The irritant action of oxygen is greater in a dry than in a humid atmosphere, so that administration of it is an additional reason for maintaining the relative humidity at 60 per cent or higher. Supersaturation of the atmosphere of the incubator to create a mist reduces insensible water loss from the lungs, but it has not been shown to affect the prognosis of the infant, nor has the addition of surface-tension-reducing agents to the nebulized water.

**Feeding.** There are a variety of techniques for the feeding of premature infants. There is general agreement on the importance of avoiding fatigue and the aspiration of food as fed or by regurgitation. No one method of feeding will avoid these risks unless the person using it has been well trained in the process. Large premature infants can often be fed by bottle or at breast. Since the effort of sucking is usually the limiting factor, breast feeding is least likely to be successful. In bottle feeding, effort may be reduced by use of special small, soft nipples with large holes or standard nipples with large holes boiled until soft. Infants as small as 3 pounds at birth are occasionally vigorous enough for bottle feedings. Smaller or less vigorous premature infants should be fed by gavage; a soft plastic tube of no. 5 French external and approximately 0.05 cm. internal diameters with a rounded atraumatic tip and two holes on alternate sides is preferable. The tube is passed through the nose until approximately 1 inch of the lower end should be in the stomach. The free end of the tube is then placed under water. If bubbles appear with each expiration, the catheter is in the trachea and must be reinserted into the proper position. The free end of the tube has an adapter into which the tip of a glass syringe is fitted, and the measured amount of feeding is allowed to flow in by gravity. Such tubes may be left in place for three to seven days before replacement by a similar tube through the alternate nostril. The tubes may be cleaned, sterilized, and reused, but are usually dis-

carded after one use. An occasional infant has enough local irritation from an indwelling tube that troublesome secretions gather around it in the nasopharynx. In such instances a sterile no. 10 French catheter may be passed through the mouth by a skilled person and removed at the end of each feeding. Change to bottle or breast feeding may be instituted gradually as soon as the infant displays general vigor adequate for oral feeding without fatigue. The so-called Breck feeder, with which food is forced into the infant's mouth, is unsafe in any hands. Premature infants can be fed successfully and safely with a rubber-tipped medicine dropper by a nurse skilled in the procedure.

The comparative inactivity of premature infants, their low heat production, if heat is artificially conserved, and, perhaps, their relatively large body water content at birth, all reduce the immediate need for calories, water and electrolytes. Nothing seems to be gained by giving food during the first twenty-four hours after birth, and much may be lost if aspiration or undue fatigue occurs. The smaller and less active infants may be safely allowed at least two days without intake. The first feedings should be sterile 5 or 10 per cent solutions of glucose in water. The interval between them is generally somewhat shorter for smaller infants, and may be even less than two hours when feeding is by an indwelling tube. Experience and observation of the individual infant best determine intervals and amounts, but some such routines as those in Table 56 are suitable for most infants. The main principle should be to proceed more gradually the smaller the infant, but never to hurry with any.

After the eighth feeding, as indicated in Table 56, increases can be made daily with not more than 4 cc. added to each of the eight daily feedings (32 cc. per day) for the smaller infants or 8 cc. to each of the six feedings (48 cc. per day) for the larger ones. By the time the infant is a week of age he should be receiving approximately 40 to 50 calories per pound (90 to 110 per kilogram), and by two weeks, 50 to 60 calories (110 to 130 per kilogram).

Some physicians prefer mixtures of partly skimmed cow's milk, water and carbohydrate for feeding premature infants (see p. 124). As shown in Table 57, such mixtures provide more protein and carbohydrate and less fat than does human milk; the intake of minerals is about threefold. The proponents of human milk contend that calories lost as fecal fat

Table 56. General Plans for Beginning Feeding in Premature Infants

	Infant of 2-2½ Lb. (1000-1200 Gm.)	Infant of 4-4½ Lb. (1800-2000 Gm.)
Feeding interval.....	2-3 hours	4 hours
Age at first feeding.....	36 hours or more	24 hours or more
Composition and Amount of Individual Feedings		
Order of Feedings	10% Glucose    Breast Milk or Formula	10% Glucose    Breast Milk or Formula
1st.....	4 cc.    —	8 cc.    —
2nd.....	8 cc.    —	16 cc.    —
3rd.....	12 cc.    —	24 cc.    —
4th.....	16 cc.    —	32 cc.    —
5th.....	12 cc.    4 cc.	24 cc.    8 cc.
6th.....	8 cc.    8 cc.	16 cc.    16 cc.
7th.....	4 cc.    12 cc.	8 cc.    24 cc.
8th.....	16 cc.	—    32 cc.

Table 57. Four Foods Commonly Used for Premature Infants

Foods	Calories		Percentage of Weight			Percentage of Calories		
	Per oz.	Per ml.	P	F	CHO	P	F	CHO
Human milk.....	20	0.7	1.25	3.5	7.5	8	50	42
Boston Lying-in Hospital formula*	20	0.7	2.3	2.3	10.0	13	30	59
New Haven Hospital formula†	24	0.8	3.5	1.3	13.0	16	18	66
New York Hospital formula‡	24	0.8	4.0	1.4	12.8	20	16	64

Ingredients	B. L.-i. H.**	N. H. H.†	N. Y. H.‡
Evaporated milk.....	10.5 oz. (330 ml.)	—	—
Powdered whole milk.....	—	7 tbs. (60 gm.)	—
Powdered skim milk.....	—	5 tbs. (43 gm.)	—
Powdered ½-skim milk.....	—	—	6.7 tbs. (72 gm.)
Carbohydrate (by wt.).....	2 oz. (57 gm.)	3 oz. (86 gm.)	2.5 oz. (73 gm.)
6% sodium citrate solution.....	—	½ oz. (17 ml.)	—
Water to make total.....	—	32 oz. (1000 ml.)	—

\* Boston Lying-in Hospital formula usually prescribed after 2 to 4 weeks on human milk.

\*\* S. H. Clifford, in Grulee and Eley: The Child in Health and Disease. Baltimore, Williams & Wilkins Company.

† G. G. Powers: Some Observations on Feeding of Premature Infants Based on 20 Years Experience at New Haven Hospital. Pediatrics, Vol. I.

‡ H. H. Gordon, S. Z. Levine, and H. McNamara: Feeding of Premature Infants. A Comparison of Human and Cow's Milk. Am. J. Dis. Child., Vol. 73.

may be compensated by slightly increasing the total feeding; moreover, investigations have shown higher retentions of the fat of human milk than that of cow's milk. The increased retention of nitrogen with cow's milk mixtures has not been demonstrated to be of critical importance. The excess mineral content of cow's milk requires removal by the

kidney; whether this constitutes a "load" of clinical importance is not known.

Within the limits mentioned above, there is no clinical evidence to indicate that the composition of the food is a significant factor for survival or subsequent growth.

There is need for an increased intake of vitamins C and D. Intermediary metabolism



of phenylalanine and tyrosine is incomplete unless ascorbic acid is provided. Moreover, any tendency to loss of fecal fat involves loss of fat-soluble vitamins and calcium. Approximately 50 mg. of ascorbic acid and 1000 I.U. of vitamin D daily begun during the second and third weeks, respectively, appear to be ample. It has not been shown that supplementation with any other vitamins is necessary. The addition of iron to the diet is discussed on page 932.

Application of the foregoing general principles of nutrition will generally result in satisfactory rates of growth, but individual differences are to be expected. Therefore the needs of the individual infant should be followed, and the usual caloric recommendations after the second week of life are to be applied only as an approximation. Certain infants with small gastric capacities may require caloric concentrations as high as 30 per ounce in order to gain weight satisfactorily.

The properly fed premature infant may have from one to six stools of semisolid consistency daily; sudden increase in number is more reason for alarm than any arbitrarily stated frequency. He should not vomit or regurgitate. He should be satisfied and relaxed after a feeding, but may normally show the activity of hunger shortly before the next one. All these signs are more important than his rate of gain in weight.

**Prevention of Infection.** Prevention is accomplished by safeguarding the infant's food and the few objects which come in contact with him, reducing his direct and indirect contacts with nursery personnel (including other infants) and preventing contamination of the air he breathes. No one should enter the nursery unless his presence is essential, and no adult with an infection has a responsibility toward a premature nursery as essential as staying out of it. Gowns, caps, masks and hand scrubbing techniques do not guarantee safety of the infants if an infected person enters the nursery.

Prevention of transmission of infection from infant to infant is difficult because clinical evidence of infection is infrequently clearly manifest by either term or premature newborn infants. If the unit admits infants born outside the hospital, it should be assumed that they are infected until a week or more of observation in a special nursery or an incubator with an individual air supply proves otherwise. If the only admissions are infants born in the hospital, the possibility

that one will introduce infection is greatly reduced, provided careful attention is given to the obstetric history.

Perhaps the most important factor in the successful care of premature infants is the skill, experience and number of the *nursing* staff. It is as much the responsibility of the physician to insist upon expert nursing as upon the details of care.

**General Considerations of Disease.** Prematurity tends to increase the severity and to reduce the clinical manifestations of all neonatal diseases. Subcutaneous and intracranial hemorrhage, "primary" atelectasis, hyaline membrane syndrome, pneumonia, bacteremia and hyperbilirubinemia occur more frequently among premature than among term infants. Retrolental fibroplasia is seen almost exclusively in premature infants.

**Drugs.** Renal clearances for almost all substances excreted in the urine are diminished in all newborn infants, and perhaps more so in prematures. One half or less of the customary dose of any drug excreted chiefly by the kidney is usually adequate to maintain a therapeutic level, when given at longer than the customary interval between doses. For instance, highly satisfactory levels of penicillin and streptomycin are maintained on doses given at twelve-hour intervals. Drugs detoxified in the liver or requiring chemical conjugation before renal excretion should also be given with caution and in smaller than usual doses. Intramuscularly administered broad-spectrum antibiotics are absorbed less well

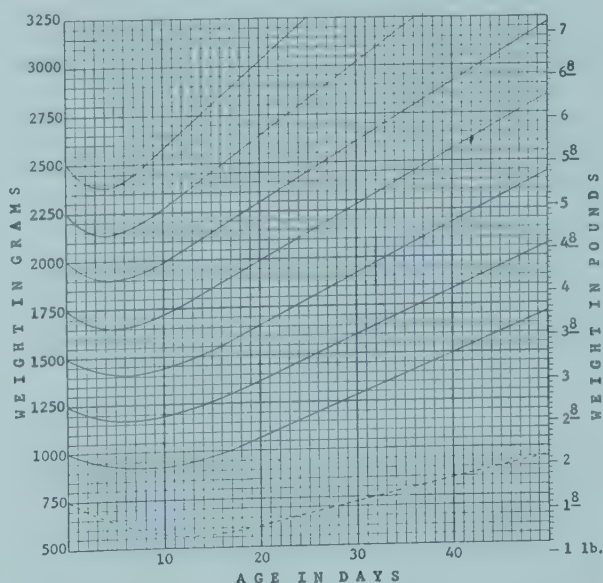


FIG. 72. Grid for recording weights of premature infants. The average weight increments are indicated on the basis of weight at birth. (J. Dancis et al.: *J. Pediat.*, Vol. 33.)

Table 58. Estimated Developmental Ratings Achieved by 370 Infants Less than 1250 Gm. in Birth Weight\*

Rating	Number so Rated (1 to 28 Years after Birth)	
	Physical Development	Mental Development
Normal, average or above . . .	200	264
Slight deviation from expecta- tion for age . . . . .	116	68
Poor . . . . .	36	23
Bad . . . . .	13	6
Extremely subnormal . . . . .	5	9

\* Arranged from data of Hess: Pediatrics, Vol. 11.

than penicillin and streptomycin, presumably owing to the severity of local tissue reaction and to relative circulatory inadequacy. Broad-spectrum antibiotics are also poorly absorbed from the intestinal tract unless administered in dilute form, again presumably because of local irritant effects. Decision as to the administration of antibacterial agents to possibly infected infants should be made on an individual rather than on a routine basis, owing to the dangers of (1) development of infections with organisms resistant to antibacterial agents, (2) destruction or inhibition of intestinal bacteria which manufacture significant amounts of essential vitamins (e.g., vitamin K and thiamine) and (3) possible deleterious interference in important metabolic processes (e.g., the role of sulfisoxazole in hyperbilirubinemia).

Since pure food and drug laws and regulations are based on toxicity studies on adult animals and human beings, apparently "safe" drugs may not be so for newborn infants, especially premature ones. Oxygen, vitamin K analogues and sulfisoxazole (Gantrisin), all presumably "safe" drugs, have proved to be toxic to newborn premature infants in amounts not harmful to term infants. Thus administration of any drug to newborn infants, particularly in large doses, should be done with care and never as a "routine."

Gamma globulin levels of premature infants at birth are significantly lower than those of their mothers at the time of delivery or than those of term infants; since they undergo the usual "physiologic" decrease during the first months of life, the routine administration of gamma globulin on discharge from the hospital has been advocated as a

prophylactic measure. As yet no adequate evaluation of this procedure is available.

**Prognosis.** (See p. 306 for mortality rate within first few weeks of life.) Recent evidence indicates that the mortality of premature infants who survive to be discharged from the hospital is approximately three times that of full term infants during the first two years of life. Most of these deaths are attributable to infection and are, therefore, at least theoretically preventable.

Data in regard to attainments in growth and development are inadequate to permit more than general deductions. Physical growth usually tends to overtake that of term infants during the second year; this occurs earlier in premature infants of larger size at birth and tends to be later in the more premature, among whom a few remain small throughout childhood (see Table 58). Premature birth in itself may prejudice later development, and there is also a greater frequency of other obstetric factors, such as intrauterine anoxia and intracranial hemorrhage, than would occur in infants born at term.

A high incidence (50 per cent) of refractive errors presumably unconnected with retrolental fibroplasia has been reported by Howard and Worrell in twenty-two children of birth weight below 4 pounds (1820 gm.) examined at ages of eight to nineteen years.

Behavior and personality problems also appear to be common in children born prematurely. The circumstances of nursery care in early infancy and of home care thereafter conspire against a normal relationship between the prematurely born infant and his family. The extent to which natural parental anxiety and overprotectiveness may foster an abnormal emotional environment for the growing infant should be greatly reduced by avoiding unnecessarily prolonged hospitalization and by painstaking education of the families.

**Home Care.** While the infant is in the hospital the mother should be instructed for her responsibilities when the baby is discharged. This program will include at least one visit to her home by a person capable of evaluating domestic arrangements and of advising as to improvements, if needed. Premature infants are usually sent home when they reach 5½ pounds (2500 gm.) in weight, but many may go before that time, while others should be kept longer.



# POSTMATURITY AND PLACENTAL DYSFUNCTION

Postmaturity is defined as a gestation exceeding the normal by seven to twenty days or more. Large size of the infant does not correlate well with late delivery, but does tend to correlate with large size of either parent, multigravidity, and diabetes or the prediabetic state in the mother and possibly also in the father.

Often associated and frequently confused with postmaturity is a syndrome termed *placental dysfunction syndrome*.

## POSTMATURITY

**Incidence and Etiology.** The incidence of postmaturity varies with its definition and with local obstetric practices. Approximately 25 per cent of all pregnancies end on or after the 287th day of gestation, 12 per cent on or after the 294th day, and 5 per cent on or after the 301st day. The etiology of postmaturity will presumably remain unknown until the mechanism of onset of labor is fully understood.

**Clinical Manifestations.** The appearance and behavior of the postmature infant approximate those of an infant one to three weeks of age. He tends to have absence of lanugo, long nails, abundance of scalp hair, white skin and an increased alertness. The skin may be parchment-like with desquamation, which is the result of gradual but progressive diminution of vernix caseosa beyond term.

**Prognosis.** When postmaturity exceeds three or more weeks, there is a significant increase in mortality, which in some series has approximated three times that of a control group of infants born at term; the fetal mortality exceeds that of the neonatal period. Each has been lowered markedly through improved obstetric management. Primiparity and maternal age over twenty-five years appear to increase the mortality rates.

**Treatment.** The induction of labor before the cervix is soft and dilated is felt by most obstetricians to be a greater risk than is postmaturity itself. A possible exception is the performance of cesarean section on elderly primigravidas who go more than a week or two beyond term, particularly if there is any evidence of fetal distress.

## PLACENTAL DYSFUNCTION SYNDROME

**Incidence and Etiology.** The incidence of some clinically recognizable form of placental dysfunction is said by Clifford to be as high as 12 per cent of all births. The incidence of the clearly recognizable form of the syndrome, with yellow staining of the vernix and skin, is approximately 1.2 per cent of all births. *Only about 20 per cent of infants with placental dysfunction syndrome are postmature.* Premature infants and infants of toxemic mothers, elderly primigravidas and women with "reproductive inefficiency" often associated with small or poorly attached placentas account for the major portion of the remainder. It has been postulated that this syndrome is the result of degenerative changes in the placenta resulting in progressive reduction of oxygen and nourishment for the fetus.

**Clinical Manifestations.** Clifford divides infants with the placental dysfunction syndrome into three groups, assuming that they are postmature (see above): *stage I*—infants



FIG. 73. Placental dysfunction syndrome, stage III. Note long, thin infant with loose, peeling, parchment-like skin, alert expression, staining of skin and nails. (From Clifford: *Advances in Pediatrics*, Vol. 9. Yearbook Publishers, Inc.)

with the usual signs of postmaturity, which are desquamation, long nails, abundant hair, white skin and alert facies and loose skin, especially around the thighs and buttocks, giving the appearance of recent loss of weight; *stage II*—infants with the changes of stage I plus meconium-stained amniotic fluid, skin, vernix, umbilical cord and placental membranes, possibly a manifestation of fetal anoxia; *stage III* (Fig. 73)—infants with the signs of stages I and II, except that their nails and skin are stained a bright yellow and the umbilical cord yellow-green.

**Prognosis.** Stage I infants have no known mortality associated with the syndrome, although up to one third of them have been reported as showing some evidence of respiratory distress or central nervous system irrita-

tion. Stage II infants are born at the height of intrauterine anoxia. About two thirds of them have severe respiratory symptoms, apparently resulting from the aspiration of meconium-containing amniotic fluid. A smaller number have clinical signs of anoxic cerebral damage. The over-all mortality is estimated to be about 35 per cent. Live-born stage III infants have presumably survived the acute anoxic phase of stage II; they have the same clinical problems, but with a lower morbidity, and a mortality of approximately 15 per cent.

**Treatment.** The treatment of placental dysfunction lies chiefly in preventing the conditions which predispose to it. It therefore constitutes an obstetric and perhaps a genetic and social problem. Aspiration pneumonia and cerebral anoxia are treated symptomatically.

## DISEASES OF THE NEWBORN INFANT: FULL TERM AND PREMATURE

### CONGENITAL ANOMALIES

Congenital anomalies are important as a cause of stillbirths and of neonatal deaths, but are perhaps even more important as causes of physical defects and of metabolic disorders. Anomalies are discussed in general on page 243 and specifically in the sections on the various systems of the body. For congenital mental defects, see page 1129, and for congenital metabolic and chemical disorders, see page 250.

Recognition of anomalies as early as pos-

sible is desirable. For some, such as tracheoesophageal fistula or intestinal obstruction, immediate medical and surgical therapy is mandatory for survival. For others, such as stenosis of the posterior nares, early treatment will avoid subsequent difficulties. Furthermore, early diagnosis permits a planned approach to parents, who are likely to be assailed by anxiety and guilt when they become aware of the existence of a congenital anomaly.

### CLINICAL MANIFESTATIONS OF DISEASE DURING THE NEWBORN PERIOD

Recognition of disease in the newborn infant is dependent upon knowledge and appraisal of the significance of a limited number of relatively nonspecific clinical signs and symptoms.

*Cyanosis* usually indicates respiratory insufficiency which may be due to pulmonary conditions or secondary to intracranial hemorrhage. If it is due to the former, respirations tend to be rapid and may be accompanied by thoracic cage retraction of varying degrees. If it is due to the latter, respirations tend to be irregular and weak and often slow. Cyanosis

persisting for several days, when unaccompanied by obvious signs of respiratory difficulty, is suggestive of cyanotic congenital heart disease or methemoglobinemia. Episodes of cyanosis may be the presenting sign of bacteremia or meningitis.

*Convulsions* usually point to the central nervous system and suggest intracranial hemorrhage, cerebral anomaly, subdural effusion, meningitis, tetany or, rarely, pyridoxine dependency or hypoglycemia. They may also be the first sign of bacteremia or other severe infection and are often seen as a nonspecific



sign in any severe illness. Rapid or striking changes in serum electrolyte concentrations may also cause convulsions, as may "withdrawal changes" in infants of mothers addicted to narcotics.

*Lethargy* is seen in the anoxic infant, in the infant with cerebral defect, either congenital or acquired, in the infant with severe infection, and, indeed, in the presence of almost any severe disease. Lethargy appearing after the second day should in particular suggest infection.

*Irritability* may be a sign of discomfort accompanying intra-abdominal conditions, meningeal irritation, infections, or any condition producing pain. Toward the latter part of the newborn period, as in later infancy, the ear drums should always be examined as a possible source of pain.

*Failure to feed well* is seen in most sick newborn infants and should always occasion a careful search for possible abnormalities.

*Fever* may be the result of too high an environmental temperature due to hot weather, overheated nurseries or incubators, or too many clothes or bedclothes. It is also seen in "dehydration fever" of newborns. If the preceding causes of fever can be eliminated, serious infection (pneumonia, bacteremia, meningitis) must be ruled out. On the other hand, serious infections often occur without provoking any febrile response in newborn infants.

*Jaundice during the first twenty-four hours of life* should be considered due to erythroblastosis fetalis until proved otherwise. Cytomegalic inclusion disease and toxoplasmosis should also be considered.

*Jaundice after the first twenty-four hours*

may be "physiologic," due to septicemia, hemolytic anemia, galactosemia, cytomegalic inclusion disease, hepatitis, congenital atresia of the bile ducts, inspissated bile syndrome following erythroblastosis fetalis, syphilis or toxoplasmosis.

*Vomiting* during the first day of life suggests intestinal obstruction or increased intracranial pressure. Anteroposterior and lateral *upright* films of the abdomen are indicated, followed by barium studies if the diagnosis remains in doubt. Later, although it still points to the central nervous system or gastrointestinal tract, vomiting may be a non-specific symptom of an illness such as septicemia. It is also seen as a common manifestation of overfeeding, pyloric stenosis, milk allergy, duodenal ulcer, adrenal insufficiency and a reflection of a "nervous" or apprehensive mother, or of an actual emotional upset in the parents. Infants placed in body casts for orthopedic treatment often vomit transiently, apparently as a manifestation of frustration of physical movement. Vomitus containing dark blood is usually a sign of terminal illness, whatever the cause.

*Diarrhea* may be a symptom of overfeeding, acute gastroenteritis or a nonspecific symptom of infection (*parenteral diarrhea*). It may be seen in conditions accompanied by compromised circulation of part of the intestinal or genital tract such as strangulated hernia, intussusception, and torsion of the ovary or testis.

*Failure to move an extremity* or part of an extremity suggests fracture, dislocation or nerve injury. It is also seen in osteomyelitis and other infections which cause pain on movement of the affected part.

## DISTURBANCES RELATED TO INTRAUTERINE CONDITIONS OR TO DELIVERY

### BIRTH INJURY

The term *birth injury* is used to denote not only avoidable and unavoidable trauma incurred by the infant at the time of birth, but also permanent damage occurring during or shortly after birth, particularly to the central nervous system. Most lay persons interpret *birth injury* as meaning avoidable trauma incurred through lack of medical skill or attention. In order to prevent later misunderstandings, recriminations and self-recriminations on the part of parents of a child who has

residuals from birth trauma, anoxia or disease, it is important that the physician take time to inform them about the broad use of the term "birth injury" and the fact that trauma or anoxia may, in our present state of obstetrical knowledge and skill, be unavoidable during the process of birth.

### HEAD

*Caput succedaneum* is a diffuse, edematous swelling of the soft tissues of the scalp involving the portion presenting during delivery. General or localized ecchymotic discolor-



FIG. 74. Cephalhematoma of the right parietal bone.

oration may be present. The edema disappears within the first few days of life. Analogous swelling, discoloration and distortion of the face are seen in face presentations.

*Molding* of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded, but disappear during the first weeks of life.

*Erythema, abrasions, ecchymoses and subcutaneous fat necrosis* (p. 1278) may be seen after forceps deliveries. Their location depends upon the area of application of the forceps. Ecchymoses may be seen after manipulative deliveries and occasionally in premature infants for no discernible reason.

*Subconjunctival hemorrhages* are frequent, and *petechiae* of the skin of head and neck are not uncommon. Both are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that they are temporary and the result of normal hazards of delivery.

*Cephalhematoma* (Fig. 74) is a subperiosteal hemorrhage, hence always limited to the surface of one cranial bone. Other points of distinction from caput succedaneum are that there is no discoloration of the overlying scalp due to subcutaneous hemorrhage and that visible swelling usually is not present for several hours after birth, since subperiosteal bleeding is a slow process. In approximately 25 per cent of cephalhematomas there is an underlying skull fracture. It is rarely of the depressed type, although a sensation of central depression suggesting underlying fracture or bony defect is usually encountered on palpation of the rim of a cephalhematoma. Cranial meningocele may be differentiated

from cephalhematoma by pulsation, increased pressure on crying and the roentgenographic evidence of bony defect. Cephalhematomas begin to calcify by the end of the second week. Most are resorbed during the first six weeks of life.

A few remain as bony protuberances for years, however, detectable roentgenographically as widening of the diploic space; cyst-like defects may persist for months or years. Despite these residuals, cephalhematomas require no treatment. Since the introduction of infection, especially with antibiotic-resistant staphylococci, is the only serious complication, incision or aspiration accompanied by antibacterial therapy is contraindicated.

*Fractures of the skull* may occur as a result of pressure from forceps or against the maternal symphysis pubis, sacral promontory or ischial spines. Linear fractures are the most common. They cause no symptoms and require no treatment. Depressed fractures are usually indentations of the calvarium similar to a dent in a Ping-pong ball. It is advisable to elevate such depressions surgically to prevent cortical injury from sustained pressure. Fracture of the occipital bone with separation of the basal and squamous portions almost invariably causes fatal hemorrhage, owing to disruption of the underlying sinuses. It ordinarily results from traction on the hyperextended spine of the infant with the head fixed in the maternal pelvis during breech deliveries. It is rarely seen with skilled obstetric techniques.

#### INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage may result from trauma or anoxia and, rarely, from a primary hemorrhagic disturbance or congenital vascular anomaly. Traumatic hemorrhage is especially likely when the fetal head is large in proportion to the size of the mother's pelvic outlet; when for other reasons the labor is prolonged; in breech deliveries; in precipitate deliveries; or when there is injudicious mechanical interference with delivery. On the other hand, the proper use of forceps is thought to decrease the incidence of intracranial bleeding in prolonged, hard labors. Intracranial hemorrhage may occur in infants, especially prematures, delivered spontaneously without apparent trauma. In premature infants subependymal, subarachnoid, intracerebral and intraventricular hemorrhages are common (Fig. 75). Spontaneous intraventricular hemorrhage in which no physical damage to the tentorium, falx or



other structures is found at autopsy is practically limited to premature infants. Conversely, massive subdural hemorrhages, often associated with tears in the tentorium cerebelli or less frequently in the falx cerebri, are encountered more often in full term than in premature infants. Hemorrhage due to anoxia tends to be petechial, and subarachnoid and intracerebral in distribution. There is usually only mild extravasation of erythrocytes, and symptoms and sequelae are dependent more on anoxia than on hemorrhage. Primary hemorrhagic disturbances usually give rise to subarachnoid hemorrhage, and vascular anomaly to subarachnoid or intracerebral hemorrhage.

**Clinical Manifestations.** Symptoms of intracranial hemorrhage may be present at birth or may not appear for a variable time after delivery. The commonest symptoms soon after birth are a general failure to move normally, diminished or absent Moro reflex, lethargy and somnolence. Great irregularity of respirations in the absence of other signs of respiratory distress is often a sign of severe hemorrhage. Pallor, cyanosis, cyanotic attacks, failure to suck well, forceful vomiting, anxiety and restlessness, a high-pitched, shrill cry, muscular twitchings, convulsions, or paralyzes may be the first indications that intracranial hemorrhage is present. The fontanel *may* be tense and bulging, and an adder-like protrusion of the tongue may be seen. Retinal hemorrhage, ocular palsies, inequality

in the size of the pupils, failure of them to react to light, or nystagmus may be observed.

**Diagnosis** is based chiefly on the history of delivery, the clinical manifestations and the course. It should be recognized that the nonlocalizing signs of intracranial hemorrhage are identical with those caused by cerebral edema or anoxia, and before carrying out any diagnostic procedure the chance of helping the patient should be weighed against the risk. Subdural taps are usually unrewarding, even in the presence of subdural hemorrhage, since it is likely that the blood will have clotted; on the other hand, they are occasionally lifesaving. Trephining with direct visualization of the meninges is rarely used, owing to the poor condition of most infants in whom the question arises and to the remoteness of the possibility that it will be either diagnostically or therapeutically efficacious. For similar reasons ventricular taps are rarely done even when there is suspicion of intraventricular hemorrhage. Lumbar puncture is definitely indicated in the presence of signs of increased intracranial pressure to identify gross subarachnoid hemorrhage, to rule out the possibility of bacterial meningitis, and possibly to relieve pressure on vital structures.

Since a small amount of bleeding often occurs in the course of normal and even cesarean deliveries, small numbers of red blood cells or slight xanthochromia in sub-

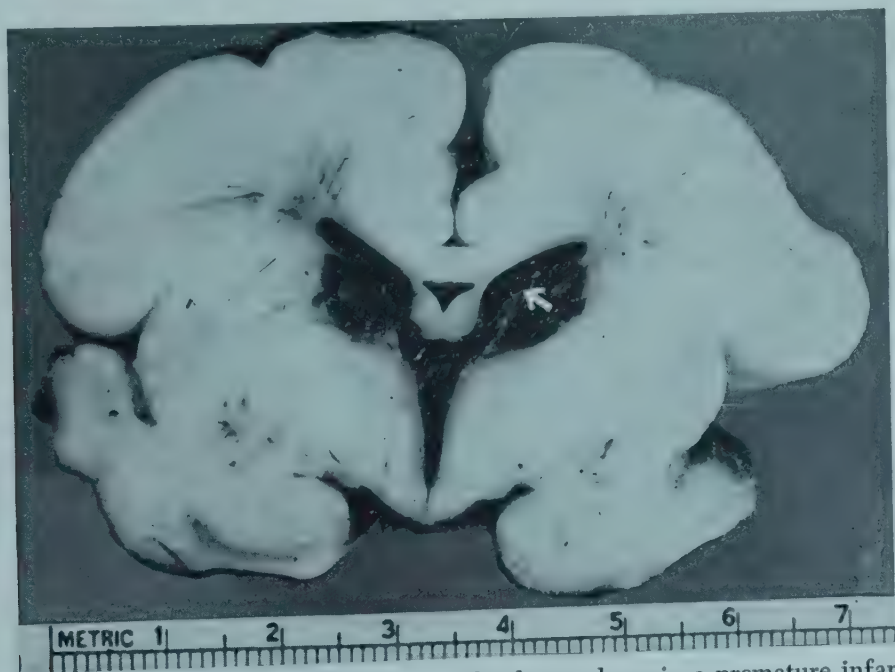


FIG. 75. Bilateral subependymal and intraventricular hemorrhage in a premature infant. The floor of the lateral ventricle is marked by an arrow, outside of which is a large subependymal hemorrhage. (From Arey and Dent., *J. Pediat.*, Vol. 42.)

arachnoid fluid is not necessarily indicative of significant intracranial hemorrhage. Bilirubin may produce a yellowish discoloration of the cerebrospinal fluid in jaundiced infants; conversely, the subarachnoid fluid may be absolutely clear in severe subdural or intracerebral hemorrhage when there is no communication with the subarachnoid space.

**Prognosis.** Death may occur intrapartum in the more severe cases; postnatally, fatalities usually occur within the first three days and result from respiratory failure. If an infant survives, recovery often may be complete, or there may be permanent residuals mainly in the category of cerebral palsy. Presumably some of the membrane-enclosed subdural effusions observed in later infancy may have their origin in subdural hemorrhage at birth. Statistics on incidence and prognosis of intracranial hemorrhage in the newborn are not available, since autopsy material is the only source and since one can rarely be certain of the diagnosis in the surviving patient.

Because the majority of parents are aware of and fear the possibility of cerebral residuals following intracranial hemorrhage or cerebral anoxia, it is probably wisest to give them an opportunity to air their anxiety in a frank discussion of the problem, during which their questions should be invited rather than suppressed or evaded. As optimistic an attitude as possible, consistent with the physician's opinion of the prognosis of the individual case, should be maintained.

**Prevention.** Prophylactic measures exist in better obstetric management; many instances of intracranial hemorrhage are avoidable.

**Treatment.** The infant should be handled as little and as gently as possible. He is best kept in an incubator which allows good temperature control, continuous observation, and easy administration of oxygen for cyanosis. Sodium phenobarbital (8 mg. [ $\frac{1}{8}$  grain]), administered intramuscularly, or other anti-convulsant drugs in appropriate doses, may be used to control convulsive movement. A small dose of vitamin K or, preferably, K<sub>1</sub> oxide should be administered (see Hyperbilirubinemia, p. 334). A small (5 ml. per pound of body weight) transfusion of fresh blood is indicated in the presence of hemorrhagic disease of the newborn. There is lack of agreement about the advisability of performing spinal punctures for the relief of increased intracranial pressure and to remove gross blood in order to reduce its irritant effect on the cerebral cortex and to prevent

possible interference with the normal resorptive mechanisms for cerebrospinal fluid. In our opinion such punctures are indicated, particularly in the presence of grossly bloody spinal subarachnoid fluid.

Neurosurgical procedures are of doubtful advantage; most of them are aimed at relieving pressure which is usually readily accomplished by withdrawal of spinal fluid at lumbar puncture, owing to the relative expandibility of the cranial compartment.

*Cerebral edema* may result in any or all of the clinical signs produced by intracranial hemorrhage. Trauma and anoxia are the usual etiologic factors. Treatment is directed toward relieving increased intracranial pressure, usually by lumbar puncture.

#### SPINE AND SPINAL CORD

Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral may rarely produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury is most commonly at the level of the seventh cervical and first thoracic vertebrae. Transection of the cord may occur, but hemorrhage and edema may produce neurologic signs indistinguishable from those of transection, except that they are not permanent. There is complete paralysis of voluntary motion below the level of injury, though the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion. Severe spinal cord injuries usually cause death soon after birth. In the survivors there is usually permanent partial injury. In compression from a fracture or dislocation the prognosis is related to the time elapsing before the compression is removed.

#### PERIPHERAL NERVE INJURIES

##### BRACHIAL PALSY

Injury to the brachial plexus may cause paralysis of the upper arm with or without paralysis of the forearm or hand. Such an injury occurs when traction is exerted on the head during delivery of the shoulder.

In *Duchenne-Erb's paralysis* the injury is limited to the fifth and the sixth cervical nerves. The infant loses the power to abduct the arm from the shoulder, to rotate the arm externally and to supinate the forearm. The



characteristic position consists in adduction and internal rotation of the arm with pronation of the forearm. The power of extension of the forearm is retained, but the biceps reflex is absent. The Moro reflex is absent on the affected side (Fig. 76). There may be some sensory impairment on the outer aspect of the arm. The power in the forearm and the hand grasp are preserved unless the lower part of the plexus is also injured; the presence of the hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve, alteration of the diaphragmatic excursion may be observed fluoroscopically.

*Klumpke's paralysis* is a rarer form of brachial palsy; injury to the seventh and eighth cervical nerves and the first thoracic nerve produces a paralyzed hand, and ptosis and miosis, if the sympathetic fibers of the first thoracic root are also injured.

The mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury, from fracture, dislocation or epiphysial separation of the humerus, and from fracture of the clavicle.

The *prognosis* depends upon whether the nerve was merely injured or was lacerated. If the paralysis was due to edema and hemorrhage about the nerve fibers, there should be



FIG. 76. Brachial palsy of the left arm (asymmetric response to Moro reflex).



FIG. 77. Phrenic paralysis in a newborn infant. The right leaf of the diaphragm is elevated, owing to injury to the right phrenic nerve. Fluoroscopically, the right and left leaves of the diaphragm moved in a "seesaw" manner. There were also fractures of both clavicles and a right brachial palsy.

a return of function within a few months; if due to laceration, permanent damage may result. The involvement of the deltoid is usually the most marked; dropping of the shoulder may result from muscle atrophy.

*Treatment* consists in relaxation of the paralyzed muscles by preventing the antagonistic pull of the nonparalyzed muscles. While the infant is in his crib the wrist can be held by a clove-hitch to the head of the bed so that the arm is maintained abducted and rotated externally, with the elbow flexed. If the hand is paralyzed, padding should be placed in the fist. Later an airplane splint may be used to hold the arm in proper position. Physical therapy is a necessary adjunct to the treatment. If the paralysis persists, because of laceration of the nerve fibers, for two or three months, neuroplasty offers hope for partial recovery.

#### PHRENIC NERVE PARALYSIS

Phrenic nerve injury with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries are usually associated with a brachial palsy. Breathing is thoracic in type, so that there is no bulging of the abdomen with inspiration. Breath sounds are diminished on the affected side. The *diagnosis* is established by fluoroscopic examination which reveals the elevation of the diaphragm on the paralyzed side and the seesaw movements of the two sides of the diaphragm during respiration. There is no specific *treatment*; the infant should be placed on the involved side; oxygen therapy may be necessary. Feeding by gavage often saves the infant energy for maintenance of the labored respiratory movements. Recovery usually occurs. Pulmonary infections are a serious complication, and prophylactic antibiotic therapy is indicated.

#### FACIAL PALSY

Rarely facial palsy is nonobstetric, resulting from nuclear agenesis of the facial nerve. Usually, however, the paralysis is peripheral and results from pressure over the facial nerve in utero during labor or from forceps during delivery. When the infant cries, there is movement on only one side of the face, and the mouth is drawn to that side. On the affected side the eye cannot be closed and the nasolabial fold is absent. The *prognosis* depends upon whether the nerve was injured by pressure or whether the nerve fibers were torn. Improvement will occur within a few

weeks in the former instance. Care of the exposed eye is essential. Faradic stimulation is probably of no benefit, but neuroplasty may be indicated when the paralysis is persistent.

#### OTHER PERIPHERAL NERVES

Other nerves are seldom injured at birth, except as they are involved in fractures or hemorrhages.

#### VISCERA

The *liver* is the only internal organ other than the brain injured with any frequency. The damage usually occurs from pressure on the liver during delivery of the head in breech presentations. Overzealous manual attempts to apply artificial respiration during resuscitation are a less frequent cause. The injury is rupture of the liver with formation of a subcapsular hematoma. The hematoma may be large enough to cause anemia. Shock and death occur if the hematoma breaks through the capsule, reducing pressure and allowing fresh hemorrhage from the liver. Alertness to the possibility of this condition in infants delivered by breech presentations and in infants who receive manual resuscitation should make it possible to save some of them and to prevent the condition in others.

Although *adrenal hemorrhage* occurs with some frequency, especially after breech delivery, it is not known whether it is traumatic in origin, due to anoxia, or the result of severe stress, as in overwhelming infections. In older infants old calcified central hematomas of the adrenal have been identified at autopsy, suggesting that not all adrenal hemorrhages are fatal. The diagnosis is usually made at postmortem examination. The symptoms are profound shock and cyanosis. If adrenal hemorrhage is suspected, the treatment is the same as for acute adrenal failure (p. 1185).

#### INJURY OF THE STERNOCLEIDOMASTOID

A firm mass 1 to 2 cm. in diameter is occasionally noted in the midportion of the sternocleidomastoid muscle about the second week of life, although it may be present shortly after birth. It is believed by most to be a small hematoma resulting from injury to the muscle at birth, by others to be a fibromatous malformation of the muscle. Contrary to general belief, it does not always result in torticollis to the affected side. The majority of these tumors resolve spontaneously within the first year of life, and any



accompanying torticollis disappears. In the presence of torticollis and as a prophylactic measure the mother can be taught to over-extend the affected muscle by turning the infant's head in the opposite direction and at the same time flexing the neck toward the unaffected side twenty to twenty-five times on two or three occasions daily. This is best done with the baby lying supine on the lap of the sitting mother, the infant's head projecting beyond her knees and his feet against her abdomen. If torticollis persists beyond one to two years, surgical correction may be undertaken.

### FRACTURES

**Clavicle.** The clavicle is fractured more frequently than any other bone and is particularly vulnerable when there is difficulty in delivery of the shoulder. The infant characteristically fails to move, or to move freely, the arm on the affected side, and crepitus may be elicited. The Moro reflex is absent on the affected side, and there is spasm of the sternocleidomastoid muscle with obliteration of the supraclavicular depression at the site of the fracture. In greenstick fractures there may be no limitation of movement and the Moro reflex may be present. Fracture of the humerus or brachial palsy may also be responsible for limitation of movement of an arm and the absence of a Moro reflex on the affected side. The *prognosis* is excellent. *Treatment*, if any, consists in immobilization of the arm and shoulder on the affected side. A remarkable degree of callus develops within a week at the site of the fracture. This may be the first evidence of an unsuspected fracture.

**Extremities.** In fractures of the long bones spontaneous movement of the extremity is usually absent. The Moro reflex is absent from the involved extremity. The possibility of associated nerve involvement must be considered. Satisfactory results for a fractured humerus are obtained by strapping the arm to the chest or applying a Velpeau bandage, and later an airplane splint or a shell cast. For fracture of the femur, good results are obtained with Buck's extension. Splints are effective for treatment of fractures of the forearm or leg. Healing is usually accompanied by excess callus formation.

Dislocations and epiphysal separations rarely result from birth trauma, although epiphysal separations are probably as common as fractures. The upper femoral epiphysis may be separated by forcible manipu-

lation of the infant's leg, as, for example, in breech extraction or after version. There is swelling, slight shortening, limitation of active motion, painful passive motion, and external rotation of the leg. The diagnosis is established roentgenographically. The prognosis is good for the milder injuries, but coxa vara frequently results from extensive displacement.

**Nose.** The most prevalent injury of the nose is a dislocation of the cartilaginous portion of the septum from the vomerine groove and the columella. The infant may have difficulty in nursing and some impairment in nasal respiration. Treatment should be instituted immediately.

### ANOXIA

Anoxia is not a clinical entity, but a term which has been loosely applied to indicate the end result of lack of oxygen from a number of primary causes, some known and some unknown. Separate consideration will be accorded it, however, since it is the leading immediate, though not basic, cause of perinatal death or permanent damage to central nervous system cells which shows up as cerebral palsy and/or mental deficiency in later childhood. Its prevention and treatment are essentially those of the basic conditions which cause it, although death and disability may sometimes be prevented through symptomatic treatment with oxygen or artificial respiration.

*Fetal anoxia* may result from (1) inadequate oxygenation of maternal blood as in cardiac failure or carbon monoxide poisoning, (2) low maternal blood pressure as in the hypotension which may complicate spinal anesthesia, (3) inadequate relaxation of the uterus to permit placental filling as in uterine tetany caused by administration of Pituitrin or Pitocin, (4) inadequate attachment of the placenta as in premature separation of the placenta, (5) impedance to the circulation of blood through the umbilical cord as in compression or knotting of the cord, and (6) placental inadequacy from numerous causes, including toxemia and postmaturity.

After birth, anoxia may result from (1) anemia severe enough to lower the oxygen content of the blood to a critical level as in severe anemia due to hemorrhage or hemolytic disease, (2) shock severe enough to interfere with the transport of oxygen to vital cells as in adrenal hemorrhage, ventricular hemorrhage, overwhelming infection or massive

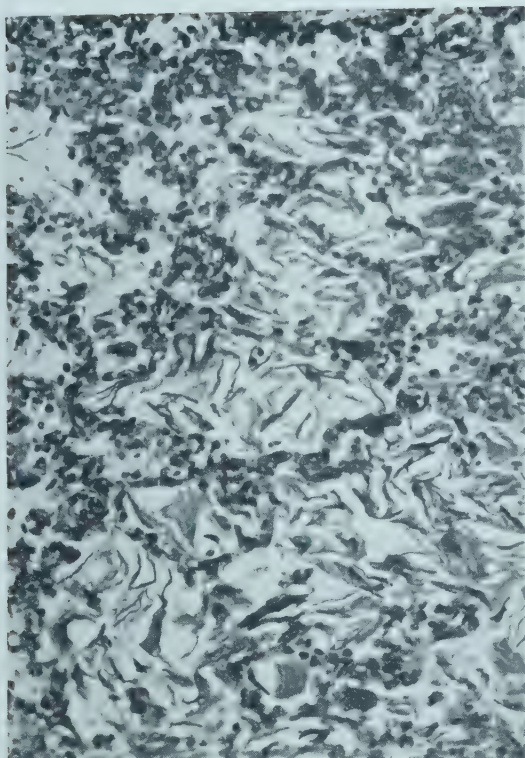


FIG. 78. Excessive amniotic debris in the lung of a stillborn infant.

blood loss, (3) poisoning of tissue cells so that they are unable to use oxygen as in narcosis from barbiturates or other drugs, (4) a deficit in arterial oxygen saturation due to failure to breathe adequately postnatally, owing to narcosis or cerebral defect or injury, and (5) failure of oxygenation of an adequate amount of blood as in severe forms of cyanotic congenital heart disease or deficient pulmonary ventilation.

Careful studies have failed to show any significant correlation between oxygen content of cord or arterial blood immediately after birth and later intellectual development. Therefore most of the deaths and cerebral damage which result from anoxia are probably related to fetal or postnatal periods of anoxia. The unknown duration of anoxia just before birth or at other times during intrauterine life, body temperature and individual variations in metabolic needs for oxygen are all factors which have probable influence on what constitutes a critical level or duration of anoxia after birth. The known resistance to anoxia demonstrated by newborn infants may be related to oxygen-saving short-cuts in essential metabolic pathways. It is possible that these factors are absent or diminished in individual infants as a result

of deficiency of the enzymes essential for them.

**Clinical Manifestations.** The signs of anoxia in the *fetus* are usually noted a few minutes to a few days before delivery. There is a sudden increase in fetal activity as if the baby were struggling in utero, which may be followed by diminished activity. The fetal heart rate slows, and the beat may become weak and irregular. Particularly in the infant near term, these are signs which should lead to immediate delivery to avoid death or central nervous system damage.

At the *time of delivery* the presence of yellow, meconium-stained amniotic fluid and vernix caseosa is a warning that there has been fetal distress, probably anoxic. Pallor, cyanosis, apnea, slow heart rate, unresponsiveness to stimulation, and muscular flaccidity are definite signs of anoxia.

*After delivery* anoxia is due to respiratory failure and will be discussed under that heading.

**Pathology.** The pathologic changes which result from anoxia per se are principally those caused by congestion and increased capillary permeability. Congestion and petechiae are found in all organs, but are especially noticeable in the pleura, pericardium, thymus, adrenals, brain and meninges. Cerebral edema is common. Gross subarachnoid, intraventricular or adrenal hemorrhage may be present without demonstrable tear of blood vessels. Histologic study of the brain and liver, particularly the right lobe, may show cellular degenerative changes similar to those produced experimentally by anoxia. Fetal anoxia is characterized pathologically by the additional finding of large amounts of amniotic debris in the respiratory passages (Fig. 78).

## RESPIRATORY DISTRESS AND FAILURE

Most disorders of respiration in the newborn infant fall into two principal groups (see Table 59): one resulting from failure of the respiratory center (central nervous system failure) and the other resulting from interference with alveolar exchange of oxygen and carbon dioxide (peripheral respiratory difficulty). The causes of the latter are discussed in the section on Disturbances of the Respiratory Tract. Cyanosis occurs in both central nervous system failure and peripheral respiratory difficulty; the latter merges into the former when anoxia is severe.



Table 59. Respiratory Distress and Failure in Newborn Infants

Type	Manifestations	Examples
Central nervous system failure	Apnea Slow, irregular, gasping respiratory efforts	1. Narcosis 2. Prenatal or paranatal anoxia 3. Intracranial hemorrhage or trauma 4. CNS anomalies
Peripheral respiratory difficulty	Rapid respiratory rate Increasing respiratory rate Chest lag Intercostal retraction Xiphoid retraction Chin tug Expiratory grunt Frothing at lips	1. Primary atelectasis 2. Congestive pulmonary failure 3. Hyaline membrane syndrome 4. Aspiration of meconium-containing amniotic fluid 5. Pneumonia 6. Diaphragmatic hernia 7. Lung cysts 8. Lobar emphysema 9. Pneumothorax 10. Aspiration of food or mucus

CENTRAL NERVOUS SYSTEM FAILURE

*Narcosis* results from heavy doses of morphine, Demerol or barbiturates to the mother shortly before delivery or from maternal anesthesia, especially if prolonged, during delivery. The infant is cyanotic at birth and slow to cry or breathe; when respiration is established, it is extremely slow.

Narcosis is rarely excusable and should be avoided by appropriate analgesic and anesthetic practices.

Treatment consists of physical stimulants such as frequent snapping of the soles of the feet to stimulate crying and deeper breathing, or insertion of a catheter through the nostril into the nasopharynx to produce reflex irritation and breathing. Caffeine with sodium benzoate, U.S.P., 0.5 cc. intramuscularly, may be used as often as every twenty to thirty minutes, if necessary and effective in stimulating the infant. If narcosis is due to morphine or its derivatives, n-allyl normorphine (Nalline), 0.1 mg. per kilogram of body weight, should be injected intravenously. Oxygen should be administered as long as cyanosis is present without it, and some form of artificial respiration may be necessary until

a regular and adequate respiratory pattern is established.

*Prenatal or paranatal anoxia*, whatever the cause, if sufficiently severe, will produce a central nervous system type of respiratory failure. Death is due to apnea in any event, and may be prevented by resuscitation, provided the basic cause of the anoxia can be eliminated within a reasonable time and while artificial respiration, if necessary, is being carried out. As a supplement to resuscitation and removal of the basic cause of anoxia, the use of hypothermia has been advocated, particularly in premature infants, as a means of temporarily reducing metabolic needs for oxygen during the period of oxygen want. Evidence to date is contradictory as to the value of this procedure, and further investigation is needed.

*Intracranial hemorrhage and trauma* (see p. 316).

*Central nervous system anomalies* may produce respiratory failure through a primary maldevelopment of the respiratory center or secondarily through damage to the respiratory center by pressure from a gross anatomic abnormality. It is of interest that immaturity in itself seldom interferes with central respiratory mechanisms.

DISTURBANCES OF ORGAN SYSTEMS

Disturbances of the Respiratory Tract

The various congenital anomalies and localized injuries which may interfere with respiration such as atresia of the anterior or posterior nares, hypoplasia of the mandible

with posterior displacement of the tongue, malformation of the epiglottis, malformations or injury of the larynx, tracheo-esophageal fistula, evulsion of the phrenic nerve

and diaphragmatic hernia are described elsewhere in their appropriate sections.

Here, attention is directed to pulmonary disturbances which give rise to any or all of the symptoms of postnatal respiratory distress as listed in Table 59. Rapid or increasing respiratory rate usually constitutes the earliest and most consistent sign of pulmonary disease in the newborn infant. Notwithstanding the differences listed in Table 59, clinical distinction between intracranial lesions and pulmonary disorders as the cause of respiratory distress or failure is not always clear, and, of course, they may coexist.

### ATELECTASIS

Atelectasis of varying degree is almost constantly present in infants dying shortly after delivery. It is no longer considered to be an adequate explanation for death; careful post-mortem examination usually reveals a cause for persistent atelectasis. Primary atelectasis (failure of initial alveolar expansion), common among premature infants without other apparent abnormality at autopsy, is to be considered due to immaturity of the diaphragm and other respiratory muscles, hypermobility of the thoracic cage, or to other defects of the peripheral respiratory mechanism. It is also seen as a result of brain injury. Secondary atelectasis (alveolar collapse after initial expansion by air) may be seen as a gross or microscopic finding in all types of pulmonary disease in the newborn.

**Pathology.** In the stillborn infant the lungs have a uniformly beefy red appearance. Histologically, the interstitial tissues are congested, and the alveoli present a crumpled sac appearance. The degree of crumpling varies inversely with the amount of expansion of the alveoli by fluid presumed to be amniotic. With sudden anoxia in utero there may be more vigorous inspiratory movements than usual, with an increase in aspiration of amniotic fluid and perhaps also diminished absorption of it from the alveoli. The later in pregnancy this takes place, the more likely is one to find squamous epithelial cells and debris in the alveolar spaces (Fig. 78).

If an infant has breathed, the lungs may show beefy red areas alternating irregularly with lighter, aerated, raised portions. Histologically, the red areas are congested, and the alveolar spaces may be filled with varying amounts of blood or edema fluid. The lighter, aerated portions show varying degrees of distention of alveoli. If there has been vigorous

inspiration, either natural or artificial, one may find irregular areas of overdistention of alveoli. Some of these may have ruptured with resultant interstitial emphysema and, at times, pneumomediastinum and pneumothorax. Whether or not rupture of these overdistended alveoli occurs, they may prevent entrance of air into other parts of the lung.

**Clinical Manifestations.** Cyanosis and poor respiratory exchange on auscultation of the chest are the cardinal signs of atelectasis, which may be confirmed roentgenographically.

**Prevention and Treatment.** Prevention of premature labor, fetal and neonatal anoxia, intracranial hemorrhage, hyaline membrane disease and pneumonia would presumably eliminate most of the causes of atelectasis. Treatment should be aimed at early recognition and proper management of these underlying conditions.

### CONGESTIVE PULMONARY FAILURE

For purposes of identification this term may be arbitrarily applied to infants who show the clinical and pathologic manifestations considered characteristic of hyaline membrane disease, with the exception that hyaline membranes are not found on histologic examination of the lungs.

### HYALINE MEMBRANE DISEASE

Although its acceptance as a clinical and pathologic entity is frequently challenged, hyaline membrane disease is the most widely used term to describe a syndrome of neonatal respiratory distress also designated as abnormal pulmonary ventilation, postnatal asphyxia with atelectasis or perinatal distress syndrome. Pulmonary hyaline membranes are the most frequent pathologic finding in premature infants dying during the first week of life. They are found almost as commonly among full term infants of diabetic mothers and infants born by cesarean section who die with respiratory distress. Occasionally they occur among infants in whom no predisposing factor is apparent.

**Etiology.** It is now widely accepted that hyaline membranes can be produced as the result of (1) effusion from the pulmonary circulation; (2) conversion of fibrinogen in the effusion fluid to fibrin (possibly enhanced by the thromboplastic activity of aspirated amniotic fluid); and (3) syneresis of the



fibrin to form a membrane. Left-sided heart failure, aspiration of regurgitated amniotic fluid present in the stomach at birth, and the use of oxygen have all been proposed as factors contributing to the pathogenesis of the membranes.

**Pathology.** The lungs appear deep purplish-red and noncrepitant. Microscopically, there is extensive atelectasis, engorgement of the interalveolar capillaries, and a number of the alveolar ducts, alveoli and respiratory bronchioles are lined by acidophilic, homogeneous or granular membranes. Amniotic debris, intra-alveolar hemorrhage, pneumonia and interstitial emphysema are additional but inconstant findings (Fig. 79).

**Clinical Manifestations.** Usually the infant with hyaline membrane disease, except for other disturbance, appears normal at birth, but within a few hours, very rarely as long as twenty-four hours, begins to show signs of respiratory distress (see Table 59 for symptoms). In some instances, and especially early in the disease, evidences of emphysema are more striking than are those of atelectasis. When the signs are severe, death occurs within a few hours, but in milder cases the symptoms reach a peak within three days, after which gradual improvement sets in and recovery occurs. On auscultation air exchange usually seems to be within normal limits and rales are rarely heard. When present, they probably signify concomitant pneumonia. Roentgenographically (Fig. 80), the lungs show a reticulogranular appearance which is characteristic but not pathognomonic. It usually disappears with subsidence of respiratory distress, but occasionally persists for one to two weeks. In retrospect most infants who have hyaline membrane disease have shown some evidence of respiratory difficulty, particularly rapid or increasing respiratory rate, during the first hour of life. By using respiratory rates during the first hour or so of life, it is therefore possible to anticipate hyaline membrane disease before sternal retraction, cyanosis and other signs of severe difficulty appear.

**Prognosis.** Since definitive diagnosis can be made only at autopsy, there are no statistics on the prognosis of hyaline membrane disease. When recovery occurs, there are no apparent residuals even though cyanosis has been severe.

**Prevention.** The prevention of prematurity, avoidance of unnecessary cesarean section and careful management of the diabetic mother are the most important factors in the

prevention of hyaline membrane disease. Gastric suction immediately after birth and preferably before the first breath should be performed to prevent possible aspiration of regurgitated amniotic fluid. Although there are conflicting reports as to the benefit of this procedure, it is harmless. Aerosolized water mist with or without wetting, fibrinolytic or proteolytic agents has not been shown to affect the incidence of the disease, nor has the current decrease in the use of oxygen.

**Treatment.** Owing to the frequency of accompanying pneumonia, antibacterial agents, usually penicillin, 100,000 to 200,000 units, and streptomycin, 50 to 100 mg. (except as there is staphylococcal infection in the nursery—see p. 345), according to the size of the patient, may be administered intramuscularly every twelve hours until recovery occurs. Sulfisoxazole should be avoided because it increases the risk of hyperbilirubinemia and kernicterus, and intramuscular preparations of broad-spectrum antibiotics are often poorly absorbed, especially in prematures. Supersaturation of the inspired air with water mist has no advantage over atmospheres of 80 to 90 per cent relative humidity, nor has the inclusion of wetting agents in nebulized water mist been shown to increase its efficacy. Aerosolized proteolytic or fibrinolytic enzymes such as trypsin

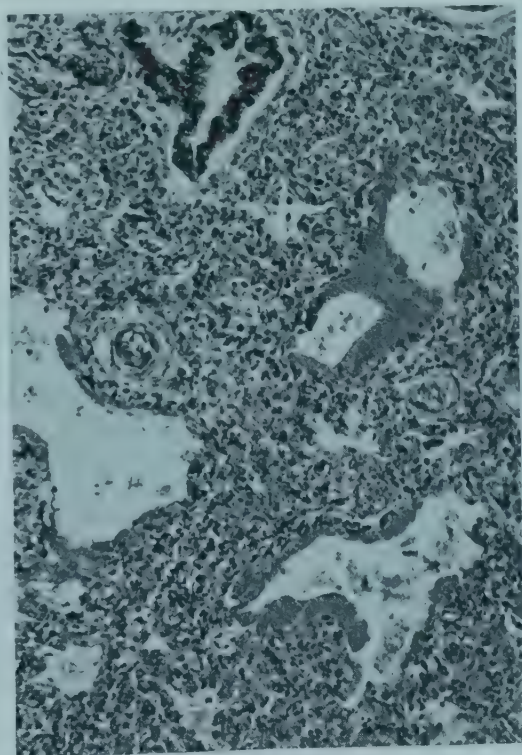


FIG. 79. Pulmonary hyaline membranes lining the air spaces of the lung in a premature infant.



FIG. 80. Hyaline membrane syndrome. A diffuse reticulogranular pattern is evident throughout the lungs. The air-containing bronchi are visible by virtue of surrounding nonaerated lung, particularly on the left.



FIG. 81. Fetal distress syndrome.

Figures 80 and 81 show the contrasting radiographic pictures seen in infants with neonatal respiratory distress. Figure 80 shows the uniform reticulogranular pattern consistently seen in but not pathognomonic of hyaline membrane disease. The apparent cardiac enlargement is also characteristic. Figure 81 shows the coarsely granular pattern with irregular aeration typical of fetal distress syndrome (meconium aspiration pneumonia).

and streptokinase-streptodornase to dissolve the hyaline membranes have also been without proved benefit. Moist oxygen should be used only in quantities sufficient to relieve cyanosis when it is present. A few infants in whom cyanosis and respiratory failure could not otherwise be controlled have appeared to respond to the use of the Bloxsum Airlock, although most authorities doubt its efficacy and decry its use. Sternal traction via a suture passed through the xiphoid has been advocated as producing more efficient respiratory efforts, but clinical results are inconclusive. The rocking-bed respirator and a patient-cycled tank respirator, used in conjunction with oxygen, have proponents, but little convincing evidence to support their use in hyaline membrane disease. The same is true of hypothermia.

## PNEUMONIA

Histologic evidence of pneumonia is a frequent finding at autopsy in newborn infants, particularly among those who die after signs

of respiratory distress, even when the primary lesion is obviously cerebral hemorrhage, hyaline membrane disease, aspiration of amniotic contents or feedings, or one of the various forms of emphysema or pneumothorax. Its role as a cause of death is not always clear in such instances, and the clinical manifestations may merge indistinguishably with those of the primary disturbance. Pneumonia does account for about 10 per cent of neonatal deaths.

**Etiology.** Pneumonia in the newborn is caused by bacteria and perhaps by viruses from aspiration of infected amniotic contents or vaginal secretions, through the blood stream, or through the respiratory tract, particularly when there is contact with adults who have respiratory infections. The *Pneumococcus*, beta-hemolytic *Streptococcus* and *H. influenzae*, the commonest acute pulmonary pathogens in older infants and children, are rare etiologic agents of pneumonia during the first two weeks of life, whereas coliform organisms, enterococci, *Klebsiella*, *Pseudomonas*, *Proteus*, *Salmonella* and *Staphylococ-*



cus are common ones. Of these, the coliform organisms are the most frequent, with the *Staphylococcus* second.

**Pathology.** Pneumonia in early infancy is usually bronchopneumonic in type, occasionally interstitial or lobar.

**Clinical Manifestations.** The first signs of pneumonia in the newborn are usually non-specific. They include loss of appetite, listlessness, poor color which may or may not be definable as cyanosis, a rise or sudden fall in body temperature, abdominal distention, sudden loss or gain in weight, and a general impression on the part of the nurse or mother that the baby is doing less well. Cough is inconstant, but almost always means pneumonia when present. A significant increase in respiratory rate, usually to about 80, is a constant and early finding. It, too, should always arouse suspicion of pneumonia. Flaring of the alae nasi, accentuation of the normal irregularity of breathing, and respiratory distress may be present.

**Diagnosis.** Often no physical signs are elicited, although careful auscultation will usually reveal fine, crackling rales which are most commonly heard in the perihilar areas posteriorly, but may be localized in any portion of the lungs. It is important to auscultate the chest with the baby crying as well as quiet, since rales are frequently heard only

at the end of the deep inspirations which come only with crying in the newborn. Areas of hyperresonance may indicate compensatory emphysema. Roentgenograms of the chest are often helpful. Nasopharyngeal and blood cultures are helpful in making an etiologic diagnosis.

For reasons not clear, pneumonia frequently accompanies or follows diarrhea during the first few months of life, and should be kept in mind as a possible complication of enteritis.

**Aspiration Pneumonia.** A history of single or repeated attacks of coughing or apparent choking followed by signs of pneumonia or merely by the infant doing less well than before should suggest the possibility of aspiration pneumonia.

Aspiration pneumonia can be prevented in most instances by care in feeding plus prompt upending of the infant should choking or severe coughing occur during feeding. Small infants should be left lying on their right side or abdomen after feeding rather than on the back. Contents of the stomach should always be aspirated through a soft rubber catheter just before operation or other procedure requiring anesthesia. Procedures which may significantly disturb the infant, and particularly those which interfere with changing the infant to the head-down position, such as



FIG. 82. Staphylococcal pneumonia in an infant 7 months of age. A, The diffuse inflammatory process involving the left lung and pleura is evident. B, Five days later, just before death, there are multiple air-containing cavities in the lung and pleura.

jugular or femoral puncture, lumbar puncture and subdural taps, should be performed at least two hours after a feeding.

*Staphylococcal pneumonia* (see also p. 344) should be suspected in any infant who shows slight and nonspecific untoward signs and who has been exposed to staphylococcal skin infections. Empyema and pneumothorax are frequent complications. The latter constitutes such an immediate threat to life that infants with staphylococcal pneumonia must be watched closely for acute onset of respiratory distress, so that treatment by closed thoracotomy drainage can be carried out without delay.

**Treatment.** Since the usual etiologic organisms are coliforms or staphylococci, chemotherapeutic agents effective against them must be used until a specific bacteriologic diagnosis can be made. Very large doses of penicillin and streptomycin in combination at times are effective even when the organism concerned appears to be insensitive to each of them on laboratory testing. As a single drug, chloramphenicol is the agent of choice, since it is effective against most strains of both coliforms and staphylococci. It has the disadvantage that it probably must be administered orally or intravenously for maximum effect, particularly in premature infants. Once a bacteriologic diagnosis is made, treatment should be directed accordingly. In the presence of known exposure to an epidemic of staphylococcal infection the therapy should include the agent or combination of agents known to be most effective against that particular strain. Gamma globulin may be administered intramuscularly in an attempt to bolster the infant's immune defenses.

## PNEUMOTHORAX AND PNEUMOMEDIASTINUM

Asymptomatic pneumothorax, either unilateral or bilateral, is estimated to occur in as much as 1 per cent of all newborn infants; symptomatic pneumothorax and pneumomediastinum are less common.

**Etiology.** Since pneumothorax is seen frequently among newborn infants who have been subjected to resuscitative measures, it seems likely that the most common cause is overinflation and resulting alveolar rupture. If the ruptured alveoli are on the pleural surface, pneumothorax without pneumomediastinum occurs. If they are not, pulmonary interstitial emphysema results. If the volume

of escaped air is great enough, it is believed to follow the vascular sheaths to the mediastinum, causing mediastinal emphysema. In turn, the mediastinal air may "break" into the pleural space to cause pneumothorax, or into the subcutaneous tissues of the neck and chest to cause subcutaneous emphysema. Ball-valve types of bronchial or bronchiolar obstruction resulting from aspiration may also cause alveolar overinflation which, if mild, produces local emphysema, but, if severe, results in alveolar rupture and pulmonary interstitial emphysema, pneumomediastinum or pneumothorax.

Pneumothorax may also result from direct trauma such as puncture from a broken rib or from rupture of a lung abscess associated with staphylococcal pneumonia. It also occurs from rupture of pulmonary cysts, congenital or acquired. It occurs rarely as a result of alveolar rupture in lobar emphysema.

**Clinical Manifestations.** Localized areas of emphysema frequently seen in roentgenograms of the chest of newborn infants may represent ball-valve bronchial obstruction, pulmonary interstitial emphysema or emphysematous blebs (cysts). The physical findings of asymptomatic pneumothorax are hyperresonance and diminished breath sounds over the involved side of the chest.

Symptomatic *pneumothorax* is characterized by respiratory distress which varies from increased respiratory rate to severe dyspnea and cyanosis. The onset may be sudden or gradual. The chest may appear asymmetric with increased anterior-posterior diameter and bulging of the intercostal spaces on the affected side, and there are hyperresonance and diminished or absent breath sounds. The heart is displaced toward the unaffected side, and the diaphragm is displaced downward. This may produce a finding of apparent hepatomegaly with right-sided pneumothorax. Since both sides may be affected, symmetry of findings does not rule out pneumothorax.

With *pneumomediastinum* the degree of respiratory distress is again dependent on the amount of trapped air. If it is great, there is bulging of the midthoracic area, the neck veins are distended, and the blood pressure is low. The last two findings are the result of blockage of the circulation by compression of the systemic and pulmonary veins. Subcutaneous emphysema in the newborn is almost pathognomonic of pneumomediastinum.

**Diagnosis.** Pneumothorax and pneumome-





FIG. 83. Pneumomediastinum in a newborn infant. Anteroposterior view demonstrates compression of lungs and the lateral view bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

diastinum should be suspected in any newborn infant with respiratory distress; the diagnosis is established roentgenographically (Fig. 83).

**Treatment.** Asymptomatic pneumothorax or pneumomediastinum requires no treatment. If severe respiratory or circulatory embarrassment is present, needle aspiration is indicated. If unsuccessful in maintaining relief of distress, it should be followed by closed thoracotomy with the tube connected to a water trap so that air may escape, but not enter the chest.

## LOBAR EMPHYSEMA

Localized and fixed overdistention of an entire lung, lobe or segment may cause respiratory distress at any time during the newborn period. The condition resembles that due to a check-valve type of obstruction in the bronchus supplying the affected area. Although chondromalacia, bronchial stenosis or web, localized redundancy of bronchial mucosa (valves), endobronchial proliferation of aberrant tissue and external compression by anomalous blood vessels have all been proposed or reported as etiologic factors, no clear cause for lobar emphysema is found in many instances. It causes respiratory distress

through compression of surrounding lung tissue on the same side. If it is severe, the involved area may extend to the opposite side of the chest; the heart is displaced to the opposite side. The physical findings are indistinguishable from those of severe tension pneumothorax, and differentiation from tension pneumothorax and cystic disease of the lung may be difficult even roentgenographically. The treatment is usually surgical removal of the involved area.

## LUNG CYSTS

The great majority of lung cysts during the newborn period are acquired as the result of rupture of alveoli from overinflation or by infection, often staphylococcal; congenital cysts are rare. They may be solitary or multiple, air-containing or filled with fluid, and are believed to result as a developmental anomaly of the bronchial buds. Air-filled cysts on the surface of the lung, whatever their origin, sometimes rupture and cause pneumothorax. This is particularly true of multicystic disease. Since most cystic areas discovered by roentgenologic examination will disappear spontaneously, treatment, which is surgical removal, should be reserved for those which cause severe respiratory distress.

## Disturbances of the Digestive System

### VOMITING

Infants at times vomit mucus, often blood-streaked, in the first few hours after birth. This vomiting infrequently persists after the first few feedings; it may be due to irritation of the gastric mucosa by material swallowed during delivery. If the vomiting is protracted, gastric lavage with physiologic saline solution may relieve it.

Vomiting is a relatively frequent symptom during the newborn period. In the majority of instances it is simply regurgitation from overfeeding or from failure to permit the infant to eructate swallowed air. When vomiting occurs shortly after birth and is persistent, the possibility of increased intracranial pressure or of intestinal obstruction must be considered.

Obstructive lesions occur most frequently in the esophagus (p. 640) and intestines (p. 665). Vomiting from esophageal obstruction occurs with the first feeding. The diagnosis of *esophageal atresia* can be suspected if there is unusual drooling from the mouth and if resistance is encountered in the attempt to pass a catheter into the stomach. There is considerable advantage in establishing the diagnosis before the infant chokes on oral feedings and endangers himself to aspiration pneumonia. *Cardiospasm* is a rare cause of vomiting in the newborn infant; it is demonstrable roentgenographically by obstruction at the cardiac end of the esophagus, without organic stenosis. Regurgitation of feedings due to continuous relaxation of the esophageal-gastric sphincter, *chaliasia*, is an infrequent cause of vomiting, which can be controlled by keeping the infant in a semi-upright position. Vomiting from obstruction of the small intestine usually begins on the first day of life and is frequent, persistent, usually nonprojectile, copious and, unless the obstruction is above the ampulla of Vater, bile-stained; it is associated with abdominal distention, visible deep peristaltic waves, and constipation. Upright roentgenographic films of the abdomen will show the distribution of air in the intestine and often aid in the location of the site of the obstruction; the use of contrast material for these studies is usually unnecessary. Persistent vomiting may occur with congenital hernia of the diaphragm (p. 692) when the viscera are crowded. The

vomiting of *pyloric stenosis* may begin any time after birth, but does not assume its characteristic pattern before the second or third week. Vomiting may occur with many other disturbances which do not obstruct the digestive tract, such as celiac disease, milk allergy, septicemia, meningitis and other infections. It is common with urinary tract infections.

### THRUSH

(ORAL MONILIASIS)

Thrush of the mouth is discussed on page 633. It is mentioned here to emphasize its importance in newborn infants. At this age healthy infants are infected; later, the infection is rare except in debilitated infants and children and those receiving antibiotic therapy.

There is a positive correlation between maternal vaginal and infantile oral moniliasis. The maternal source appears to be the principal primary means of infection in healthy newborns. Secondary cases develop in the hospital nursery, presumably by contact with infected infants and contaminated supplies.

Occasionally a heavy coat forms on the tongue, but its appearance is not that of thrush, nor have cultures from it revealed *Candida albicans*. It can be removed by one or two applications of 1 per cent aqueous solution of gentian violet.

Oral thrush in an otherwise healthy infant is usually a self-limited infection, but treatment is advised (see p. 634). Special sterilization precautions should be taken with nipples, bottles and other materials used by the infant to prevent spread of the infection.

### DIARRHEA

(See pp. 187, 346, 655.)

### CONSTIPATION

More than 90 per cent of newborn infants pass meconium within the first twenty-four hours, and most of the remainder do so within thirty-six hours. Therefore the possibility of intestinal obstruction should be considered in any infant who does not pass meconium within that time. Intestinal atresia or stenosis (p. 665), congenital aganglionic megacolon



(p. 674), meconium ileus or meconium plugs should be suspected. Constipation not present from birth, but appearing during the first month of life, suggests congenital aganglionic megacolon, cretinism or anal stenosis. It must be kept in mind that infrequent bowel movements do not necessarily mean constipation (p. 652). Breast-fed infants may rarely go as long as ten days without a bowel movement and without evidence of discomfort, and then pass a large but otherwise normal stool.

### MECONIUM PLUGS

Anorectal plugs (Fig. 84) of lower water content than normal may be a cause of intestinal obstruction in newborn infants. Rarely a firm mass of meconium may form elsewhere in the intestine and cause intra-uterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis of the pancreas. Likewise, anorectal plugs may cause intestinal ulceration and perforation. The plug is usually easily removed by the examining finger, but may require irrigation with isotonic sodium chloride solution or half-strength hydrogen peroxide for evacuation. After removal of a meconium plug the infant should continue to be observed closely for the possible presence of congenital aganglionic megacolon.

### MECONIUM BODIES

These light yellow particles are usually no more than 1 mm. in diameter, but may rarely be large enough to cause distortion of the intestine (Fig. 85). They are occasionally associated with intestinal atresia.

### MECONIUM ILEUS

Impaction of meconium is a relatively rare cause of intestinal obstruction in the newborn infant. It is almost invariably associated with cystic fibrosis of the pancreas. The depletion or absence of the pancreatic ferments prohibits normal digestive activities in the intestinal tract, and meconium is left in a viscid, mucilaginous state. It clings to the intestinal wall and is moved with difficulty or not at all by intestinal peristalsis. Why meconium ileus is a relatively uncommon manifestation of congenital pancreatic deficiency is not clear, but it may be that it occurs only in association with reduction or absence of pancreatic ferments.

The inspissated and impacted meconium fills the intestinal canal, but is most concentrated in the lower ileum. The pancreatic and bile ducts may be plugged by the viscid meconium.

Clinically, the pattern is that of congenital intestinal obstruction with or without intestinal perforation (see Meconium Peritonitis, p. 332). Abdominal distention is prominent, and persistent vomiting soon occurs. Infrequently, one or more inspissated meconium stools may be passed shortly after birth.

The *differential diagnosis* involves other

FIG. 84.

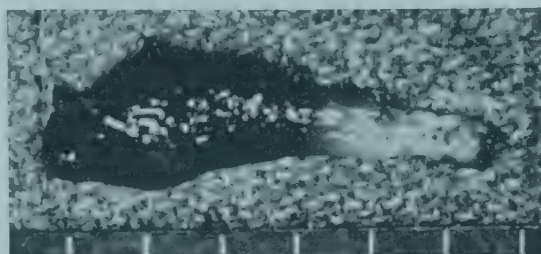


FIG. 85.

FIG. 84. Anorectal plug, from child who had not passed meconium for 2 days after birth, is indistinguishable from normal plug. Pale end was adjacent to anus.

FIG. 85. Cecum with large meconium bodies. (From J. L. Emery: Abnormalities in Meconium of Fetus and Newborn. Arch. Dis. Childhood, Vol. 32.)



FIG. 86. Meconium ileus. Impacted meconium with small amounts of air interspersed throughout it in loops of intestine on right side of abdomen; intestinal loops above this impaction are greatly distended.

causes of intestinal obstruction; an exact diagnosis cannot be made except by laparotomy. A presumptive diagnosis can be made on the basis of a history of cystic fibrosis of the pancreas in a sibling, by palpation of doughy or cordlike masses of intestines through the abdominal wall and by the roentgenographic appearance. In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and not be as evenly filled with gas. At points of heaviest meconium concentration the infiltrated gas may create a granular appearance (Figs. 86, 87).

The case fatality rate is high, but a number of infants have survived the neonatal period; their subsequent prognosis is dependent upon the basic disturbance, cystic fibrosis of the pancreas.

*Treatment* is surgical. A number of operative techniques have been used. Gross recommends the so-called Mikulicz resection of the terminal portion of the ileum, with a temporary double ileostomy through which the intestine can be lavaged with dilute hydrogen peroxide solution.

### MECONIUM PERITONITIS

Perforation of the intestine may occur in utero or shortly after birth. The tear may be sealed by natural processes relatively quickly with only a small amount of meconium escaping, or the meconial contents may largely

be emptied into the peritoneal cavity. Such perforations occur most often as a complication of meconium ileus in infants with cystic fibrosis of the pancreas, but occasionally the perforation is due to a meconium plug, meconium bodies or intestinal obstruction of whatever cause.

When the intestinal perforation is spontaneously sealed with the escape of only a small amount of meconium, and there are no subsequent signs of intestinal obstruction or peritonitis, the event may never be known, or, if some of the meconial particles become calcified, they may subsequently be discovered fortuitously on roentgenograms of the abdomen. Otherwise the clinical picture is dominated by the signs of intestinal obstruction and/or peritonitis. Characteristically, there are abdominal distention, vomiting and absence of stools. The treatment is primarily elimination of the intestinal obstruction and drainage of the peritoneal cavity. Supportive fluid therapy is detailed on page 186.

### JAUNDICE IN THE NEWBORN INFANT

**Etiology.** Recent investigations have shown that lipid-soluble bilirubin (indirect-reacting) must be converted to water-soluble glucuronides of bilirubin (direct-reacting) before it can be excreted in either bile or urine. This conversion appears to require adequate amounts of an enzyme, tentatively named bilirubin transferase. However, there is some evidence that this enzyme may not be specific for the conversion of bilirubin, but is concerned with glucuronic acid conjugation in general and might be more accurately labeled glucuronic acid conjugase. The enzyme seems to be present either in small amounts or in an inactive state in newborn infants, particularly in premature infants. Therefore any factor which increases the load of bilirubin to be metabolized by the liver (erythroblastosis fetalis, other hemolytic anemias, infection), any factor which may damage or reduce the activity of the enzyme (anoxia, infection, possibly hypothermia and thyroid deficiency), any factor which may compete for or block the enzyme (drugs and other substances requiring glucuronic acid conjugation for excretion) or any factor leading to absence or decreased amounts of the enzyme (genetic defect, prematurity) may be expected to cause or increase the degree of jaundice. Since most neonatal jaundice is due to increased serum levels of indirect-reacting bilirubin, it is logical to expect that



the magnitude of these levels will be dependent on the degree and duration of deficiency of this enzyme.

**Clinical Manifestations.** Jaundice may be present at birth or may appear at any time during the neonatal period, depending on the condition responsible for it. Its intensity bears no dependable relationship to the degree of hyperbilirubinemia. Jaundice resulting from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange; jaundice of the obstructive type (direct bilirubin), a greenish or muddy yellow. This difference is usually apparent only in severe jaundice. The infant may be lethargic, feed poorly and become dehydrated.

**Differential Diagnosis.** Jaundice present at birth or appearing within the first twenty-four hours of life should be considered due to erythroblastosis fetalis (p. 955) until proved otherwise; cytomegalic inclusion disease (p. 524) and congenital toxoplasmosis (p. 616) are other rather infrequent possibilities. Jaundice which first appears on the second or third day is usually "physiologic," but may represent the more severe form now called hyperbilirubinemia of the newborn. Familial nonhemolytic icterus also is seen initially on the second or third day. *Jaundice appearing after the third day and within the first week should suggest septicemia as the*

*most likely cause; it may be caused by other infections, notably syphilis, toxoplasmosis and cytomegalic inclusion disease.*

Neonatal jaundice initially noted after the first week of life suggests congenital atresia of the bile ducts (p. 714), homologous serum hepatitis, herpetic hepatitis, idiopathic dilatation of the common bile duct (p. 714), galactosemia (p. 274), congenital hemolytic anemia (spherocytosis) or possibly the crises of other hemolytic anemias such as thalassemia, sickle cell disease, hereditary nonspherocytic anemia or hemolytic anemia due to idiosyncrasy to drugs or other substances.

Persistent jaundice during the first month of life suggests the so-called inspissated bile syndrome, which may follow erythroblastosis fetalis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus (p. 702), congenital atresia of the bile ducts, idiopathic dilatation of the common bile duct, or galactosemia. Rarely, physiologic jaundice may be prolonged for several weeks. When this occurs, the possibility of cretinism should also be considered.

**Physiologic Jaundice (Icterus Neonatorum).** Since so-called physiologic jaundice now appears to be due to a temporary metabolic defect, the term is misleading and should be discarded. The usually slight degree of jaundice which is clinically visible

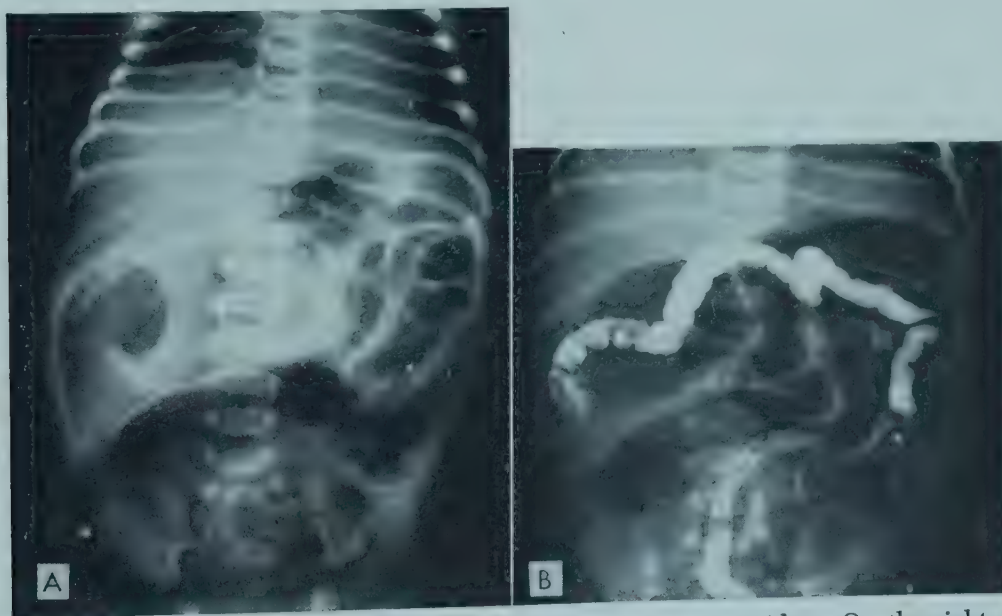


FIG. 87. Meconium ileus. A, Multiple loops of distended bowel are evident. On the right side of the abdomen a large section of small intestine containing inspissated meconium is suggestive of a solid mass. The meconium is characteristically interspersed with small bubbles of air, creating a granular appearance. The large loops of distended bowel in the pelvis proved to be loops of ileum. B, The colon is outlined by contrast material. The colon is small because meconium has not reached it as is the case in meconium ileus or atresia of the ileum. The small circumscribed radiolucencies in the colon represent air injected with the contrast material and mucus present in the colon.

**Table 60.** Relation of Maximum Total Serum Bilirubin Concentration to Incidence of Kernicterus

Maximum Bilirubin Concentration (Mg./100 Ml.)	Kernicterus
10-18.....	0
19-24.....	7%
25-29.....	30%
30-40.....	70%

Adapted from Mollison and Cutbush: Recent Advances in Paediatrics. London, J. & A. Churchill, Ltd., 1954, p. 112.

on the second or third day in about two thirds of full term newborn infants and which ordinarily disappears between the fifth and the seventh days of life is termed physiologic jaundice. It is dependent on the normal neonatal rise in serum bilirubin level which, in turn, is believed to be the result of the breakdown of fetal red cells combined with transient deficiency of bilirubin transferase in the liver. Among premature infants this rise in serum bilirubin tends to be a little slower and of longer duration, resulting in generally higher levels, the peak being reached between the fourth and seventh days; peak levels in term infants usually occur on the second or third day of life.

**Hyperbilirubinemia of the Newborn.** When total serum bilirubin levels reach 18 to 20 mg. per 100 ml. during the first week of life, bilirubinemia beyond "physiologic" bounds (hyperbilirubinemia) is considered to be present. This may occur as an exaggeration of "physiologic" jaundice, particularly in prematures, or as a result of excessive hemolysis, as in erythroblastosis fetalis. The term *hyperbilirubinemia of the newborn*, however, should be reserved for those infants whose primary problem is a deficiency or inactivity of bilirubin transferase rather than an excessive load of bilirubin for excretion. Serum bilirubin may reach the alarming level of 60 to 70 mg. per 100 ml. in full term or premature infants in the absence of any blood group incompatibility.

The *significance* of hyperbilirubinemia lies in the high incidence of kernicterus associated with serum bilirubin levels over 18 to 20 mg. per 100 ml. and the fact that this condition rarely occurs in infants who do not have levels of that magnitude. The correlation between serum bilirubin levels and kernicterus in infants with erythroblastosis fetalis (Table 60) undoubtedly holds for infants without blood group incompatibilities.

The *incidence* of hyperbilirubinemia among term infants without blood group incompatibility is about 5 per cent; among premature infants without blood group incompatibility it varies from 10 to 40 per cent in different series. Because the incidence of kernicterus varies from 2 to 16 per cent of all autopsies done on premature infants, there is little doubt that factors other than the initial unavailability of bilirubin transferase play a role. Some of these factors are known. Vitamin K analogues (72 mg. to the mother during labor and 10 to 30 mg. to infants over the first few days of life) are associated with a high incidence of hyperbilirubinemia. Sulfisoxazole (Gantrisin) predisposes to the development of kernicterus in premature infants at relatively low serum bilirubin levels. Prolonged neonatal cyanosis, bacteremia and a diabetic mother predispose the infant to hyperbilirubinemia. Negro infants appear to be less susceptible, but studies to date deal only with babies premature by weight, and it is well known that Negro infants tend to weigh less than white infants of the same gestational age. Since hyperbilirubinemia is related to short gestational age rather than to low birth weight, the supposed difference between white and Negro infants may be more apparent than real.

**Inspissated Bile Syndrome.** In a few infants with erythroblastosis fetalis and marked hyperbilirubinemia the icterus persists and is associated with a significant and increasing elevation of direct as well as of indirect bilirubin. It is not known whether this condition occurs in association with hyperbilirubinemia due to deficiency of bilirubin transferase. It has been postulated that the syndrome is the result of obstruction from swollen liver parenchymal cells damaged by erythroblastosis. An alternate theory is that the hemolytic process produces an overload of bile pigment causing stasis and blockage in the intrahepatic ducts, particularly in the presence of dehydration. Its onset appears to be too early to be the result of homologous serum hepatitis acquired through the blood used for transfusion of the erythroblastotic infant, and it has become increasingly rare with the more liberal use of repeated exchange transfusions to lower serum bilirubin levels. The obstruction and jaundice clear spontaneously within a few months, and there is no mortality related to it; the possibility of neurologic damage must be considered.

**Neonatal Hepatitis.** About 25 per cent of cases of prolonged obstructive jaundice in



infancy are due to neonatal hepatitis with onset during the first few weeks of life. The etiology is not clear, since it is rarely, if ever, associated with hepatitis in the mother during pregnancy. It is most likely caused by the virus of homologous serum hepatitis, the mother being a carrier. A few cases of hepatitis and icterus caused by generalized infection with the virus of herpes simplex (p. 493) have been reported. Hepatitis is characterized by jaundice chiefly of the obstructive type, acholic stools, dark urine and moderate hepatomegaly and splenomegaly. Microscopic examination shows great variation in the size of liver cells, and multinucleated giant cells are diffusely distributed throughout the lobules.

Clinically it is impossible to differentiate neonatal hepatitis from congenital atresia of the bile ducts, idiopathic dilatation of the common bile duct or inspissated bile syndrome following erythroblastosis fetalis, although a history of severe hemolytic disease of the newborn strongly suggests the last. Differentiation on the basis of cephalin flocculation and thymol flocculation and turbidity tests is impossible because these usually give normal results in all four conditions. Administration of cortisone orally for ten days may be helpful diagnostically. It will occasionally relieve the obstructive factor in neonatal hepatitis and dramatically lower the serum bilirubin. Its effect on the ultimate course of the disease remains to be determined; it has no effect on prolonged obstructive jaundice from other causes in early infancy, and it should probably be avoided in herpetic hepatitis. Close observation of the infant and the pattern of his bilirubinemia for one month will on occasion clarify the diagnosis and probably will not harm the infant with surgically remediable biliary tract obstruction. If the diagnosis is still in doubt, a small abdominal incision should be made, a cholangiogram obtained after injection of dye into the gallbladder and a biopsy of the liver obtained. Extensive surgical exploration carries too high a mortality rate for the relatively frequent patient with neonatal hepatitis to

justify it as a means of early discovery and treatment of the rare instances of surgically reconstructive extrahepatic biliary malformations. About two thirds of infants with neonatal hepatitis recover completely, about 20 per cent succumb, and the others suffer cirrhosis of the liver. No specific treatment is available.

**Kernicterus.** The pathology and clinical manifestations of kernicterus, one of the principal causes of neurologic abnormalities, are described on pages 958 and 1077. Most studies suggest that kernicterus results from deposition of indirect-reacting bilirubin in brain cells. This rarely occurs with serum levels of indirect bilirubin under 20 mg. per 100 ml., and it appears that such levels must be maintained for at least twenty-four hours for kernicterus to occur. Any factor which tends to produce or prolong high serum indirect bilirubin levels increases the incidence of kernicterus.

**Prevention and Treatment.** Except for physiologic jaundice, icterus in the newborn is, as has been indicated, usually a sign of some other disease, and the treatment is that of the basic condition. However, jaundice itself requires treatment when bilirubinemia reaches levels at which kernicterus is a risk. At present, treatment consists of exchange transfusions repeated as frequently as necessary to keep indirect bilirubin levels under 20 mg. per 100 ml. After four to six transfusions the increasing risk of complicating infection, the technical difficulties and the apparent futility of the procedure usually justify cessation of treatment. A more logical approach is through avoidance of the use of sulfisoxazole, high doses of vitamin K, anoxia, prematurity and other at present unknown factors which may predispose the infant to kernicterus or to toxic levels of serum bilirubin. Prevention of hyperbilirubinemia through the early administration of substances designed to enhance the pathways for metabolism and excretion of bilirubin is still in the experimental stage, but offers promise.

## *Disturbances of the Blood*

### **ANEMIA IN THE NEWBORN INFANT**

Anemia at birth is manifest by pallor or shock. It is usually caused by hemolytic disease of the newborn (p. 955), but may also be the result of tearing or cutting of the umbilical cord during delivery or of hemor-

rhage from the fetal side of the placenta. The last may be caused by accidental incision of the placenta in the course of cesarean section or by so-called transplacental hemorrhage. Anemia at birth may also be seen in one of twins with conjoined placental circulation, in which case the anemic twin "bleeds into"

the other, who is larger and polycythemic.

*Transplacental hemorrhage* (see p. 943) with bleeding from the fetal into the maternal circulation is probably more common than is generally recognized, but is usually not sufficient to cause clinically apparent anemia at birth. The etiology of transplacental hemorrhage is not clear, but the condition has been proved as an entity through the demonstration of significant amounts of fetal hemoglobin and of red cells from the baby in the maternal blood on the day of delivery. This condition is the only proved means by which fetal red cells enter the maternal circulation to cause production of antibodies which result in hemolytic disease of the newborn.

Anemia appearing in the first few days after birth is most frequently the result of hemolytic disease of the newborn. Other causes are obvious hemorrhage as in hemorrhagic disease of the newborn and bleeding from an improperly tied or clamped umbilical cord; large cephalhematomas, which are a frequently unrecognized source of anemia during the newborn period; and intracranial hemorrhage or subcapsular bleeding from rupture of the liver (p. 320). Rapid decreases in hemoglobin or hematocrit values during the first few days of life may be the initial clue to either of the two last-named conditions.

Later in the newborn period delayed anemia from hemolytic disease of the newborn, with or without exchange transfusion, may be seen. Vitamin K (as Synkavite) in large doses has recently been considered a cause of anemia in premature infants characterized by inclusion bodies (Heinz bodies) in the erythrocytes. Congenital hemolytic anemia (spherocytosis) occasionally makes its appearance during the first month of life, and hereditary nonspherocytic hemolytic anemia in a newborn infant has been described. Bleeding from hemangiomas of the upper gastrointestinal tract or from ulcers caused by aberrant gastric mucosa in a Meckel's diverticulum or duplication are rare sources of anemia in the newborn.

Since further "physiologic" fall in erythrocyte and hemoglobin content is to be expected in all newborn infants (p. 932), *treatment* consists not only in removing the source of the anemia, if it is still present, but also in whole blood transfusion which probably should be mandatory for hemoglobin levels below 8 gm. per 100 ml. There is inconclusive evidence that early feeding of red

meats or administration of intramuscular iron may be effective in enabling anemic infants to show an increase rather than a decrease in erythrocyte and hemoglobin concentrations before the second or third month of life.

## HEMORRHAGE IN THE NEWBORN INFANT

*Hemorrhagic disease of the newborn* is a rare condition characterized by a tendency to spontaneous and prolonged bleeding, especially from the gastrointestinal tract or into the central nervous system, between the second and fifth days of life. The skin, umbilicus, conjunctiva, retina, nose, mouth, lungs and genitourinary tract may be other sites of bleeding. The disease has been thought to be related to the deficiency in prothrombin which is present during the first five days of life. Routine administration of small amounts of vitamin K to the mother in labor or to the newborn infant will correct the deficiency of prothrombin and appears to have reduced the frequency of hemorrhagic disease of the newborn. This exogenous vitamin K is presumed to supply the infant's needs until his intestinal bacterial flora is sufficiently established to supply the normal needs of this substance.

The actual relation of prothrombin and vitamin K deficiencies to hemorrhagic disease of the newborn is uncertain, and it is thought that there may be an unknown additional factor. An identical clinical picture may result from PTA (plasma thromboplastin antecedent) deficiency and probably from AHG (antihemophilic globulin) or PTC (plasma thromboplastin component) deficiency, or from afibrinogenemia or other congenital defects in blood coagulation.

In infants with hemorrhage not obviously related to trauma or anoxia an attempt should be made to identify any coagulation defect which may be present, and to carry out treatment as indicated. In the presence of severe bleeding in apparent hemorrhagic disease of the newborn a small transfusion (10 ml. per kilogram of body weight) of fresh compatible blood will stop the bleeding promptly if it is due to prothrombin deficiency or to one of the various types of hemophilia. Vitamin K administration is useful only in prothrombin deficiency due to lack of vitamin K, and there is a lag of several hours in its effect, so that it is of doubtful value in hemorrhagic emergencies.

The so-called *swallowed blood syndrome*, in which blood or bloody stools are passed, usually on the second or third day of life,



may be confused with hemorrhage from the gastrointestinal tract, or *melena neonatorum*. The blood may be swallowed during delivery or from a fissure in the mother's nipple. Differentiation from gastrointestinal hemorrhage is based on the fact that the infant's blood contains mostly fetal hemoglobin, which is alkali-resistant, whereas swallowed blood from a maternal source contains adult hemoglobin, which is promptly changed to alkaline hematin upon the addition of alkali. Apt has devised the following test for this differentiation:

(1) Rinse a blood-stained diaper or some grossly bloody stool with a suitable amount of water to obtain a distinctly pink supernatant hemoglobin solution. (2) Centrifuge the mixture. Decant the supernatant solution. (3) To five parts of the supernatant fluid add one part of 0.25 normal (1 per cent) sodium hydroxide. Within one to two minutes a color reaction takes place: a yellow-brown color indicates that the blood is maternal in origin; a persistent pink, that it is from the infant. A control test with known adult or fetal blood, or both, is advisable.

*Congenital thrombocytopenic purpura* (p. 976) may occasionally be confused with hemorrhagic disease of the newborn. It usually occurs in the infants of mothers with thrombocytopenia or possibly of those who have been sensitized to platelet antigens by previous transfusion or pregnancy. The labo-

ratory findings are those of thrombocytopenic purpura. The mother will in each instance have platelet agglutinins in her serum. Infants of mothers with thrombocytopenic purpura should be observed carefully for hemorrhage. Conversely, thrombocytopenia in the infant may be the first clue to the disease in the mother. The platelet agglutinins usually disappear from the baby's blood in a few days or weeks, and the platelet count returns to normal.

The widespread subcutaneous ecchymoses frequently seen in premature infants at or immediately following birth are apparently a result of *fragile superficial blood vessels* rather than of a coagulation defect. In any event vitamin K administration to the mother during labor seems to have little effect on their incidence. An occasional infant is born with petechiae or a generalized bluish suffusion limited to the face, head and neck. These are probably the result of *venous obstruction* caused by sudden increases in intrathoracic pressure during delivery. It may take two to three weeks for such suffusions to disappear.

Generalized petechiae suggest thrombocytopenia or infection. Acute leukemia is an exceedingly rare cause. Cytomegalic inclusion disease and syphilis should always be considered.

## Disturbances of the Genitourinary System

See also section on Genitourinary System.

One or both kidneys are often easily palpable in the newborn infant since the lower pole normally lies at the level of the pelvic brim. When both are palpable, there is usually no particular diagnostic problem, but when only one kidney can be felt, it frequently gives the impression that it is larger than normal or represents or is displaced by an intrinsic or extrinsic mass. Marked fetal lobulation may contribute to the impression of abnormality. Usually the problem resolves itself as the kidney becomes progressively less easily palpable during the early months of life. Since palpable enlargement or displacement of the kidney in the newborn may rarely be due to an embryoma, polycystic disease or hydronephrosis, an abdominal scout film and/or intravenous urograms are indicated if there is serious question about the nature of the palpable mass. Owing to the poor concentrating ability of the neonatal kidney, relatively large amounts of the con-

trast material (10 to 20 cc. of Diodrast) must be injected to get satisfactory films. Elevations of blood urea nitrogen may be seen during the newborn period in association with polycystic disease and hydronephrosis without necessarily implying a poor prognosis.

During the newborn period moderate elevation of the blood urea or nonprotein nitrogen is common and does not necessarily signify renal disease. The urine may contain casts and cellular elements which are apparently a manifestation of dehydration, since they are most often seen in dehydrated infants and disappear with the ingestion of adequate amounts of fluid.

### BILATERAL RENAL AGENESIS

Infants with bilateral renal agenesis have a characteristic facies (Potter): a general appearance of premature senility, a mild increase in width between the eyes, with a prominent fold of skin arising at the inner

canthus and extending downward and laterally below the eyes to form a wide semicircle, and unusual flattening and slight broadening of the nose, a recession of the chin, and large, low-lying ears with incomplete cartilaginous development. There is usually a diminished quantity of amniotic fluid, presumably due to lack of urine formation. At autopsy there is no evidence of the ureters or kidneys. Pulmonary hypoplasia has also been observed. The anomaly has occurred predominantly in male infants. In some of the female infants there has been failure of development of the uterus and the vagina, the gonads and the fallopian tubes being present. In male infants the prostate, seminal vesicles, ductus deferens and testes are normally formed. The bladder is a tubelike structure with little musculature. The rudimentary

adrenal glands are normal. The outlook is hopeless, the infant dying during labor or shortly after birth.

### URINARY TRACT INFECTION

In contrast to the sex distribution in later infancy, pyuria may occur more frequently in the male than in the female newborn infant. The etiologic agent is usually the colon bacillus, although it may be any of the urinary tract pathogens.

The symptoms may be vague; on occasion they are predominantly gastrointestinal. Fever, difficulty in feeding and failure to gain weight are commonly encountered; jaundice and meningismus are occasional features. There may be urinary suppression.

For diagnosis and treatment see page 1032.

## *Disturbances of the Cranium*

(See also Hydrocephalus, Anencephaly, Microcephaly and Craniosynostosis).

### CRANIOTABES

(CONGENITAL CRANIAL OSTEOPOROSIS)

Palpation of the skull of the newborn infant may reveal areas of softening along the suture lines, especially in the parietal area, which indent from pressure of the fingers with the resilience of a Ping-pong ball. This phenomenon is demonstrated more frequently in premature infants, but occurs in 10 to 35 per cent of all newborn infants. The failure to observe it in breech presentations has led to

an assumption that it may be due to intra-uterine pressure against the maternal pelvis. This condition is a harmless and physiologic result of incoordination between the rapid growth of the brain and the calcification processes in the vertex in the last month of gestation and is associated with a generalized osteoporotic process in the newborn infant. Differentiation must be made from the craniotables of rickets, from lacunar skull, in which honeycombed areas of porotic bone create a characteristic appearance in the roentgenogram of the skull, and from osteogenesis imperfecta.

## *Disturbances of the Skin*

Skin conditions which occur in older as well as in newborn infants are discussed in the section on The Skin. For Erysipelas, see page 410.

### LOCALIZED SKIN DEFECTS

Congenital skin defects may occur on various parts of the body, but especially on the scalp and along the vertebral column. The scalp defects vary in size up to a centimeter or so and may occur in the midline or over the parietal bones; they are at times mistaken for obstetric injuries. There is no hair over the involved portion, since the defect extends

through the dermal layer and, on occasion, into the deeper tissues, including the meninges. On the scalp and along the vertebral column they have their greatest significance when a sinus tract extends to the meningeal space. Such a defect and its sinus tract constitute an entry for meningeal infection and should be removed surgically as a prophylactic measure.

### ERYTHEMA TOXICUM

Erythema toxicum is a transient, blotchy erythematous rash occurring predominantly in the first few days of life. Characteristically,



there is a small whitish wheal in the center of the erythematous areas. The lesions develop on any part of the body, but especially on the back, the shoulders and the buttocks. The cause is obscure. The rash has been attributed to contact from clothing, to irritation from oil or soap and to a hypersensitivity to human or cow's milk or other allergens. The rash is likely to change remarkably within a few hours. There are no general symptoms, and no treatment is necessary.

## MILIA

Milia (see also p. 1280) occur commonly on the face of the newborn infant; they are pinpoint-sized, white spots which result from retention of sebaceous material within the sebaceous glands. They are especially prominent on the nose and chin, but occur on other parts of the face and on the body. They usually disappear with the normal process of desquamation in the newborn period.

## IMPETIGO NEONATORUM

See also Staphylococcal Infections (p. 344).

Impetigo neonatorum is presumably caused by staphylococci or streptococci. The source of the infection in a hospital nursery is often not determined; outbreaks have been attributed to a skin lesion of the mother or an attendant. Lesions not distinguishable from impetigo neonatorum have been noted at birth; their etiology is unknown.

The lesion is a superficial vesicle on a



FIG. 88. Impetigo neonatorum.

reddened base surrounded by an erythematous areola. The blister is often wrinkled, but contains some fluid and is easily denuded by slight trauma, usually without formation of crusts (Fig. 88). The lesions tend to appear on moist or opposing surfaces of the skin, as under the abdominal band or diaper, in the groin, in the axilla and in the folds of the neck. Serious local lesions are not common, and constitutional manifestations are rare.

Impetigo neonatorum is important principally because it is contagious. On rare occasions septicemia and pemphigus occur as complications. All infants in a hospital nursery who contract impetigo should be isolated. Local therapy which tends to macerate the skin is contraindicated. The exfoliated epidermis should be removed with alcohol on cotton and the denuded area exposed to dry heat. Rapid control of the infection may be obtained with bacitracin ointment. Most impetiginous lesions heal without scarring; only the larger, deeper ones are likely to leave scars.

## PEMPHIGUS NEONATORUM

The term "pemphigus" is applied to superficial bullous lesions of severe impetigo widely distributed over the surface of the body, with the exception of the palms and soles. The absence of lesions on the palms and soles serves as a differentiation from syphilitic pemphigus. The constitutional reaction is usually severe, and the prognosis is serious. Recovery can be expected, however, if antibiotic therapy is started early. Penicillin should be administered systemically after blood for bacterial culture has been secured.

## PARONYCHIA

Sucking of the thumb or finger is a common habit in newborn infants, possibly because of the active sucking reflex and the sensitivity of the lips. Maceration or traumatization from the sucking may predispose to infection with the development of paronychia or onychia. Mittens may be worn as a prophylactic measure. In the early stage of infection, cleansing with alcohol and application of bacitracin ointment may avert the need for surgical treatment.

Paronychia congenita is described on page 1276.

## MASTITIS NEONATORUM

Engorgement of the breasts is physiologic in newborn infants. Infection may be abetted by undue manipulation of the breasts and is manifest by redness, local heat, swelling and pain. Fever and other general symptoms may also be present. The prognosis is favorable unless septicemia develops. Prophylaxis con-

sists in avoidance of manipulation or other trauma of the engorged breasts. Treatment includes systemic antibiotic therapy and hot compresses applied locally. If an abscess develops, it should be incised and drained. Sequels from scar formation include impairment of the secreting power of the mammary gland in later life and distortion of the nipple.

## Disturbances of the Eye

These are discussed in the section on The Eye. See Conjunctivitis, Obstruction of the

Nasolacrimal Duct, Cataract and Retrolental Fibroplasia.

## The Umbilicus

**Umbilical Cord.** The cord contains the two umbilical arteries, the vein, the rudimentary allantois, the remnant of the omphalomesenteric duct and a gelatinous substance called the jelly of Wharton. The sheath of the umbilical cord is derived from the amnion. The arteries have a strong contractile capacity, whereas that of the vein is less, and as a result it retains a fairly large lumen after birth. When the cord sloughs, portions of these structures remain in the base. The blood vessels are functionally closed, but are patent anatomically for twenty to twenty-five days. The arteries become the lateral umbilical ligaments; the vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. During this interval the umbilical vessels are potential portals of entry for infection.

**Types of Navel.** There are three types of navels: normal, amniotic and the skin or cutis navel. When the skin of the abdominal wall meets the umbilical cord at the level of the abdomen, there remains only a small amount of skin at the base when the cord sloughs, and a *normal* umbilical cicatrix results. If the skin does not extend to the base of the cord and the amniotic membrane must cover the skin surface adjacent to the base, a small superficial ulcer will result which closes in by granulation and leaves the flat scar of the *amniotic* navel. When the skin extends up the sides of the cord, a protruding stump, the *skin* navel, remains after the cord has sloughed. The protrusion of the skin or cutis navel must be differentiated from a postnatal hernia, with which, of course, it can be associated; a skin navel, per se, does

not have a defect in the abdominal wall and therefore is not exaggerated when the infant strains or cries. Usually the cicatrix shrivels, so that eventually the skin navel becomes less prominent.

## ANOMALIES

*Patency of the omphalomesenteric duct* may be responsible for an intestinal fistula, prolapse of the bowel, polyp or a Meckel's diverticulum. If a portion of the umbilical vessels remains patent, there may be a fistula, or intestinal obstruction may result.

A *persistent urachus* (urachal cyst) is due to failure of closure of the allantoic duct. Patency should be suspected if there is a clear, light yellow, urine-like discharge from the umbilicus. Methylene blue, injected subcutaneously or given orally, can be recovered from the umbilical wound if a connection to the urinary bladder exists and permits discharge of urine through the navel.

## CONGENITAL OMPHALOCELE

An omphalocele is a herniation or protrusion of abdominal contents into the base of the umbilical cord. In contrast to the more common umbilical hernia, the sac is covered merely with peritoneum without overlying skin. The size of the sac which lies outside the abdominal cavity depends upon its contents. It has been estimated that there is herniation of intestines into the cord in about one of 5000 births and of liver and intestines in one of 10,000 births. The abdominal cavity is proportionately small, owing to deficient impulse to grow and develop.



Immediate surgical repair, before infection has taken place and before the tissues have been damaged by drying or the sac has ruptured, is the only possibility for the infant's survival.

## TUMORS

Tumors of the umbilicus are rare; they include angioma, enteroteratoma, dermoid cyst, myxosarcoma and cysts of urachal or omphalomesenteric duct remnants.

## HEMORRHAGE

Hemorrhage from the umbilical cord may be due to trauma, to inadequate ligation of the cord or to failure of normal thrombus formation. Hemorrhage may also be an evidence of hemorrhagic disease of the newborn, septicemia or local infection. The infant should be observed frequently during the first few days of life so that, if hemorrhage does occur, it will be detected promptly.

## GRANULOMA OF THE UMBILICUS

The umbilical cord usually dries and separates within six to eight days after birth. The raw surface becomes covered by a thin layer of skin, scar tissue forms, and the wound is usually healed within twelve to fifteen days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection may result in a moist granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

The persistence of exuberant granulation tissue at the base of the umbilicus is not uncommon. The tissue is soft, vascular and granular, and dull red or pink, and may have a seropurulent secretion. Differentiation must be made from a *polyp*, a rare anomaly consisting of remnants of the omphalomesenteric duct. The tissue of the polyp is firm and resistant, and bright red, and has a mucoid secretion; it persists for years and is unaffected by astringents. Histologically, the polyp consists of intestinal tissue in contrast to the scar tissue of the granuloma.

The *treatment* is cauterization with silver nitrate, which should be repeated at intervals of several days until the base is completely dry.

## INFECTIONS OF THE UMBILICUS

Inflammation in the umbilical region, which may be caused by any of the pyogenic bacteria, is especially serious because of the danger of hematogenous spread or extension to the liver or peritoneum. The general manifestations may be minimal even when septicemia or hepatitis has resulted. Prevention of infection depends upon maintenance of a clean umbilical field. *Treatment* includes prompt antibacterial therapy and, if there is abscess formation, surgical incision and drainage.

## UMBILICAL HERNIA

Umbilical hernia is due to an imperfect closure or weakness of the umbilical ring and is often associated with diastasis recti. It is common in all races, but especially in the Negro. It appears as a soft swelling covered by skin which protrudes during crying or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from less than a centimeter in diameter to as much as 5 cm., but large ones are rare. Most of the smaller ones disappear spontaneously during the first year or so of life.

Traditionally, umbilical hernias are kept "strapped" continuously during infancy from the time when the umbilical wound is epithelized, it being assumed that, if there is no tension on the umbilical ring, its margins will grow together. There is reason to doubt the effectiveness of the method for a hernia of any size, since the smallest ones close apparently irrespective of treatment, and the larger ones tend to persist. Until more adequate information is available, "strapping" of those of 1 or 2 cm. in diameter for six or seven months would seem justifiable. The hernia can be reduced by finger pressure and held in this position by drawing each side of the adjacent abdominal wall over it. A deep fold is thus formed and held by broad adhesive tape tightly applied. A coin or button should not be placed beneath the umbilical dressing, since it prohibits adequate approximation of the margins of the hernia. If the skin becomes irritated from the adhesive tape, the strapping should be discontinued temporarily until the skin heals. Application of tincture of benzoin to the skin affords protection against such irritation and ensures better

adherence of the tape. There are differences of opinion concerning the ideal age for surgical repair of the larger hernias and of the smaller ones that persist. For those of several centimeters in diameter there is no point in delay, and closure can be accomplished at any

age. For those of moderate size one may justifiably wait two or three years on the possibility that spontaneous closure might occur. In the female the eventual possibility of complications during pregnancy is an added reason for repair of the hernia during childhood.

## METABOLIC DISTURBANCES

The physiologic handicaps of the newborn infant in the maintenance of his water and electrolyte balance are discussed on page 290.

### TRANSITORY FEVER OF THE NEWBORN

Elevations of temperature ( $100^{\circ}$  to  $104^{\circ}$  F.) are occasionally noted on the second or third day of life in infants whose clinical course has been otherwise satisfactory. This disturbance has been termed "transitory fever of the newborn" and "dehydration fever." It is especially likely to occur in breast-fed infants whose intake of supplementary fluids such as glucose water or water has been particularly low or in infants exposed to high environmental temperatures, either in the nursery or in a bassinet near a radiator or in the sun. The lack of consistent relationship with the extent of weight loss or inadequacy of fluid intake may be a reflection of variation in initial stores of body water. The rise in temperature is associated with an increase in concentration of the serum protein; the fall, with an increase in plasma water. The rapid alleviation of symptoms by oral or parenteral fluids can leave no doubt as to the etiology.

The infant may be restless, and there may be a precipitous drop in weight. The urinary output and frequency of voiding diminish. The skin may show some loss of elasticity, and the fontanel may be depressed. The infant appears unhappy and takes fluids avidly. The usual apparent vigor of the infant is in contrast to the appearance of "being sick" in the presence of infection, although fever caused by infection may sometimes occur even earlier in the neonatal period, and at times without signs of prostration.

Oral administration of fluids leads to prompt reduction of the fever.

### EDEMA

Generalized edema occurs in association with the most severe forms of iso-immunization,

and varying degrees are seen in the offspring of diabetic mothers. Some premature infants may have considerable puffiness for no apparent reason. Edema of the face and scalp may result from pressure from the umbilical cord around the neck, and transient localized swellings of the hands or feet may similarly be due to intrauterine pressures. Edema may be present with heart failure due to congenital cardiac lesions; a lag in renal excretion of electrolytes and water may result in edema when there has been a sudden large increase in intake of electrolytes, particularly with feeding of concentrated mixtures of cow's milk. It is difficult to show a relation between low serum protein or low hemoglobin and the occurrence of edema in older premature infants, but occasionally the therapeutic response to plasma or blood transfusion is prompt. Rarely "*idiopathic hypoproteinemia*" with edema lasting weeks or months is observed in term infants. The etiology is unclear; and the disturbance is benign.

Scleredema is described on page 1278.

### TETANY

Tetany unrelated to a deficiency of vitamin D occurs occasionally in newborn infants, usually within the first week of life. The increased neuromuscular irritability stems from a decrease in serum calcium associated with an increase in serum phosphate (see p. 1110). The serum phosphatase is normal. Transient physiologic hypoparathyroidism, diminished ability of the neonatal kidney to excrete phosphate, and a high phosphate load from undiluted cow's milk formulas have all been considered contributory.

Irritability, muscular twitchings, tremors and convulsions are the symptoms. Laryngospasm and carpopedal spasm are less common. Since a positive Chvostek's sign is frequently observed in normal newborn infants, it cannot be interpreted as a sign of tetany of the newborn. The level of the serum calcium is regularly reduced below 7 or 8 mg. per 100 ml., and that of the serum phosphate is



elevated; an absolute diagnosis cannot be made in the absence of these chemical findings. The favorable response of symptoms to administration of calcium is not sufficient in itself to make the diagnosis, since calcium may act nonspecifically as a sedative. Furthermore, symptoms such as irritability and tremors may subside spontaneously, and convulsions resulting from cerebral edema, anoxia or injury may not be repeated during the neonatal period. The good prognosis of hypocalcemic convulsions and the guarded to poor prognosis for convulsions of other causes in the newborn period make establishment of the diagnosis by chemical examination of the blood desirable. When there is associated

albuminuria, pyuria and/or a persistently high blood urea not associated with dehydration, urologic studies are indicated.

The response to calcium therapy is dramatic, convulsions being controlled by the intravenous administration of 5 to 10 cc. of calcium gluconate in 10 per cent solution. Intramuscular injection of calcium is contraindicated because local induration and necrosis may occur. Calcium should be given orally for approximately a week, preferably as calcium chloride (1.0 gm.) or calcium lactate (2 to 3 gm. a day) in 10 per cent solution. The use of parathyroid extract or of dihydrotachysterol is not indicated; vitamin D is not effective.

## DISTURBANCES OF THE ENDOCRINE SYSTEM

Details of diagnosis and management of the endocrinopathies are covered in the section on The Endocrine System. The purpose of this section is merely to call attention to those endocrine disturbances which may be identified at birth or during the first month of life.

*Pituitary* dwarfism is usually inapparent at birth, the infant being of normal size. Conversely, constitutional dwarfs usually demonstrate length and weight consistent with prematurity, but are born after a normal gestational period and have the physical appearance of infants born at term.

*Thyroid* deficiency may be apparent at birth in genetically determined cretinism or in infants of mothers treated with thiouracil or its derivatives during pregnancy. Constipation, prolonged jaundice, lethargy or poor peripheral circulation as manifested by persistently mottled skin or cold extremities should always rouse suspicion of *cretinism*. Temporary hyperthyroidism may be seen at birth in the infants of mothers with hyperthyroidism or of those who have been on thyroid medication.

Transient *hypoparathyroidism* may be manifest as tetany of the newborn (p. 342).

The *adrenal gland* is subject to numerous disturbances which may be manifest and require lifesaving treatment during the newborn period. Acute adrenal *hemorrhage* and failure may be seen after breech or other traumatic deliveries or in association with overwhelming infection. Phallic or clitoral

enlargement apparent at or soon after birth may be the clue to *adrenal cortical hyperplasia*. Signs of deficiency of salt and water hormone with vomiting, diarrhea, dehydration, convulsions or shock may be present. Since the condition is genetically determined, newborn siblings of patients with adrenal cortical hyperplasia who are salt-losers should be observed closely for manifestations of adrenal insufficiency. *Congenitally hypoplastic adrenal glands* may also give rise to adrenal insufficiency during the first few weeks of life.

Anomalies of the *gonads* may be apparent at birth. Of particular interest is gonadal dysgenesis (Turner's syndrome, Bonnevie-Ullrich syndrome, ovarian agenesis). Female infants with webbing of the neck, lymphangiectatic edema, hypoplasia of the nipples, cutis laxa, low hairline at the nape of the neck, deep-set ears, high-arched palate, deformities of the nails, cubitus valgus and other anomalies should be suspected of having gonadal dysgenesis. Approximately 80 per cent of these apparent females have a male chromosomal sex pattern.

Transient *diabetes mellitus* of unknown etiology is occasionally and only seen in the newborn. It usually presents as dehydration, loss of weight, or acidosis. Hypoglycemic convulsions may occur during the first few days of life in the infants of diabetic mothers, and children with so-called idiopathic hypoglycemia may have the onset of symptoms during the neonatal period.

## INFECTIONS OF THE NEWBORN

The reader is referred to other sections for discussion of specific diseases which may be particularly important in the newborn infant. See, in particular, Syphilis, Tetanus, Cytomegalic Inclusion Disease, Toxoplasmosis.

Infections of the newborn infant may be caused by any pathogenic bacterial or viral agent. He is more susceptible, however, to organisms which are usually nonpathogenic for older children and for adults outside of the geriatric age group, in whom such infections are again seen with relatively greater frequency. The *Pneumococcus*, beta-hemolytic streptococcus, and *H. influenzae*, common pathogenic agents in later infancy, are relatively uncommon causes of infection in the first few weeks of life. At this time coliform organisms and *Staphylococcus aureus* are the most frequent causes of severe infections; other relatively common bacterial pathogens are enterococci, *Klebsiella*, *Pseudomonas*, *Proteus* and *Salmonella*. Nursery epidemics caused by any organism with antibiotic susceptibility are probably best managed by routine administration for several weeks of an appropriate antibiotic to every infant in the nursery in a manner similar to that to be described for the prevention of epidemics of staphylococcal infection.

The most frequent serious infections of the newborn are pneumonia, septicemia, diarrhea, meningitis and peritonitis. Of these, pneumonia and septicemia are common; diarrhea has become relatively uncommon in the United States, but has a high incidence in individual epidemics; meningitis is present in approximately 25 per cent of cases of septicemia; and peritonitis is rare as a well developed clinical syndrome, presumably because of the effectiveness of modern chemotherapy against the beta-hemolytic *Streptococcus* and against the spread of blood-borne infection to the peritoneal cavity.

In pneumonia, septicemia and meningitis the prognosis is heavily influenced by early diagnosis and institution of specific treatment with appropriate antibacterial agents. All three are distinguished by their lack of specific signs or symptoms in the early stages (see Clinical Manifestations of Disease in the Newborn, p. 314, and of pneumonia on p. 326). In the absence of dehydration or high environmental temperature they are the

commonest causes of body temperatures over 100° F. in the newborn infant. Frequently, however, there is no elevation of temperature, or the temperature may be subnormal, and failure to feed well, lethargy, irritability, vomiting or episodes of cyanosis may be the only evidence of any one of these major infections. Icterus after the second or third day of life is especially suggestive of septicemia. The classic signs of meningitis in the small infant (bulging fontanel, high-pitched cry, vomiting and convulsions) are late signs, and the diagnosis must be made before they appear in order to reduce the mortality and morbidity of the disease. Acute meningitis caused by gram-negative bacilli, in particular, frequently becomes chronic, with a high incidence of permanent residuals. Timely diagnosis of pneumonia, septicemia and meningitis depends on the use of liberal indications for securing a roentgenogram of the chest and a blood culture and for performing a spinal puncture in infants who "are not doing well." Premature infants are especially prone to serious infections with few or no clinical manifestations.

### ESCHERICHIA COLI INFECTIONS

The commonest *etiologic agent* of all serious infections (pneumonia, septicemia, meningitis and diarrhea) of the newborn is *E. coli*. Ten serologic types of this organism have been linked to individual epidemics of diarrhea of the newborn, types 0111:B4, 055:B5, 026:B6 and 0127:B8 being the most common. The relation of these particular strains of *E. coli* to infections other than diarrhea has not been clearly defined; they have not been shown to produce epidemic disease other than diarrhea.

Systemic infections caused by *E. coli* are best treated with chloramphenicol, tetracycline or streptomycin. Initial resistance of the organism is least likely with chloramphenicol, but may develop with it or any available antibiotics. In intestinal infections neomycin is the drug of choice (see p. 221).

### STAPHYLOCOCCAL INFECTIONS

Second in frequency to *E. coli* as a cause of infection in the newborn, *Staphylococcus*



*aureus* has assumed relatively greater importance in recent years, owing to the frequent occurrence of epidemic nursery infections with strains resistant to most of the commonly used antibacterial agents.

Although staphylococcal pneumonia, septicemia or enteritis may occur without warning in the newborn infant, each is usually preceded by apparent skin infections of the infant or of contacts which may consist of small pustules or furuncles, or of large furuncles, cellulitis, bullous impetigo or breast abscess. Retro-orbital abscess complicating osteomyelitis of the maxilla, presumably as the result of infection entering through an abrasion of the upper gum, has received recent attention. Osteomyelitis elsewhere and meningitis are relatively frequent complications of septicemia. Staphylococcal meningitis without bacteremia suggests the presence of a communication (dermal sinus) between the skin and the subarachnoid space. A leaking meningocele is an obvious portal of entry. The umbilicus, a circumcision wound or other surgical incision may serve as a route for staphylococci to reach the blood stream, as may any abrasion of the skin.

Nursery epidemics of staphylococcal infection usually begin with increasingly frequent appearance of small pustules. More severe infections of the skin, septicemia or enteritis are usually seen next. Although the initial infection is acquired in the nursery, these and other serious manifestations may not make their appearance for weeks or even months after the baby has been discharged. Therefore the existence of an epidemic of major proportions may not be suspected unless the infants are followed up carefully after discharge and unless all cases of furuncles, breast abscess, pneumonia and other less frequent staphylococcal infections during the first months of life are reported to the nursery where the patients were born. A high incidence of small pustules may be the only evidence in the nursery of an epidemic which is resulting in major staphylococcal infections among 15 to 20 per cent of discharged infants and among other members of their families.

Recent investigations suggest that epidemics are due to certain strains of hemolytic *Staphylococcus aureus* which appear to be of particular pathogenicity. One such strain (phage type 42B, 47C, 44A, 52, 80, 81) was shown to be the causative organism of nineteen epidemics throughout the world in

1954–1956. The pathogen is undoubtedly introduced initially into the nursery by personnel or by an infant who acquires it from his mother during the periods of contact with her. Once the organism has been introduced, the infants in the nursery, as well as adult carriers, constitute the reservoir of infection and spread it from baby to baby. Anatomic areas of the infant which constitute particular reservoirs are the skin, the anterior nares and the umbilical cord stump.

**Prevention.** All persons with skin infections should be excluded from the nursery and from contact with the infant after discharge. Mothers with staphylococcal infections should be isolated and treated while their infants remain in the nursery out of contact with them. Use of soap or detergent containing hexachlorophene tends to reduce the bacterial population on the skins of nursery personnel. The latter should also be specifically instructed that the anterior nares constitute the chief reservoir in carriers. Initial and daily bathing of the infants with a soap or detergent containing hexachlorophene reduces the incidence of skin infection, but not of infection of the anterior nares. Daily painting of the umbilical cord stump with bactericidal dyes reduces the incidence of nasal and skin colonization of staphylococci, provided all infants in the nursery are so treated. Avoidance of overcrowding in the nursery is important. Once an epidemic is started, the usual measures of prompt isolation of new cases, tightening up on all nursery techniques, scrubbing the nursery and its contents, and changing the location of the nursery are usually of little avail. On the other hand, the exclusion of personnel who are carriers of the pathogenic strain, and routine oral administration of chloramphenicol or erythromycin in dosage of approximately 50 mg. per kilogram per twenty-four hours in divided doses to each infant from the day of admission through the day of discharge usually results in prompt disappearance of the epidemic. Maintenance of this regimen for three weeks ordinarily is sufficient to control the epidemic.

**Treatment.** The treatment of staphylococcal infections is best accomplished by systemic administration of an antibiotic effective against the particular organism involved. Chloramphenicol, erythromycin or novobiocin in that order are the drugs of choice. The tetracyclines, penicillin, streptomycin and the sulfonamides are ineffective against a high

percentage of pathogenic staphylococci, and no drug is effective against more than 85 to 95 per cent of strains. Therefore tests of antibiotic sensitivity in vitro should always be done and the medication changed accordingly if the drug being used is not producing a satisfactory clinical response. In the presence of an obviously good clinical response, a shift of medication on the basis of the results of sensitivity tests in vitro should be questioned. As noted on page 325, the broad-spectrum antibiotics are less well absorbed from the intramuscular spaces than are penicillin and streptomycin, and they require more fluid (about 1 cc. per milligram of drug) for absorption from the intestine than does penicillin.

In addition to systemic therapy, bathing with soaps or detergents containing hexachlorophene and the local application of bacitracin ointment will aid in eradicating skin lesions. Accumulations of pus, wherever encountered, should be drained surgically.

## DIARRHEA IN THE NEWBORN

Traditionally a scourge of all nurseries because of its great contagiousness and high morbidity and mortality rates, epidemic diarrhea of the newborn is now a relatively infrequent but still serious problem in the United States. *Etiologically*, it is not an entity. A number of bacterial and viral agents have been identified as the causative or probable causative agents in individual epidemics. With the possible exception of pathogenic strains of *E. coli* and occasional viruses causing respiratory or oral infections in adults, they do not differ significantly from the usual etiologic agents of diarrhea (p. 655). On the basis of present evidence it would appear that certain types of *E. coli* (p. 344) are responsible for a high percentage of nursery epidemics of diarrheal disease. The specificity and severity of the disease are related principally to the host factors of low immunity, small metabolic reserve of water and electrolytes, and poorly developed homeostatic mechanisms. The universal presence of a large, changing, crowded and susceptible population in almost any newborn nursery is also an ideal environmental situation for any contagious disease to become epidemic. Premature or debilitated infants are especially susceptible. Sporadic cases are also seen; they usually occur in the home after exposure to an older sibling or adult with an enteric infection.

**Clinical Manifestations.** The incubation period is most commonly one to three days. At onset the infant usually becomes listless or fretful, nurses less well than usual, fails to gain or may actually lose weight. Vomiting is an inconstant symptom, as is abdominal distention. The temperature is usually normal, but may rise to 100° to 104° F. When the diarrhea starts, the stools tend to be watery, yellowish (later greenish) and acid enough to produce irritation of the skin of the buttocks within a few hours. They are usually frequent and passed explosively. On the other hand, an occasional infant may go into shock and die from water and electrolyte loss into the intestinal lumen before a diarrheal stool is passed. Mucus, pus and macroscopic blood are commonly absent, although in southern Europe a highly fatal form of diarrhea of the newborn characterized by the passage of copious amounts of green mucus is seen. As the diarrhea progresses the infant becomes increasingly restless with a frequent short and feeble cry. With progressive dehydration, thirst may give way to refusal to feed, and the infant becomes drowsy and, finally, comatose. In the final stages of dehydration the infant's face resembles that of a mummy, the eyes are deep-sunken, the skin takes on a grayish cast, and there is circumoral cyanosis and an apparent state of shock. Hyperpnea is frequently absent in spite of acidosis with carbon dioxide levels as low as 2 mEq. per liter. There is hemoconcentration, and protein, white cells and casts are found in the urine in considerable quantities. As in most diseases, the severity and the presence or absence of the various clinical manifestations vary greatly from patient to patient.

The clinical course varies from a few days to several weeks. Relapses or exacerbations are common. Complications include otitis media, bronchopneumonia, bacteremia, peritonitis from perforation of an intestinal ulcer, and renal vein and cerebral sinus thrombosis.

**Prevention.** The hospital nursery technique should be designed to eliminate chances of infection or cross infection among the infants. This involves adequate floor area to avoid overcrowding, complete individual bassinets and equipment for each infant, careful supervision of the preparation of formulas, and well-trained, conscientious personnel who are numerically adequate.

Any direct or indirect contact with persons with intestinal disease or direct contact with



any with respiratory infections must be avoided. This means the exclusion from the nursery of all personnel who have had even mild diarrhea or vomiting within forty-eight to seventy-two hours, and of all personnel having more than the most fleeting contact with active cases of diarrhea either professionally or at home. In nurseries a high index of suspicion must be maintained, especially since the onset of an epidemic may be so insidious that the possibility is not considered until several infants have diarrhea. A frequent cause of this situation is the discharge from the nursery of the initial case or cases before definite signs of the disease have appeared, but after the contagious state is already present. Therefore it is essential that the development of diarrhea in an infant after discharge be reported immediately to the person in charge of the newborn nursery. Immediate reporting to local or state health officials is equally important.

Nursery personnel must be constantly on the alert for abnormal stools among their charges. Differentiation must be made between diarrhea and the loose and frequent movements characteristic of transitional stools. The breast-fed infant may have more frequent and more liquid stools than the bottle-fed infant, and may be affected by the dietary or medicinal intake of his mother. Overfeeding, high carbohydrate content of the formula, intestinal intolerance to cow's milk or the use of soybean or protein hydrolysate formulas may be responsible for loose stools in the bottle-fed infant. Aganglionic megacolon may be manifest initially in the newborn as diarrhea. Once a baby in a nursery for newborns is identified as having diarrhea he should be isolated in a separate nursery and cared for by personnel who do not have contact with the remaining infants. The latter and those discharged from the exposed nursery must be watched closely for any untoward signs. New infants should not be admitted to the nursery from the time of recognition of the second case until it has been cleared of its current population. It should then be thoroughly scrubbed and aired before admissions are resumed.

**Prognosis.** The average fatality rate in epidemics of recent years has been about 40 per cent. With presently available treatment it should be lower, and in a few epidemics all affected infants have survived. The subsequent course of surviving infants is, in general, uneventful, although chronic in-

testinal disturbances are an uncommon sequel.

**Treatment.** Except for those epidemics due to bacteria against which effective specific antibacterial agents are available, treatment is symptomatic and supportive. It does not differ from that of diarrheal disturbances in later infancy (pp. 187 and 189). Neomycin is the only antibiotic which has been found effective in breaking a nursery epidemic due to the specific serologic types of *E. coli* which have been shown to be pathogenic. For this reason it is recommended that 50 mg. of neomycin per kilogram of body weight per day be administered orally in divided doses to all infants in the nursery up to the time of discharge of the last infant present at the time the medication is started. Nursery personnel should also be cultured, since they may be asymptomatic carriers of pathogenic strains of *E. coli*. Any carriers discovered should be relieved of duty and treated with neomycin until the organism has been eradicated from their intestinal tracts.

## NEONATAL INFECTION DUE TO

### LISTERIA MONOCYTOGENES

Of the human infections caused by *Listeria monocytogenes*, that of purulent meningitis is the one most commonly recognized (p. 424), but a generalized *miliary granulomatosis* in stillborn fetuses and newborn infants is unique. The incidence is not known, probably because the infection is most often not identified; in one rather large series *L. monocytogenes* was responsible for 2 per cent of neonatal deaths.

The fetus is apparently infected transplacentally and usually dies before birth. In those born alive manifestations may be apparent from the time of birth or may be delayed a week or so. The clinical pattern is not characteristic. There is often brownish discoloration of the amniotic fluid. When the onset is shortly after birth, the principal signs are those of cardiorespiratory distress. Diarrhea and vomiting are common. When the onset is delayed, it may be gradual, but the course is progressive and is usually characterized by bronchopneumonia. Meningitis is not uncommon. Granulomas appearing as dark red or livid papules may be present on the oropharynx and the skin.

Pathologically there are microscopic to pinhead-sized nodules in many organs, viz.,

liver, spleen, adrenals, lungs, pharynx, gastrointestinal tract, brain and meninges and skin.

The diagnosis is established by identification of the organism in the urine or blood of the infant, and suggested by similar identifications in the mother. High agglutinative titers may be observed for a short time after the infection.

Most of the available antibiotic agents are effective against *L. monocytogenes*; penicillin is probably the agent of choice.

## COXSACKIE VIRUS INFECTION IN THE NEWBORN

An acute fulminating febrile illness may result from infection of newborn infants with Coxsackie virus, group B. It may be associated with minor respiratory or other infection in the mother shortly before delivery or may occur in apparently epidemic form in the nursery. At autopsy the characteristic finding is diffuse myocarditis, and other organs may be involved (see p. 529).

## HERPES SIMPLEX OF THE NEWBORN INFANT

Severe generalized infection of the newborn infant may be caused by the virus of herpes simplex (see p. 493).

R. J. MCKAY, JR.  
CLEMENT A. SMITH

### REFERENCES

#### *Physiology of the Newborn*

- Barcroft, J.: *Researches on Prenatal Life*. Oxford, Blackwell Scientific Publications, 1946, and Springfield, Ill., Charles C Thomas, Vol. I.
- Barnett, H. L., and Vesterdal, J.: The Physiologic and Clinical Significance of Immaturity of Kidney Function in Young Infants. *J. Pediat.*, 42:99, 1953.
- Clifford, S. H.: Postmaturity; in Levine, S. Z., and others: *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1957, Vol. 9, p. 113.
- Day, R. L., and Silverman, W. A.: Premature and Newborn Infants. Report of a Seminar. *Pediatrics*, 20:143, 1957.
- Dunham, E. C.: *Premature Infants. A Manual for Physicians*. 2nd ed. New York, Paul B. Hoeber, Inc., 1955.
- Knop, C.: The Dynamics of Newly Born Babies. *J. Pediat.*, 29:721, 1946.
- Levine, S. Z., and Gordon, H. H.: Physiologic Handicaps of the Premature Infant. I. Their Pathogenesis. II. Clinical Applications. *Am. J. Dis. Child.*, 64:274, 1942.
- Moss, A. J., Liebling, W., Austin, W. O., and Adams,

F. H.: An Evaluation of the Flush Method for Determining Blood Pressure in Infants. *Pediatrics*, 20:53, 1957.

Reardon, H. S., Wilson, J. L., and Graham, B. D.: *Physiologic Deviations of the Premature Infant, with Summary of Principles of Care*. *Am. J. Dis. Child.*, 81:99, 1951.

Smith, C. A.: *The Physiology of the Newborn Infant*. 3rd ed. Springfield, Ill., Charles C Thomas, 1958.

#### *The Newborn Infant*

- Benirschke, K., and Brown, W. H.: A Vascular Anomaly of the Umbilical Cord. The Absence of One Umbilical Artery in the Umbilical Cords of Normal and Abnormal Fetuses. *Obst. & Gynec.*, 6:399, 1955.
- Brown, A. K., and Zuelzer, W. W.: Studies in Hyperbilirubinemia. I. Hyperbilirubinemia of the Newborn Unrelated to Isoimmunization. *A.M.A. Am. J. Dis. Child.*, 93:263, 1957.
- Cook, C. D., and others: Apnea and Respiratory Distress in the Newborn Infant. *New England J. Med.*, 254:562, 604, 651, 1956.
- Craig, W. S.: Intracranial Irritation in Newborn: Immediate and Long-Term Prognosis. *Arch. Dis. Childhood*, 25:325, 1950.
- Epstein, H. C., and Crouch, W. L.: Herpes Simplex of the Newborn Infant. *Pediatrics*, 13:553, 1954.
- Florman, A. L., and Bergher, M.: Benign Pharyngeal Erythema and Follicle Formation in the Newborn. *A.M.A. Am. J. Dis. Child.*, 91:549, 1956.
- Graham, C. G., Barness, L. A., and György, P.: Serum Calcium and Inorganic Phosphate in the Newborn Infant, and Their Relation to Different Feedings. *J. Pediat.*, 42:401, 1953.
- Hoeprich, P. D.: Infection Due to *Listeria Monocytogenes*. *Medicine*, 37:143, 1958.
- Illingworth, R. S.: Cyanotic Attacks in Newborn Infants. *Arch. Dis. Childhood*, 32:328, 1957.
- Jellard, J.: Umbilical Cord as Reservoir of Infection in a Maternity Hospital. *Brit. M. J.*, 1:925, 1957.
- Keith, H. M., Norval, M. A., and Hunt, A. B.: Neurologic Lesions in Relation to Sequelae of Birth Injury. *Neurology*, 3:139, 1953.
- Kendall, N., and Woloshin, H.: Cephalhematoma Associated with Fracture of the Skull. *J. Pediat.*, 41:125, 1952.
- Kibrick, S., and Benirschke, K.: Acute Aseptic Myocarditis and Meningoencephalitis in the Newborn Child Infected with Coxsackie Virus Group B, Type 3. *New England J. Med.*, 255:883, 1956.
- Meyer, H. F.: *Essentials of Infant Feeding for Physicians*. Springfield, Ill., Charles C Thomas, 1952.
- Mitchell, F. T., Ed.: *Symposium on Care of the Premature Infant*. *Pediat. Clin. North America*, 1:513, 1954.
- Moncrieff, A.: Infection in the Newborn Baby. *Brit. M. J.*, 1:1, 1953.
- Nelson, W. E., Ed.: *Symposium on Respiratory Disorders*. *Pediat. Clin. North America*, Feb., 1957.
- Nesbitt, R. E. L., Jr.: *Perinatal Loss in Modern Obstetrics*. Philadelphia, F. A. Davis Company, 1957.
- Potter, E. L.: *Pathology of the Fetus and Newborn*. Chicago, Year Book Publishers, Inc., 1952.
- Rosenfeld, G. B., and Bradley, C.: Childhood Behavior Sequelae of Asphyxia in Infancy; With



- Special Reference to Pertussis and Asphyxia Neonatorum. *Pediatrics*, 2:74, 1948.
- Schaffer, T. E., Sylvester, R. F., Jr., Baldwin, J. N., and Rheins, M. S.: Staphylococcal Infections in Newborn Infants. II. Report of 19 Epidemics Caused by an Identical Strain of *Staphylococcus Pyogenes*. *Am. J. Pub. Health*, 47:990, 1957.
- Sherwood, D. W., Smith, R. C., Lemmon, R. H., and Vrabel, I.: Abnormalities of the Genitourinary Tract Discovered by Palpation of the Abdomen of the Newborn. *Pediatrics*, 18:782, 1956.
- Smith, R. T., Platou, E. S., and Good, R. A.: Septicemia of the Newborn. Current Status of the Problem. *Pediatrics*, 17:549, 1956.
- Standards and Recommendations for Hospital Care of Newborn Infants, Full-Term and Premature. Evanston, Ill., American Academy of Pediatrics, Committee on Fetus and Newborn, 1954.
- Wheeler, W. O., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea Due to *E. Coli* O-111 by the Use of Chloramphenicol and Neomycin. *Pediatrics*, 14:357, 1954.
- Zuelzer, W. W., Ed.: Symposium on Pediatric Hematology. *Pediat. Clin. North America*, 4:323, 1957.

# Unexpected Sudden Death

Unexpected deaths include those which occur after a brief and apparently mild illness and sudden deaths which occur in seemingly healthy infants and children. Death may occur suddenly in many of the diseases of infancy and childhood, e.g., in diphtheria, but in such instances it cannot be considered entirely unexpected. The discussion here is limited to unexpected death for which there is no adequate clinical explanation. Such deaths are most likely to occur during the first six months of life and only rarely after the first year.

Careful postmortem studies, including histologic, bacteriologic and chemical investigations, will provide the explanation for such unexpected deaths in the majority of instances. In a few patients, however, even the most careful studies will fail to reveal an adequate cause of death; although it has been suggested that death results from overwhelming infections before morphologic changes are apparent, in the absence of positive bacteriologic studies the evidence for this is inconclusive.

**Acute Infection.** Infections of various types are the leading cause of sudden death in infants. In some instances death is preceded by a minor illness of brief duration such as a mild upper respiratory tract infection. Sometimes, however, death from an acute infection occurs suddenly with no apparent preceding illness. Postmortem examination of infants dying suddenly may reveal few or no significant macroscopic or microscopic evidences of an inflammatory process, yet culture of the heart's blood may yield virulent organisms such as pneumococci, meningococci, beta-hemolytic streptococci or *Hemophilus influenzae*. In such instances death may justifiably be attributed to an overwhelming infection which has progressed with such rapidity as to preclude the production of morphologic changes. However, the actual mechanism responsible for such deaths is not established; earlier studies suggesting the presence of hypogammaglobulinemia in these

infants have not been confirmed. The interpretation of postmortem blood cultures which contain such organisms as *Proteus*, *Pseudomonas*, *Escherichia coli* or even staphylococci is often difficult. In general, in the absence of other evidences of infection by these organisms their presence is attributed to agonal invasion of the blood stream and is not considered a cause of death.

In other instances of sudden death inflammatory processes such as pneumonia or meningitis may be demonstrable macroscopically or by histologic study at the time of autopsy. Meningococcemia and, somewhat less characteristically, septicemia associated with other organisms such as *H. influenzae* or pneumococci may proceed with terrifying rapidity to death. At postmortem examination a petechial or purpuric rash may be associated with varying degrees of bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome); in some instances a similar clinical pattern is associated with extensive cytolytic changes in the adrenal cortices (Rich) in the absence of hemorrhage. Cerebral abscess, especially in infants, may be associated with few clinical manifestations until death occurs unexpectedly after rupture of the abscess into the ventricular cavity.

**Congenital Malformations.** Unrecognized congenital cardiac malformations are occasionally responsible for unexpected death, and patients with known cardiac malformations, e.g., aortic stenosis, may die suddenly and unexpectedly. In addition, infants with endocardial sclerosis, anomalous origin of the left coronary artery, medial necrosis of the coronary arteries, and possibly those with glycogen storage disease of the heart, congenital rhabdomyomas or hamartomas of the myocardium, may die suddenly in the absence of any known pre-existing cardiac disease. Somewhat more frequently, however, the unexpected death of these infants is preceded by a brief period of respiratory distress suggestive of a pulmonary inflammatory process. Acute myocarditis (see p. 529), which may



closely simulate the aforementioned diseases, may be responsible for sudden death in an apparently healthy infant or even in an older child; occasionally it is responsible for sudden death in the neonatal period.

Patients with severe malformations of the central nervous system, known to have been present since birth or shortly thereafter, may die suddenly and unexpectedly. At autopsy little of significance may be found except for the lesions of the central nervous system. The explanation for these sudden deaths is not apparent, but it seems possible that infants and children with severe damage to the central nervous system may die as a result of relatively minor illnesses which would not be fatal to a normal child.

**Hemorrhage.** Hemorrhage into various sites, especially into the brain or abdominal cavity, may result in sudden unexpected death. In intracranial hemorrhage, such as may occur with rupture of an aneurysm of the circle of Willis, signs and symptoms referable to the central nervous system are usually apparent for at least a brief period prior to death. Small premature infants may die early in the neonatal period after only a few hours of distress as a result of rupture of a subependymal hemorrhage into the lateral ventricle. Massive intracranial hemorrhage with unexpected death may be the first apparent manifestation of acute leukemia in children. Rupture of a subcapsular hematoma of the liver in a newborn infant may be responsible for unexpected death, as may intraperitoneal hemorrhage following rupture of the liver or, less frequently, of the spleen.

**Asphyxia.** Aspiration of foreign bodies may cause complete obstruction of the larynx or trachea with resultant sudden unexpected death. The parents may be unaware of the aspiration, which is demonstrated only at necropsy. Aspirated gastric contents are often encountered in the tracheas of infants and children dying of a variety of causes; in the absence of definite evidence of obstruction, as by a bolus of food lodged in the larynx, such aspiration should not be considered a primary cause of death.

**Poisoning.** Poisoning of various types may be responsible for unexpected death, but clinical manifestations of illness are usually present for at least a brief period prior to death. No history of ingestion of poison may be elicited, since the family may be unaware of its occurrence.

**Miscellaneous Causes.** Emery has reported sudden deaths in infants associated with

multiple pulmonary thromboses. Unexpected death has occurred as a result of heat prostration in patients with fibrocystic disease of the pancreas in whom clinical manifestations of the disease were not apparent.

Although sudden unexplained deaths frequently have been attributed to *suffocation* by pillows or bedclothes, substantial evidence of such an occurrence is difficult or impossible to obtain. In the absence of an unequivocal history of suffocation, as in homicide or strangulation, death should not be attributed to this cause. Even in the absence of significant lesions following complete post-mortem examination the diagnosis of suffocation should not be made simply because an infant is found dead face down in bed. In the absence of irrefutable evidence to the contrary, the family should be made to understand that they were in no manner responsible for the death of their child.

The rapidity with which thymic involution may occur in association with a variety of illnesses is often not appreciated, nor is the relatively large size of the lymph nodes (especially those in the mesentery) and lymphoid aggregates which are encountered in children. As a result, the relatively large thymus and prominent lymphoid aggregates which are commonly observed in infants and children dying suddenly while in apparent good health, or following anesthesia, minimal infections or other trivial causes, have led to the erroneous concept of status thymicolymphaticus. These so-called thymic deaths have been attributed to a variety of vague and unproved causes, but since there is no conclusive evidence that the thymus per se is in any way responsible for these deaths, the term "status thymicolymphaticus" might better be omitted from medical literature.

SYDNEY S. GELLIS

#### REFERENCES

- Adelson, L., and Kinney, E. R.: Sudden and Unexpected Death in Infancy and Childhood. *Pediatrics*, 17:663, 1956.
- Arey, J. B., and Sotos, J.: Unexpected Death in Early Life. *J. Pediat.*, 49:523, 1956.
- Emery, J. L.: Pulmonary Thrombosis and Its Association with Unexpected Death in Childhood. *Arch. Dis. Childhood*, 28:187, 1953.
- Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections, and Its Possible Relation to Circulatory Collapse. *Bull. Johns Hopkins Hosp.*, 74:1, 1944.
- Woolley, P. V., Jr.: Mechanical Suffocation during Infancy. A Comment on Its Relation to the Total Problem of Sudden Death. *J. Pediat.*, 26:572, 1945.

# Nutritional Disturbances

## MALNUTRITION

The term "malnutrition" is commonly used to indicate a state of undernutrition rather than a disturbance of the process of nutrition, which is implied in its strict interpretation. The use of the term is further restricted to identify the general clinical manifestations of undernutrition rather than specific disturbances, e.g., rickets or scurvy, which result from lack of single essential nutrients. Malnutrition should be considered a secondary and not a primary diagnosis, and an effort should always be made to identify the underlying causative factor.

The evaluation of nutritional status is far from being adequately defined. Severe disturbances are readily apparent, but mild disturbances may be missed, not only by careful physical examination, but also by laboratory methods now available. Evaluation of nutritional status merely by some arbitrarily determined percentile deviation from average weight values for height and age is not satisfactory. It not only identifies certain naturally small but healthy children as being undernourished, but also fails to detect a larger group whose nutritional status is inadequate, although their weight is within the range of average for their height and age. The rate at which growth is progressing is a more reliable index of nutritional status and is one of the screening methods for separating from a large group those children who should be more thoroughly studied for the presence of possible defects.

Dietary surveys, when carefully carried out, provide means for identifying groups and even individuals in whom malnutrition may exist. In view of the recognized inaccuracies in obtaining a history of dietary habits, a record of the child's daily intake for a week or so is recommended. For this purpose the type of record illustrated in Table 26 (p. 134) may be used.

Measurements of blood constituents by microchemical procedures is another means of assaying the nutritional status of large

groups of persons. Methods are available for the determination of several vitamin levels (A, C and thiamine), blood and serum iron, and serum protein on 0.1 ml. of blood serum, which provide a screening method for selection of persons with manifest or potential nutritional deficiencies. *Low blood levels of the various vitamins cannot be interpreted as evidences, per se, of nutritional disturbances, since physical changes resulting from the various vitamin deficiencies require some time for their development.*

## MALNUTRITION IN INFANTS

Severe malnutrition in infants, variously termed "infantile atrophy," "inanition," "marasmus," and "athrepsia," is observed much less frequently in the United States than formerly, but is prevalent in certain parts of the world. This decrease in incidence probably represents improvement in the artificial feeding of infants and to some extent also reflects a lower incidence of severe gastrointestinal disorders and of syphilis and tuberculosis among infants.

**Etiology.** Severe malnutrition may result from an inadequate caloric intake, either because of insufficiency of the diet or because of improper feeding habits, including those of disturbed parent-child relationships. Malnutrition may also result from improperly balanced diets, from chronic disease responsible for anorexia, for deficient digestion and assimilation, for vomiting or for diarrhea, and from congenital malformations, such as cleft palate, cardiac abnormalities and congenital dilatation of the colon. Extreme malnutrition may occur in infants with cerebral damage.

**Clinical Manifestations.** The most common manifestation is failure to gain weight, followed by progressive loss of weight until emaciation results. Fat is retained in the sucking pads of the cheeks longer than in other parts of the body, and until wasting is extreme the extent of malnutrition may be missed unless the baby's body is exposed. When the loss of subcutaneous tissue is



marked, the skin loses turgor and is wrinkled over the entire body; when the fat pads in the cheeks disappear, the infant is likely to assume the appearance of a withered old man. The abdomen may be distended or may be sunken and reveal the outlines of the intestines. The muscles are usually flabby and relaxed, but there may be hypertonia sufficient to produce arching of the back and retraction of the head. A spinal puncture may be required to eliminate the possibility of meningitis. The temperature is usually subnormal, the pulse may be slow, and the basal metabolism tends to be reduced. At first the infant may be fretful, but later he becomes listless. The appetite is likely to be diminished in the later stages of inanition. There is usually constipation, but there may be so-called starvation diarrhea, and the stools may contain much mucus.

Ketonuria is common in the early stage of inanition, but frequently disappears in the later stages. Severe hypochromic anemia is almost a constant finding. Plasma protein is usually lowered, although in the presence of hemoconcentration the serum level may approximate the normal range. Glucose tolerance curves may be diabetic in type; this pattern disappears when the nutritional state is improved. There may be a positive tourniquet test for increased capillary fragility, and in some instances there is spontaneous purpura. There may also be evidences of specific deficiencies such as rickets, scurvy, beriberi, ariboflavinosis, pellagra and keratomalacia. Nutritional edema is not unusual.

Intercurrent infections are common, especially of the gastrointestinal, respiratory and urinary tracts. Oral thrush, after the newborn period, occurs almost exclusively in malnourished infants, as do atrophic ulcers over areas of pressure from bony prominences. The higher mortality from infections among infants of the lower socio-economic group may be attributed in part to nutritional deficits.

**Diagnosis.** The diagnosis of malnutrition is made from the appearance of the child, but every effort should be made to determine the cause. It will require a careful history of dietary and feeding habits and of illness and a thorough physical examination in the search for any primary or secondary disorder.

**Prevention.** Prophylactic measures are of the greatest importance and include adequate feeding, appropriate parent-child relationship, good physical hygiene, immunization against the preventable infections, and

early diagnosis and treatment of acquired infections.

**Treatment.** Any coexistent physical disturbance which is remediable should receive appropriate therapy. Initial feedings should be low in quantity and in caloric value; too rapid increase in dietary intake may result in severe digestive disturbances with vomiting and diarrhea. Half-strength skimmed lactic acid milk to which about 2 per cent sugar is added is a satisfactory starting formula. Increases in carbohydrate and protein are then made within the limits of the infant's capacity when there is no vomiting or diarrhea. Within a relatively few days the diet can be increased to full strength (nonlactic acid) milk. Caloric requirements may need to be higher than indicated by the infant's weight, and may be as much as 50 per cent greater before significant gains in weight are attained. Intramuscular injections of crude liver extracts at intervals of two or three days for several weeks may be helpful. Vitamins B and C should be supplied in amounts equal to four or five times the usual daily requirements during the first week or two, and vitamins A and D in usual amounts.

Parenteral administration of fluid may be necessary initially to correct dehydration and to establish renal function (p. 186). When continuous intravenous feeding is necessary, amino acids should be included in amounts equal to 1.5 to 2 gm. per pound (3 to 4 gm. per kilogram) of body weight daily.

Hospitalization should be limited to the stage when parenteral therapy is necessary and rarely until feeding habits are established.

#### MALNUTRITION IN CHILDREN BEYOND INFANCY

**Etiology.** Malnutrition in children more than two years of age may be a continuation of an undernourished state begun in infancy, or it may stem from factors which become operative at any time during childhood. In general, the causes are the same as those responsible for malnutrition in infants. When poor dietary habits are associated with a generally poor hygienic situation, with finical eating habits of other members of the family, with disturbed parent-child relationships, especially overanxiety concerning eating habits, or with chronic disease, the problem is complex.

Under the age of five or six years poor eating habits can often be traced directly to

parental factors, of which overconcern about the quantity or the quality of the diet is the principal one. In children of all ages inadequate rest, both from the standpoint of insufficient sleep and from too much emotional excitement, such as that associated with the movies, radio and television, is an important factor. In older children schoolwork and social activities may interfere with securing adequate rest. School-age children are also likely to develop inadequate eating habits, especially at breakfast and lunch, because sufficient time is not allotted or, at lunch, because the meal may be poorly balanced. During adolescence girls frequently restrict their dietary intake for esthetic reasons. Random between-meal eating, especially of such items as candy, ice cream and malted milks, is likely to reduce the appetite at mealtime.

**Clinical Manifestations.** Malnutrition does not invariably result in underweight. Fatigue, lassitude, restlessness and nervousness are frequent manifestations. Restlessness and overactivity are frequently misinterpreted by parents as evidences of lack of fatigue. Anorexia, easily induced digestive disturbances and constipation are common complaints, and even in older children the starvation type of mucoid diarrheal stool may be observed. Malnourished children often have a limited span of attention and do poorly in their school work. There is an increased susceptibility to infections, especially to those of the gastrointestinal and respiratory tracts. Muscular development is inadequate, and the poor tone of the flabby muscles results in the so-called fatigue posture with rounded shoulders, flat chest and protuberant abdomen. Such children often have expressions of fatigue: the face is pale, the complexion is "muddy," and the eyes lack luster. Hypochromic anemia is common. In protracted cases there may be delayed epiphyseal development, irregularities in dentition, and delayed puberty.

The appraisal should always include a careful history of dietary habits, physical hygiene and illness, a thorough physical examination, and the necessary laboratory examinations to establish, whenever possible, the cause or causes.

**Treatment.** There is a great need for individualization, with treatment directed at correction of the underlying psychologic and physical disturbances. An adequate diet (p. 111) should be outlined; vitamin concentrates may be added and continued for a time after the dietary intake has been ade-

quate. When anorexia is a problem, the essential items of the diet should be provided in as concentrated a form as possible, and the fat content should be low. Between-meal snacks need not be prohibited if they do not interfere with the appetite for the next meal, but milk and candy should be eliminated at such times and fruit or fruit juices provided. When the family eating habits are unsatisfactory, attempts should be made to correct them.

Bedtime should be sufficiently early to ensure a full night's sleep, and, if possible, there should be a nap during the daytime. Short rest or quiet periods of fifteen to twenty minutes before meals may abolish the tension which at times interferes with the appetite. Exciting stories, movies, radio and television should be avoided before bedtime, especially when there is difficulty in going to sleep. Reasonable regularity in habits without regimentation should be encouraged. Out-of-door activity is to be encouraged in sedentary children and group play for those who tend to be seclusive. Every attempt should be made, however, to permit the child to develop natural interests. In some instances the assistance of a child guidance clinic may be helpful.

## OBESEITY

Obesity is relatively common during the latter part of childhood and during adolescence. There is no exact line of demarcation between normal nutrition and overnutrition; practically, the diagnosis is made from the appearance of the child rather than from an arbitrary excess in weight. Children of the stocky type may have relatively large skeletal frames and more than the average amount of muscular tissue, so that their weight and height as well as their appearance of bigness exceed that of the average child of their age, but they are not to be considered obese. Obesity or overnutrition is simply a generalized excessive accumulation of fatty subcutaneous tissue.

Despite the fact that medical attention has been focused on obesity in the preadolescent male, Bruch's extensive studies have shown that obesity occurs with equal frequency in both sexes. Severe obesity is less common among the wealthier classes than among the poor, and more frequent in immigrant families.

**Etiology.** The principal causes are heredity, overeating, emotional or psychologic diffi-



culties, endocrine disturbances and central nervous system disorders. If one eliminates the obesity associated with hypothyroidism and with the rare instances of true Froehlich's syndrome, hypogonadism and certain adrenal cortical tumors, excessive food intake appears to be the factor mainly responsible for obesity. The reasons for the excessive intake of food, however, may differ, and adequate therapy is possible only when the underlying cause is understood.

Though the theory of a simple direct relation between caloric intake and energy output has much to commend it, the possibility of endogenous differences between persons who are naturally thin and those who are naturally obese which determine their physical activity and their appetite cannot be lightly dismissed. The two principal arguments presented in support of the endogenous theory are based on inheritance and on imbalance of the endocrine glands.

Many instances of so-called idiopathic hereditary obesity are simply reflections of familial dietary habits. Perhaps the strongest evidence in favor of a hereditary tendency to obesity is the demonstration of it in breeding experiments in mice. Supportive human data are not available.

The relation between endocrine disturbances and obesity is not clear.

Obesity has frequently been attributed to the residuals of encephalitis, possibly in the hypothalamic area. However, Greene points out that in his series loss of weight occurred approximately five times as often as did gain in weight after encephalitis. In view of the inability to assess the role of a possible anatomic residual, it would seem wise to attempt to evaluate the effects of the encephalitis on physical activity and emotional status in the individual child in order to plan his therapy as effectively as possible. Lesions of the brain in the hypothalamic region have been assumed to be etiologic factors in the production of obesity. Experiments with rats in which obesity regularly developed after the production of hypothalamic lesions are cited in support of this theory. Similar lesions in monkeys, however, do not result in obesity, so that the results of animal experimentation cannot be directly applied to human beings.

In 1901 Froehlich published a case report of a boy with a tumor at the base of the brain who presented a picture of obesity accompanied by physical and sexual infantilism. Since then the term "Froehlich's syndrome" has been loosely applied, and numerous

preadolescent obese males have been erroneously labelled with this diagnosis (see p. 1162).

Bruch believes that emotional disturbances constitute the principal cause of obesity in late childhood and adolescence. The withdrawn, unhappy child may develop an excessive appetite in his attempt to escape from a difficult environment. Though the food intake should be limited, complete therapy must of necessity include a careful search for emotional factors, and their correction if possible.

**Clinical Manifestations.** Obesity may become evident at any age from birth on, but makes its appearance in children most frequently in late childhood or in the prepuberal period, and is often designated as *obesity of adolescence*. There is no constant physical pattern of these children, many of whom are not only heavier than their cohorts, but are also taller, and their skeletal structures are generally larger. The facial features often appear disproportionately fine, the nose and mouth being small; there is often a double chin. The adiposity in the mammary regions is often of such extent as to suggest breast development, a feature usually embarrassing to the boy. The abdomen tends to be pendulous, and white or purple striae are often present. The external genitals of boys appear disproportionately small, but actually are of average size; the penis is often nearly submerged in the pubic fat. In a few instances the genitals do appear to be definitely smaller than would be expected for age, and puberty is delayed. The development of the external genitals is normal in the majority of girls, and menarche is usually not delayed. The obesity of the extremities is usually greater in the upper arm and thigh and is at times limited to them. The hands may be relatively small, and the fingers tapering. Genu valgum is common, and coxa vara and slipping of the epiphysis of the head of the femur (p. 1257) may occur.

Psychologic disturbances are common, but not invariably present, and even in the apparently well adjusted child adequate psychologic evaluation often discloses significant underlying emotional problems. These may have contributed initially to the obesity, and in any event are usually an additive factor.

**Treatment.** Since there appears to be no proved explanation for juvenile obesity other than excessive food intake, rational therapy consists in a reduction in the diet and an in-

Table 61. 1200-1400 Calorie Diet

Breakfast	
1 orange, ½ grapefruit or 1 cup of tomato juice	
1 egg	
1 slice of whole-wheat bread or 1 serving of cereal without sugar	
1 teaspoon of butter	
1 cup of whole milk	
Lunch	
2 ounces of lean meat, 1 egg or ½ cup of cottage cheese	
1 serving of raw vegetable as salad—no dressing	
1 slice of whole-wheat bread	
1 teaspoon of butter	
1 serving of fresh or unsweetened fruit	
1 cup of whole milk	
Dinner	
2 ounces of lean meat (liver once a week), poultry or fish	
2 servings of green, yellow or red vegetables*	
1 serving of fresh or unsweetened fruit	
1 cup of whole milk	
(Part or all of bread and butter from one of the other meals may be included here)	
A 1000-calorie diet may be obtained by eliminating the butter or cream from milk. In this case it becomes especially important to add vitamin A to the daily diet.	

\* Does not include Irish or sweet potatoes, parsnips, dried peas or beans, lima beans or corn.

crease in energy output. Emotional disturbances must be overcome and the child permitted to lead a natural active life. Children with moderate obesity in the prepuberty years require no therapy, since in the majority of them the obesity disappears during adolescence. When the dietary habits of the obese child are patterned after those of the family, as is frequently the case, treatment must include the entire family. Success in such instances is by no means universal.

In planning the diet, the basic nutritional needs (p. 133) must be met. If skimmed milk is substituted for whole milk, all the essential dietary needs may be included in a 1000- to 1200-calorie diet for children ten to fourteen years of age for several months. Some children avoid excessive eating after they have been allowed to return to a free choice of diet and may thus benefit permanently from the treatment. Protein, mostly of animal origin, should be equivalent to at least 1 gm. per pound of average weight for age, and the quantity of fat by weight should not be more than one fourth that of the carbohydrate. The diet should contain as much bulk as possible. At times greater co-

operation is secured if small portions of the diet are permitted between meals, especially in the afternoon. If there is reasonable doubt that the daily vitamin intake is adequate, vitamin concentrates may be prescribed. Vitamin D should be included, as it should for all growing children. Too rapid decreases in weight should not be attempted, and medical supervision should be maintained. The correction of any underlying emotional disturbance is essential and should include adequate adjustment of the child in physical and social activities of the home, school and community. There is at best a limited place for drug therapy. A trial with amphetamine in conjunction with dietary restriction and psychotherapy may be justified for children whose habits are quite sedentary and/or who have frequent states of depression.

WALDO E. NELSON

## REFERENCES

- Bruch, H.: Psychiatry Aspects of Obesity in Children. *Am. J. Psychiat.*, 99:752, 1943.
- Greene, J. A.: Clinical Study of the Etiology of Obesity. *Ann. Int. Med.*, 12:1797, 1939.
- Illingworth, R. S.: Obesity. *J. Pediat.*, 53:117, 1958.
- Rytand, D. A.: Hereditary Obesity of Yellow Mice; Method for Study of Obesity. *Proc. Soc. Exper. Biol. & Med.*, 54:340, 1943.
- Talbot, N. B.: Obesity in Infants and Children. *M. Clin. North America*, 29:1217, 1945.

## NUTRITIONAL EDEMA

(PROTEIN DEFICIENCY, HYPOPROTEINEMIA, WAR EDEMA)

During the period of growth more nitrogenous food must be consumed than is excreted (positive nitrogen balance), whereas adults need only maintain nitrogen equilibrium. Not all protein is equally efficient in the maintenance of nitrogen equilibrium or in the establishment of nitrogen retention. When the diet does not contain adequate amounts of the essential amino acids, nitrogen equilibrium is not maintained, irrespective of the total quantity of protein in the diet.

Though there are undoubtedly a number of manifestations of protein deficiency, such as inadequate growth, lack of stamina, loss of muscular tissue and increased susceptibility to infections, edema is the only one which can be considered characteristic, but even it is not specific. There is nothing to differentiate hypoproteinemic edema from that of other causes. Edema usually occurs when the serum



protein is greatly decreased, although it may occur in states of dietary deprivation without a hypoproteinemia. The function of protein in the control of water balance depends upon its osmotic effect. Though the edema level of serum protein is generally considered to be between 4 and 5 gm. per 100 ml., the serum albumin content is the most important factor, and edema tends to occur when it is below 2.5 gm. per 100 ml. Albumin has an osmotic pressure approximately three times that of globulin. The normally lower levels of serum protein in infants (4.5 to 6 gm. per 100 ml.) than in adults (6 to 8 gm. per 100 ml.) make infants especially vulnerable to protein deficiency.

The term "nutritional edema" is usually reserved for states of protein deficiency resulting from inadequate dietary intake, but hypoproteinemia sufficient to be responsible for the production of edema may also result from impaired intestinal absorption of protein (chronic diarrheal states, celiac disease), from hypogenesis of serum protein in liver disease or from renal excretion of albumin (nephrotic syndrome).

High caloric diets have a sparing action on protein, so that a smaller amount of protein may be ingested without the production of hypoproteinemia if the diet is otherwise abundant. Thus nutritional edema is more likely to occur when the diet is low in total calories and in protein.

Edema in states of nutritional deficiency is the result of a number of factors which may be operative with or without a low serum protein level. One of these appears to be an alteration in capillary permeability. Water and salt are often ingested in quantities larger than usual during periods of protein deprivation, so that they can be expected to exert a significant effect in the production of edema. Environmental temperature also seems to exert an effect in that edema tends to be more extensive in tissues relaxed by heat.

**Clinical Manifestations.** Edema, the outstanding feature, may appear abruptly and be extensive, with free fluid in the serous cavities. More frequently, however, the onset is gradual; the edema appears first in the lower extremities in ambulatory children and, unless checked, becomes generalized. In infants it is more generalized from the start, and the face especially is likely to be involved. Diets are rarely deficient in protein alone, and there are often evidences of other nutritional deficiencies, especially those of the B group of vitamins. Hypochromic anemia is

an almost constant accompaniment. The general evidences of wasting may be extreme, especially in areas of famine. The wasting, pallor, weakness, edema and potbelly present a pitiful picture.

**Prevention and Treatment.** Prophylaxis consists in an adequate protein intake. Sick children whose fluid and caloric intake must be supplied entirely or largely by parenteral means should be given amino acid solutions (2 to 4 gm. per kilogram per day); if the serum protein is low, blood or plasma may also be given.

Curative treatment in the uncomplicated case requires temporarily a high caloric, high protein diet, with much of the protein derived from milk, eggs and meat. The maintenance diet should then be an average one, but should be planned to avoid future dietary deficiency.

## KHASHIORKOR

(THIRD-DEGREE MALNUTRITION  
[GÓMEZ], PLURIDEFICIENCY SYNDROME)

*World hunger and the rise of Communism are the two things most dreaded in the free world. The two are interrelated; if we can prevent Kwashiorkor, we can prevent world hunger and other evils.—Williams.*

Kwashiorkor is the term applied to a clinical syndrome which results from a deficiency of protein and probably other nutrients, especially those of the vitamin B complex. As a clinical entity it is poorly defined, and, for practical purposes, its identification is solely by clinical means. This unique situation encompasses what is generally considered to be the most prevalent and serious nutritional disturbance and the most important medical problem among children in the world today. It is prevalent among all underprivileged peoples in the tropical and subtropical countries throughout Africa, Asia, the Far East and Central and South America. The clinical patterns vary somewhat from country to country, especially in regard to the changes of the hair and skin, but there seems to be little doubt that the basic factors are similar in all. The problem is a socio-economic one, and the real solution is educational and economic, but perhaps more could be gained quickly for world betterment by the control of this disease under medical supervision than by any other single means. The term "Kwashiorkor" is said to mean "red boy" in the "Ga" language of the Gold Coast, but another interpretation is the "syndrome of the change-



A



B

FIG. 89. A, Kwashiorkor in a 2-year-old boy. Note the generalized edema, the typical skin lesions and the state of prostration. B, Close-up of the same child showing the hair changes and psychic alterations (apathy and misery); the edema of the face and the skin lesions can be seen more clearly. (Photographs made available by the Institute of Nutrition of Central America and Panama [INCAP], Guatemala, C.A., through the courtesy of Dr. Moisés Béhar.)

ling." As will be seen in the description of the syndrome, each interpretation is meaningful in its application. The adequacy of the term is questioned by many, especially in Central and South America, but it seems well established for the present. Kwashiorkor has much in common with the *Mehlnährschaden* of Czerny and Keller in its edematous form, and with hypoproteinemic nutritional edema observed in various countries, especially in war-torn areas where starvation is common.

The syndrome (or syndromes) as it has been described among African children consists in (1) retarded growth in the late breast-feeding, weaning and postweaning ages; (2) alterations in skin and hair pig-

mentation; (3) edema usually associated with hypoproteinemia; (4) the frequent association of a variety of dermatoses; (5) fatty infiltration, cellular necrosis or fibrosis of the liver; (6) gastrointestinal disorders, including anorexia, vomiting, diarrhea and steatorrhea; (7) irritability and apathy; and (8) a high mortality rate if appropriate dietary therapy is not instituted sufficiently early. Some combination of these is essential for diagnosis.

Of 1000 cases collected by Trowell, the age distribution ranged from four months to five years, 85 per cent of the cases occurring between the seventh and thirty-sixth months. In general the affected infants appear to do



well during their early months of life while they are breast-fed; during the latter part of the first year and the early part of the second year of infancy the disease becomes prevalent. Weaning is likely to be an abrupt process among African tribes, and the new diet is high in carbohydrates and low in protein, particularly of animal origin. Cow's milk or that of other species is rarely included in the diets of these people.

Initially there is failure to grow, then loss of weight. In spite of the edema, which appears relatively early, these children are underweight and show delay in bone development. Edema usually starts in the feet, but soon involves the face, the hands, arms and genitals; ascites is rare, and effusions into the joints have not been recorded. The urine may contain small amounts of albumin, but not the large amount characteristic of nephrosis; other abnormalities of the urine are not characteristically found. There is an associated hypoalbuminemia. It is this feature in combination with the dietary history and the response to the feeding of protein of high biologic value which is responsible for the assumption that kwashiorkor is a protein deficiency state. Some emphasis has been placed on the deficiency of particular amino acids, especially methionine.

Dyspigmentation of some degree of the hair or skin is usually present and is perhaps the unique characteristic of the syndrome. The hair loses its lustre and in the Negro tends to lose its curliness and become straight and fine. It becomes pale and may be flaxen or almost reddish; in more severe forms of the disease and in other races it may become gray to white. The changes in the color of the skin are less marked and more difficult to distinguish from genetic variants. Dyspigmentation of the face is thought by some to be of nutritional origin more often than of a genetic one.

Dermatologic lesions have been observed; though skin lesions are frequently present in the well advanced cases, there is lack of agreement that any are characteristic. The possibility has been considered, but not generally accepted, that the lesions are those of pellagra. They have also been ascribed to a deficiency of vitamin A. Perhaps the commonest form is that described by Trowell:

This eruption occurs as sharply defined black varnished patches on the areas exposed to irritation (diaper area, buttocks, back and so forth) but none appears on the areas exposed to sunlight (the hands and face) on which classical pellagra should ap-

pear. These black islands rapidly enlarge, tend to coalesce and then peel to disclose a white or pink area underneath. They undergo spontaneous peeling quite independently of any specific treatment but this usually only occurs if at the same time the case is improving. (Brock and Autret.)

Widespread desquamation and scaling, amounting almost to an exfoliative dermatitis, have been described, as have thickening and fissuring of the skin (elephant skin), especially over the knees. Pemphigus-like lesions in the pelvic region in which the superficial epithelium is separated by a nonpurulent exudate have also been noted.

As the disease progresses, the child exhibits lassitude, mental apathy, photophobia and, in general, a picture of dejection and misery. The abdomen is distended, usually without ascites, and there are frequent bouts of diarrhea. The absence of pancreatic ferments has been recorded and may be responsible for the frequent occurrence of large bulky stools containing undigested material. At autopsy the disappearance of zymogen granules from acinar cells in the pancreas, atrophy of the acini and fibrosis have been observed. But in contrast to cystic fibrosis of the pancreas, the depletion of the pancreatic ferments is not permanent, if cure of the disease is effected. The principal pathologic changes are in the liver and consist in enlargement, fatty infiltration, necrosis and fibrosis.

Some degree of anemia is present in practically all instances. It is usually normocytic or slightly macrocytic, and often hypochromic. The anemia responds less slowly to high protein feeding than do other manifestations of the disease. In some instances there appears to be a favorable response to iron, but the consensus is that the anemia is not affected by vitamin B<sub>12</sub>, folic acid or liver extract.

To what extent factors other than protein deficiency are responsible for kwashiorkor or for some of the manifestations associated with it is an important question. It is probable that deficiencies of other nutrients such as of the various members of the vitamin B complex, vitamin A, certain minerals and specific amino acids are frequently contributing factors. There is also the possibility that diseases such as hookworm, malaria and dysentery may also be contributing factors in many instances. These children tolerate infections poorly, and it has been suggested that they do not tolerate antimalarial drugs in full dosage. The actual mortality rates are not known, but in the fully developed cases



FIG. 90. Jamaican infants of predominantly African stock. *Left*, Infant with "sugar-baby" kwashiorkor, showing stunting, edema of feet and hands, hepatomegaly with fatty infiltration, moon face, misery and extreme dyspigmentation of the hair (hypochromotrichia) and of the skin generally. *Right*, Normal infant of same racial group. (N.B. The hypochromotrichia here is one of the most extreme examples seen in Jamaica.) (From D. B. Jelliffe: Hypochromotrichia and Malnutrition in Jamaican Infants. *J. Trop. Pediat.*, Vol. 1.)

recovery is unusual even in hospital practice.

*Prevention* is obviously the important consideration and apparently can be accomplished by feeding an adequate diet during the postweaning phase. Because of the effectiveness of milk protein, the distribution of powdered skimmed milk protein in the indigenous areas would seem to be an effective temporary method for the rapid institution of preventive measures on a large scale. However, the problem is a much bigger one and will be solved only by the provision of adequate health facilities for all underprivileged peoples, and above all education of them in basic health measures and in improvement of their socio-economic status.

*Treatment* involves attention to the need for fluids, electrolytes, blood, plasma, a diet rich in proteins of high biologic value, vitamins and minerals and the treatment of any coexisting infections.

WALDO E. NELSON

#### REFERENCES

##### *Nutritional Edema*

Weech, A. A.: Protein Deficiency and Nutritional Edema; in Brennemann, J.: *Practice of Pediatrics*.

Hagerstown, Md. W. F. Prior Company, Inc., 1957, Vol. 3, Chap. 34.

##### *Kwashiorkor*

Brock, J. F., and Autret, M.: *Kwashiorkor in Africa*. Geneva, World Health Organization, 1952.

Gomez, F., Ramos, G., Cravioto, J., and Silvestre, F.: *Malnutrition in Infancy and Childhood*, with Special Reference to Kwashiorkor; in Levine, S. Z., and others: *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1955, Vol. 7, p. 131.

Williams, C. D.: Kwashiorkor. *J.A.M.A.*, 153:1280, 1953.

#### VITAMIN A DEFICIENCY

Carotenes and their derivative, vitamin A, are required in the diets of infants and children, since the human organism is unable to synthesize them. Carotenes of plant origin are readily converted into vitamin A by the liver, in which to a large extent it is stored, to be released as needed. In infants the vitamin A level of the blood plasma varies between 50 and 100 I.U.; in adults, between 100 and 300 I.U.\* In disorders of the liver, in diabetes mellitus and in hypothyroidism the conver-

\* One international unit (I. U.) of vitamin A is equivalent to 0.3 microgram of vitamin A alcohol.



sion of carotene may be disturbed, and it may appear in unusual amounts in the blood (carotenemia). In children with carotenemia the skin shows a yellow discoloration, but the color of the scleras remains unchanged.

**Etiology.** The liver of the newborn infant has a low vitamin A content which is rapidly augmented after birth, since colostrum and the initial breast milk furnish large amounts of the vitamin. Breast milk and whole cow's milk are satisfactory sources of vitamin A. When other foods (vegetables, fruits, eggs, butter, liver) or cod liver oil is added to the infant's diet, new sources of vitamin A are made available. The loss by cooking is small, since the vitamin is not water-soluble and is fairly stable to heat. Canning and freezing of foodstuffs do not appreciably affect their vitamin A content. Oxidizing agents, however, destroy this vitamin.

The danger of vitamin A deficiency is small in healthy children under normal living conditions. If, however, for economic or other reasons the diet is restricted for any length of time to flour mixtures, cereals or skimmed milk, symptoms of vitamin A deficiency are to be expected. Symptoms may also develop in spite of adequate intake of vitamin A under pathologic conditions which interfere with its absorption or storage. Chronic intestinal disorders, celiac disease and hepatic and pancreatic diseases, in which there is a disturbance of fat metabolism, belong in this category. The danger of vitamin A deficiency is augmented in these cases if fat-free diets, which are usually poor in vitamin A, are recommended for therapeutic purposes. The dietary regimens for infantile eczema are also often deficient. During infectious diseases the absorption of vitamin A and carotene may be diminished. Chronic use of liquid petrolatum also causes interference with the absorption of carotenes and of vitamin A.

**Pathology.** The functions of vitamin A include its participation in the formation of visual purple (rhodopsin) and the maintenance of the health of various epithelial cells. Characteristic changes in the covering epithelium resulting from deficiency of vitamin A include atrophy, followed by proliferation of the basal cells and the formation of stratified, cornified squamous epithelium, regardless of the original function or structure. Disturbance of function thus results from alteration of the epithelium, from loss of secretory ability and from obstruction by keratinized debris.

In the eye, in addition to night blindness, deficiency of vitamin A manifests itself by

dryness of the conjunctiva (xerophthalmia) and of the cornea, which may become soft (keratomalacia) and ulcerated. Follicular hyperkeratosis of the skin is more frequent in adults than in children. Changes in the respiratory system are especially important in infants, in whom obstruction of small bronchioles may cause patchy atelectasis and emphysema. Squamous metaplasia of the pelvis of the kidney, ureters, urinary bladder, enamel organs, pancreatic and salivary ducts may occur. In experimental animals compression of the brain and spinal cord has been observed as the result of their continued normal growth and the retarded growth of their osseous coverings.

**Clinical Manifestations.** The first symptom of vitamin A deficiency is cessation of growth. Later there is loss of weight and apathy. Night blindness, loss of visual acuity in dim light, may be due to vitamin A deficiency, since this vitamin plays an important role in the retina as a component of visual purple. After exposure to bright light the visual purple is converted to visual yellow, which partly reverts to visual purple in the dark. This latter process of regeneration of visual purple depends upon a sufficient supply of vitamin A.

Xerophthalmia and keratomalacia appear late in the disease. The first symptoms are dryness of the palpebral conjunctiva and in-

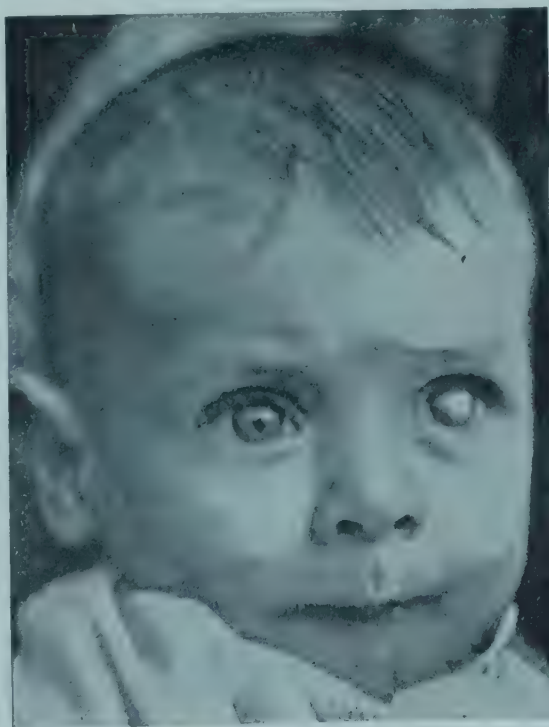


FIG. 91. Recovery from xerophthalmia, showing permanent eye lesion. (Bloch: *Am. J. Dis. Child.*, Vol. 27.)



FIG. 92. Hyperostosis of the ulna and the tibia in an infant 21 months of age, resulting from vitamin A poisoning. A, Long wavy cortical hyperostosis of ulna. B, Long wavy cortical hyperostosis of right tibia; striking absence of metaphysal and epiphysal changes. (J. Caffey: *Pediatrics*, Vol. 5. Published by Charles C Thomas, Springfield, Ill.)

jection of the bulbar conjunctiva. On the latter there are sometimes dry, yellowish patches (Bitot's spots). The dryness later extends over the cornea, which becomes cloudy and wrinkled. Photophobia is present at this stage. When the cornea becomes necrotic, superimposed infection and ulceration may be predominant. Prior to necrosis and ulceration the process is reversible when adequately treated. After ulceration has taken place healing results in formation of opaque scars and loss of vision (Fig. 91). The skin is dry and scaly, and at times follicular hyperkeratosis may be found on the shoulders, the buttocks and the extensor surfaces of the extremities.

The epithelial changes of the mucous membranes predispose to infections; pneumonia is a frequent complication and often the immediate cause of death.

**Diagnosis.** Dark adaptation tests, when made carefully and under strictly standardized conditions, may be helpful, but the method is not adaptable to routine clinical practice. If xerosis conjunctivae precedes

night blindness, it can be detected by biomicroscopic examination of the conjunctiva. Examination of the scrapings from the eye and vagina has also been recommended as a diagnostic aid. The plasma carotene level falls quickly, but the vitamin A concentration decreases more slowly. An absorption test for vitamin A is available. After fasting, a sample of blood is taken, 0.1 cc. of percomorph liver oil per pound of body weight is given, and samples are taken three, five, seven, nine and twelve hours afterwards. Low absorption curves are obtained in children with fibrosis of the pancreas, celiac disease, obliteration of the bile ducts, and cretinism.

**Prevention.** Infants should receive at least 1500 I.U. daily, older children 2000 to 4500 I.U. of vitamin A or carotene, and adults, 5000 I.U. The average diets of infants and children in this country supply enough vitamin A to prevent symptoms of deficiency. If children receive, in addition, one of the vitamin A and D concentrates or a multiple vitamin preparation, most of which contain 3000 to 5000 I.U. of vitamin A per recom-



mended dose, their requirements are more than adequately covered.

Children on a low fat diet for therapeutic reasons should receive supplementary vitamin A. In disorders which result in poor absorption of fat, water-miscible preparations of vitamin A should be administered in amounts equivalent to several times the usual daily requirement. Premature infants, who absorb fats and vitamin A less efficiently than do full term infants, should also receive water-miscible preparations.

**Treatment.** In cases of latent vitamin A deficiency a daily supplement of 5000 I.U. of vitamin A to the diet is all that is required. If symptoms are present, 20,000 to 50,000 I.U. should be given for several days, followed by the foregoing plan.

**Hypervitaminosis.** Acute hypervitaminosis A may occur in infants after the ingestion of 300,000 I.U. or more. The symptoms are nausea, vomiting, drowsiness, and bulging of the fontanel.

Chronic hypervitaminosis A appears after ingestion of excessive doses for several weeks or months. The initial manifestations are not specific. The child has anorexia, pruritus and a lack of gain in weight. There is increasing irritability, limitation of motion and tender swellings of the bones. Alopecia, seborrheic cutaneous lesions, fissuring of the corners of the mouth and hepatomegaly may develop. Roentgenograms reveal hyperostosis affecting several bones and most marked at the middle of the shafts. A history of excessive ingestion of vitamin A is helpful in the differentiation of cortical hyperostosis (Caffey's disease, p. 1260).

JOSEF WARKANY

## REFERENCES

- Caffey, J.: Chronic Poisoning Due to Excess Vitamin A. *Pediat.*, 5:672, 1950.
- Frazier, C. N., and Hu, C. K.: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency: A Study of 207 Cases. *Arch. Dermat. & Syph.*, 33:825, 1936.
- Lewis, J. M., Bodansky, O., Birmingham, J., and Cohan, S. Q.: Comparative Absorption, Excretion, and Storage of Oily and Aqueous Preparations of Vitamin A. *J. Pediat.*, 31:496, 1947.
- Marie, J., and Sée, G.: Acute Hypervitaminosis of the Infant: Its Clinical Manifestations with Benign Acute Hydrocephalus and Pronounced Bulge of the Fontanel. *Am. J. Dis. Child.*, 87:731, 1954.
- National Research Council Recommended Dietary Allowances. Reprint and Circular Series 129, Washington, D. C., 1953.
- Nieman, C., and Klein Obbink, H. J.: The Biochemistry and Pathology of Hypervitaminosis A. Vita-

mins and Hormones. New York, Academic Press, Inc., 1954, Vol. XII.

Wolbach, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies. *Physiol. Rev.*, 22:233, 1942.

## VITAMIN B COMPLEX DEFICIENCY

Vitamin B complex consists of a number of separate factors which vary greatly in chemical composition and function. Three of these factors are of outstanding importance in pediatric pathology, since definite disease can be attributed to their absence in the diet. Beriberi is considered a thiamine deficiency; pellagra, a niacin deficiency; and a clinical syndrome of cheilosis, glossitis and keratitis, a riboflavin deficiency. Factors such as pyridoxine, pantothenic acid, choline, biotin, inositol, folic acid and B<sub>12</sub> are of importance for the normal functioning of the human organism, but at present no specific deficiency syndromes can be ascribed to lack of them in the diets of children. Several members of the B complex are important constituents of enzyme systems. Since many of these enzymes are closely related in their functions, the lack of one factor can interrupt an entire chain of normal chemical processes and produce diversified clinical manifestations.

Diets deficient in one factor of the B complex are frequently poor sources of other B vitamins. It is therefore not unusual to find manifestations of several B deficiencies in one patient. In such composite disease pictures a sharp separation of the symptoms caused by deficiencies of the single factors may become impossible. In the majority of instances it is advantageous to treat a patient with the entire B complex.

## THIAMINE DEFICIENCY

### (BERIBERI)

**Etiology.** Vitamin B<sub>1</sub> (thiamine) is one of the water-soluble vitamins and, as thiamine pyrophosphate or cocarboxylase, functions as a coenzyme in carbohydrate metabolism. A deficiency of this coenzyme results in accumulation of pyruvic acid in the tissues.

The foods usually given to infants—breast milk or cow's milk, vegetables, cereals, fruits, eggs—are fair sources of thiamine. Cow's milk is a better source of thiamine than is breast milk. Mothers with thiamine deficiency produce a milk deficient in thiamine, and in infants fed their milk beriberi may develop. Older children eating a mixed diet which

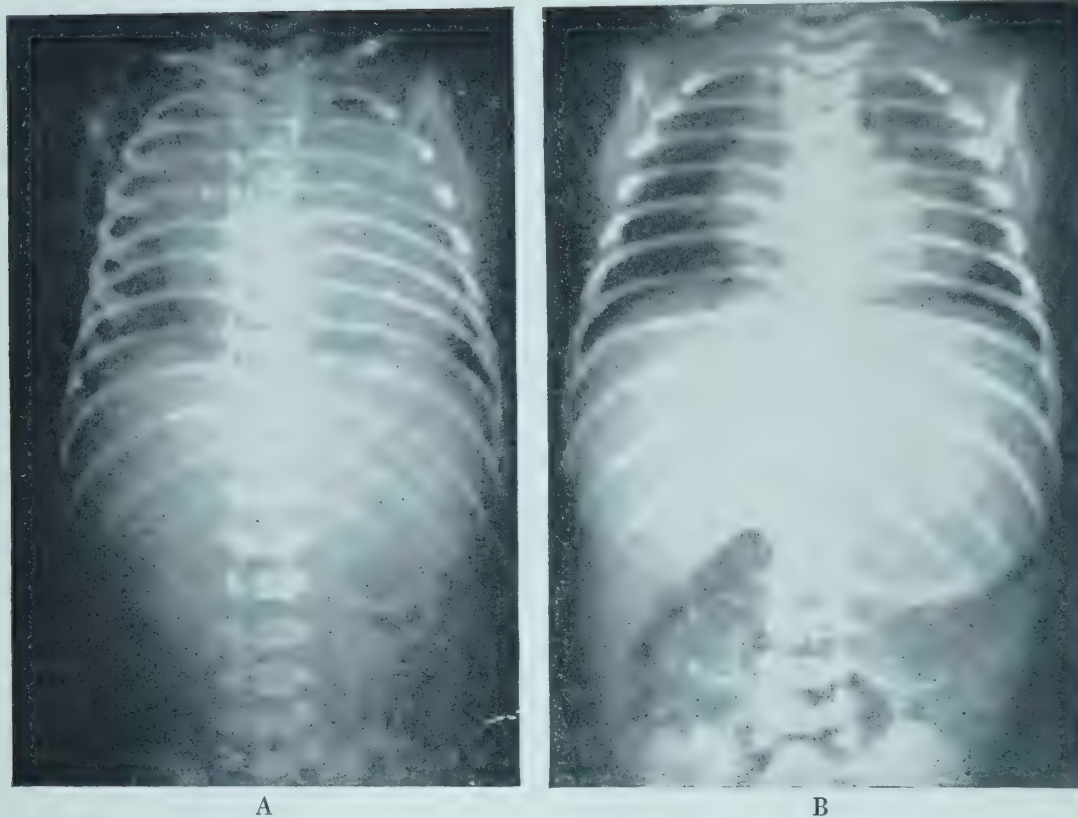


FIG. 93. A, Roentgenogram of an infant 18 hours old with congenital beriberi, before thiamine therapy was instituted, showing an enlarged cardiac shadow. B, Roentgenogram of the child 11 days after administration of the first dose of thiamine, showing reduction in size of the cardiac shadow. (From D. W. Van Gelder and F. V. Darby: *Congenital and Infantile Beriberi*. J. Pediat., Vol. 25.)

contains such good sources of thiamine as meats and legumes do not require supplements of this vitamin.

Thiamine is easily destroyed by heat in neutral or alkaline media and is readily extracted from foodstuffs by cooking water. The presence of a destructive enzymatic factor in certain types of fish explains why a diet low in thiamine induces beriberi rapidly when it is supplemented by such fish. The thiamine stores of the body are rapidly exhausted when the diet is free of this vitamin.

**Pathology.** In fatal cases of beriberi, lesions are located especially in the heart, peripheral nerves, subcutaneous tissue and serous cavities. The heart, particularly the right side, is dilated; the interstitial tissue is edematous; and fatty degeneration of the myocardium is commonly present. Generalized edema or edema of the lower extremities, serous effusions and venous engorgement of the viscera may be present. Microscopically the peripheral nerves reveal varying degrees of degeneration of myelin and of axon cylinders; the latter changes are more likely to be present in chronic states of deficiency.

**Clinical Manifestations.** Infantile beriberi is rarely seen in the United States. Information about it is based chiefly on reports from Oriental countries. Congenital beriberi in infants of mothers with a severe deficiency has been observed, but the majority of cases occur within the first three months of life. The vague initial symptoms are restlessness, anorexia, vomiting and constipation.

On the basis of physical findings, two types can be distinguished: In one the infants may appear plump, but are pale, flabby, listless and dyspneic; the heart rate is rapid and the liver enlarged. In the other type the infants are undernourished, pale and edematous. They too have dyspnea, vomiting and tachycardia. The knee and ankle jerks are absent in each type. There is no gain in weight except in infants who have edema, which is usually restricted to the distal parts of the extremities. The skin appears waxy. The urine may be scanty and contain albumin and casts.

The nervous symptoms are caused by changes in the central as well as in the peripheral nervous system. Apathy and drowsiness



are common. There may be ptosis of the eyelids and atrophy of the optic nerve. Hoarseness due to paralysis of the laryngeal nerves is a characteristic finding. Paralytic symptoms are rare in infants.

The cardiac signs at first are slight cyanosis and dyspnea. Tachycardia, enlargement of the liver, loss of consciousness, and convulsions may develop rapidly. The heart is enlarged, especially to the right. The heart sounds are rapid, and the second pulmonic sound is accentuated. As a rule there are no murmurs. Gallop rhythm may be present. The roentgenogram shows cardiac dilatation (Fig. 93), and the electrocardiogram indicates myocardial damage. Cardiac failure may terminate the disease in either the chronic or the acute form. In the latter it may occur with dramatic suddenness in infants previously considered healthy.

**Diagnosis.** The early symptoms, such as restlessness, anorexia, gastrointestinal disturbances, and pallor, are encountered in many types of nutritional disturbances which are not necessarily caused by thiamine deficiency. Najjar and Holt recommend a saturation test that consists in measuring the amount of thiamine excreted in the urine for four hours after the intravenous injection of 1 mg. of thiamine. The milk of thiamine-deficient mothers shows a delayed peroxylase reaction (negative Arakawa test). This test can be used when vague symptoms suggestive of beriberi are found in a breast-fed infant. A negative Arakawa test supports the diagnosis of thiamine deficiency.

**Prevention.** Thiamine deficiency in breast-fed infants is prevented by a maternal diet which contains sufficient amounts of this vitamin. The recommended daily dietary allowances of thiamine are 1.8 mg. during pregnancy and 2.3 mg. during lactation. Preparations of vitamin B complex, pork, dried brewer's yeast and whole cereal preparations enrich a mixed diet sufficiently to avoid thiamine deficiency. Attention should also be paid to the methods of preparation of the mother's diet, since cooking may reduce the thiamine content of good sources of this vitamin. The recommended daily dietary allowance of thiamine is 0.4 mg. for infants and 0.6 to 1.2 mg. for older children.

**Treatment.** If beriberi occurs in a breast-fed infant, the mother as well as the child should be treated with thiamine. The daily dose for adults is 50 mg., and for children 10 mg. or more. Oral administration is effective unless gastrointestinal disturbances prevent

absorption. In such a case, as well as in cardiac failure, intravenous or intramuscular injections are indicated. Such treatment is followed by dramatic improvement within two hours. Complete cure requires several weeks; the beriberi heart is not permanently damaged. There is often deficiency of other B vitamins in patients with beriberi; for this reason all the vitamins of the B complex should be administered in addition to large doses of thiamine chloride.

## RIBOFLAVIN DEFICIENCY

### (ARIBOFLAVINOSIS)

Riboflavin deficiency is rarely encountered without manifestations of other deficiencies of the B complex. Riboflavin is a water-soluble, yellow, fluorescent substance stable to heat and acids, but destroyed by light and alkalis. It is a constituent of many types of living cells and plays a role in cellular respiration. It occurs in large amounts in liver, kidney, brewer's yeast, milk, cheese, eggs and leafy vegetables. Cow's milk contains about five times as much riboflavin as human milk.

Riboflavin deficiency is usually due to inadequate food intake, but faulty absorption or utilization may be a contributory factor.

**Clinical Manifestations.** Riboflavin deficiency may manifest itself by cheilosis, glossitis, keratitis and certain lesions of the skin. Cheilosis begins as a pallor at the angles of the mouth, followed by thinning and maceration of the epithelium. Superficial fissures often covered by yellow crusts develop in the angles of the mouth and extend radially into the skin for distances of 1 to 2 cm. Cheilosis (*perlèche*) occurs in epidemics in institutions and in families where the diet is inadequate. In ariboflavinosis the tongue is smooth and shows loss of papillary structure.

Fissures and seborrheic accumulations may be seen in the nasolabial folds. Burning, itching, photophobia and lacrimation are the subjective manifestations of the ocular lesions. Examination with the slit lamp shows at first engorgement of the limbic plexus and later vascularization of the cornea, and interstitial keratitis. The corneal findings are not in themselves pathognomonic of ariboflavinosis. Scaly desquamation about the eyes and ears has been described. In addition, less characteristic symptoms such as general malnutrition, malaise and listlessness may be present. Ariboflavinosis is more frequent in the spring than at other seasons.

**Prevention.** The daily amount of riboflavin recommended for infants is 0.6 mg.; for children one to twelve years old, 1 to 2 mg.; and for adults, 2 to 3 mg. Riboflavin deficiency is usually prevented by a diet which contains adequate amounts of milk, eggs, leafy vegetables and lean meats.

**Treatment.** Treatment consists in the oral administration of 3 to 10 mg. of riboflavin daily. If no response is obtained within a few days, intramuscular injections of 2 mg. of riboflavin in saline solution may be made three times daily. The child should also be given a well balanced diet and, temporarily at least, more than the usual requirements of the B complex.

## NIACIN DEFICIENCY

### (PELLAGRA)

Pellagra (*pellis*, skin; *agra*, rough) probably has existed under certain unfavorable conditions at all times in all parts of the world.

**Etiology.** Pellagra is a systemic disease which affects all the tissues of the body. Though it is a deficiency disease, it is questionable whether all its symptoms can be attributed to the deficiency of a single vitamin. It is fairly certain, however, that the lack of niacin (nicotinic acid) is responsible for most of the manifestations.

Niacin and the physiologically active niacinamide have significance as components of coenzyme I, or cozymase, and coenzyme II. These coenzymes play a role in glycolysis as well as in respiration of the cells. Apparently the human organism cannot synthesize niacin and must depend on exogenous sources. Liver, lean pork, salmon, poultry and red meat are good sources of niacin, but most cereals contain only small amounts of it. Pellagra occurs chiefly in countries where corn, a poor source of niacin, is used as a basic foodstuff. Milk and eggs, which contain little niacin, are good pellagra-preventive foods, owing to their high content of tryptophane, which can be converted into niacin. Because niacin is a stable compound, there are only small losses by cooking if the cooking water is not excessive and not discarded.

The incidence of pellagra is increased in the spring and early summer months. This disorder is frequent in women in the post-partum period, since pregnancy and lactation increase the niacin requirement. Restricted diets given for therapeutic reasons can be just as deleterious as those enforced by unfavorable economic conditions, and a ca-

pricious appetite may also result in the development of pellagra. Pellagra usually does not occur in breast-fed infants.

**Pathology.** Histologically, there is edema and degeneration of the superficial collagen of the dermis. The papillary vessels are engorged, and there is perivascular lymphocytic infiltration in the dermis. The epidermis is hyperkeratotic and later becomes atrophic.

Changes comparable to those in the skin are present in the tongue, buccal mucous membranes and in the vagina. These changes may be associated with secondary infection and ulceration. Changes in the nervous system occur relatively late in the disease and consist of patchy areas of demyelination and degeneration of ganglion cells; demyelination in the spinal cord may involve the posterior and lateral columns.

**Clinical Manifestations.** The early symptoms of pellagra are vague. Anorexia, lassitude, weakness, burning sensations, numbness and dizziness may be prodromal symptoms. After a long period of deficiency the characteristic symptoms of pellagra appear. They may be classified as those of the skin, the alimentary tract and the nervous system. Severe manifestations may occur in children who have parasites or chronic disorders.

The most characteristic manifestations of the disease are the cutaneous symptoms, which may develop suddenly or insidiously and may be elicited by irritants, particularly by intensive sunlight. They first appear as a symmetrically developed erythema, usually on the backs of the hands, wrists, forearms, face, neck, feet, ankles and knees. The erythema resembles sunburn and in mild cases, especially in young children, may easily escape recognition. In more severe cases it becomes darker red, and is followed by drying, scaling and pigmentation of the epidermis (dry type). The lesions are usually sharply demarcated from the healthy skin around them, and their distribution may change frequently. The lesions on the hands sometimes have the appearance of a glove (pellagrous glove) (Fig. 94), and similar demarcations are occasionally seen on the foot and leg (pellagrous boot) or around the neck (Casál's necklace). In some instances vesicles and bullae develop (wet type), or there may be suppuration beneath the scaly, crusted epidermis; in others the swelling disappears after a short time and desquamation begins. The healed parts of the skin may remain pigmented.

The cutaneous lesions are sometimes preceded by symptoms in the alimentary tract,





FIG. 94. Pellagra in a boy 3 years of age, showing lesions on the hands and elbows and an early lesion over the nose and malar eminences.

such as stomatitis, glossitis, vomiting and diarrhea. Swelling and redness of the tip of the tongue and its lateral margins appear relatively early. Later there may be intensive redness of the entire tongue with swelling of the papillae and even ulceration.

Nervous symptoms include depression, disorientation, insomnia and delirium.

The classic symptoms of pellagra are usually not well developed in infants and children. Anorexia, irritability, anxiety and apathy are observed frequently in young children of "pellagra families." They may also have sore tongues and lips, and the skin is usually dry and scaly. There may be alternate diarrhea and constipation and a moderate secondary anemia. Children who have pellagra often have evidences of other nutritional deficiency diseases.

**Prevention.** The recommended daily allowance of niacin is 4 mg. for infants and 6 to 12 mg. for older children. A well balanced diet containing meat, vegetables, eggs and milk meets this requirement, so that supplements of niacin are necessary only in breast-fed infants whose mothers suffer from pellagra or in children on restricted diets.

**Treatment.** Children respond rapidly to antipellagral therapy. A liberal and well balanced diet should be supplemented with 50 to 300 mg. of niacin daily; 10-mg. tablets are recommended for children up to six years of age, and 20-mg. tablets for children from six years up to puberty. The tablets should be given not less than one hour apart. A smaller amount of niacin may be given intravenously, or approximately 100 mg. by hypodermoclysis

in severe cases or in those patients in whom intestinal absorption is poor. The administration of large doses of niacin is often followed within a half hour by a sensation of increased local heat and flushing and burning of the skin. These unpleasant effects are not produced by niacinamide.

Since vitamin deficiencies are rarely single, it is considered good practice to supplement the diet with other vitamins, especially with the other members of the B complex. Sunshine should be avoided during the active phase, and the skin lesions may be covered with soothing applications. A blood transfusion may be helpful in cases of severe anemia, and the less severe hypochromic ones should be treated with iron. The diet of the cured pellagrin should be continuously supervised to prevent recurrence.

JOSEF WARKANY

## REFERENCES

### *Thiamine Deficiency*

- Elvehjem, C. A.: Handbook of Nutrition. XI. The Water-Soluble Vitamins. J.A.M.A., 120:1388, 1942.
- Haridas, G.: Infantile Beriberi in Singapore during the Latter Part of the Japanese Occupation. Arch. Dis. Child., 22:23, 1947.
- Najjar, V. A., and Holt, L. E., Jr.: Studies in Thiamin Excretion. Bull. Johns Hopkins Hosp., 67:107, 1940.
- Van Gelder, D. W., and Darby, F. N.: Congenital and Infantile Beriberi. J. Pediat., 25:226, 1944.

### *Riboflavin Deficiency*

- Najjar, V. A., and Holt, L. E., Jr.: A Riboflavin Excretion Test as a Measure of Riboflavin Deficiency in Man. Bull. Johns Hopkins Hosp., 69:476, 1941.

- Sebrell, W. H., and Butler, R. E.: Riboflavin Deficiency in Man. *Pub. Health Rep.*, 53:2282, 1938.
- Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D.: The Ocular Manifestations of Ariboflavinosis. *J.A.M.A.*, 114:2437, 1940.
- Wolbach, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies. *Physiol. Rev.*, 22:233, 1942.

#### *Niacin Deficiency*

- Perlzweig, W. A., Sarett, H. P., and Margolis, L. H.: Studies in Nicotinic Acid Metabolism. V. A Test for Nicotinic Acid Deficiency in Man. *J.A.M.A.*, 118:28, 1942.
- Smith, D. T.: Nicotinic Acid Deficiency (Pellagra). *M. Clin. North America*, 27:379, 1943.
- Spies, T. D., Walker, A. A., and Wood, A. W.: Pellagra in Infancy and Childhood. *J.A.M.A.*, 113:1481, 1939.
- Wolbach, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies. *Physiol. Rev.*, 22:233, 1942.

### SCURVY

Scurvy is a manifestation of vitamin C deficiency. Vitamin C has been identified with l-ascorbic acid,  $C_6H_8O_6$ , a colorless, crystalline substance which can be prepared from glucose. In aqueous solution it is easily oxidized; destruction is accelerated in alkaline solutions (pH above 7) and by heating. The presence of copper, which acts as a catalyst, contributes to the destruction. In the absence of oxygen, however, and in acid solution, ascorbic acid withstands heat fairly well.

**Etiology.** Since vitamin C (ascorbic acid) is not synthesized by man, there is complete dependence upon the dietary supply. The infant is born with adequate stores of vitamin C if the mother's intake has been adequate. The vitamin C content of cord blood plasma is two to four times greater than that of maternal plasma. As a rule, breast milk contains about 4 to 7 mg. of ascorbic acid per 100 cc., thus forming an adequate source of vitamin C. However, a deficiency of vitamin C in the mother's diet may result in scurvy in her breast-fed infant. The calf is able to synthesize vitamin C, and the ascorbic acid content of cow's milk is only one fourth or so of that of breast milk. Pasteurization and passage through pipes containing a copper alloy reduce the vitamin C content of cow's milk until its antiscorbutic value becomes negligible. Therefore infants fed artificially must receive vitamin C supplements in order to avoid scurvy; such supplements will provide additional protection for the breast-fed infant.

Scurvy may occur at any age, but is ex-

tremely rare in the newborn infant. The majority of cases are seen in the latter half of the first and in the second year of life. Apparently all febrile diseases, particularly infectious and diarrheal diseases, increase the need for vitamin C; they are therefore predisposing factors in the etiology of scurvy.

**Pathology.** Deficiency of vitamin C results in defective formation and maintenance of intercellular substances in the supporting tissues of mesenchymal origin; these substances include the collagen of fibrous tissue, the matrices of bone, cartilage and dentin and the "intercellular cement" of vascular endothelium. The tendency to hemorrhage in scorbutic patients may be the result of failure of maintenance of cement substance in the walls of the vessels, or of collagen about the vessels. Although increased capillary fragility and bleeding are prominent signs, no anatomic lesions are demonstrable within the vessels. Lesions in the teeth result from defective dentin, and loosening of the teeth results from rarefaction of alveolar bone and from defective connective tissue attachments.

Endochondral bone formation ceases in the absence of vitamin C, since osteoblasts are no longer capable of forming their normal intercellular substance, osteoid. The trabeculae of calcified cartilage, normally exposed by the progressive growth of capillaries at the epiphyseal-metaphyseal junction, no longer become covered by osteoid tissue, nor are replaced by bone. These heavily calcified cartilaginous trabeculae are brittle and easily fractured (slipping or dislocation of the epiphysis). The trabeculae are surrounded by a loose, myxomatous type of tissue, poor in collagen; their cells rapidly become converted into recognizable osteoblasts after the administration of vitamin C.

Important changes also occur elsewhere in the bones. The pre-existing bone becomes rarefied, since formation of new bone does not keep pace with the physiologic destructive process. The periosteum becomes loosened, and subperiosteal hemorrhages occur, especially at the ends of the femur and tibia.

**Clinical Manifestations.** Clinical scurvy requires time for its development; after a variable period of vitamin C depletion vague symptoms of irritability, digestive disturbances and loss of appetite appear. The irritability becomes progressively greater, and there is evidence of general tenderness especially noticeable in the lower extremities when the infant is picked up or when the diaper is changed. The pain causes pseudoparalysis,





FIG. 95. Scorbutic rosary, depression of sternum and the so-called frog position.

and the legs assume the typical "frog position" (Fig. 95), which consists in semiflexion of the hips and knees with the feet rotated outward. Edematous swelling along the shafts of the legs may be found, and in some cases a subperiosteal hemorrhage can be palpated at the end of the femur. The facial expression is apprehensive. Changes of the gums, most noticeable when the teeth are erupted, are characterized by bluish-purple, spongy swellings of the mucous membrane, usually situated over the upper incisors. The swollen gums sometimes completely conceal the teeth. There may be a "rosary" at the costochondral junctions and a depression of the sternum. The angulation of the "scorbutic beads" is usually sharper than that in the rachitic rosary, since it is produced by a subluxation of the sternal plate at the costochondral junction (Fig. 95), in contrast to the widening of the softened epiphyses in rickets (p. 374).

Hemorrhages may occur in the skin, mucous membranes and in the soft tissues, as, for example, in those of the scalp. Orbital hemorrhage producing exophthalmos is rare. Blood may be vomited or passed by bowel, and there may be hematuria. Subdural hemorrhages are an occasional manifestation, whereas intracerebral hemorrhages rarely occur. A low grade fever is usually present. A moderate secondary anemia develops, but the total white blood cell count as well as the differential count is normal in uncomplicated scurvy. (See page 939 for role of vitamin C in megaloblastic anemia.)

**Roentgenographic Manifestations.** The diagnosis or exclusion of scurvy is usually based on roentgenographic changes in the long bones, especially of their distal ends. Changes, as a rule, are greatest in the area of the knee. In the early stages the appearance resembles that of simple atrophy of the bone. In the shaft the trabeculae cannot be dis-

cerned, and the bone assumes a "ground-glass" appearance. The cortex is reduced in thickness, "pencil-point thinness," and the epiphysal ends are sharply outlined. The white line of Fraenkel, which represents the zone of well calcified cartilage, can be clearly discerned as an irregular but thickened white line at the metaphysis. The epiphysal centers of ossification also have a ground-glass appearance and are surrounded by a white ring corresponding to the white line of the shaft (Fig. 97). At this stage scurvy cannot be diagnosed with certainty from the roentgenogram; if, however, under the white line at the metaphysis the zone of rarefaction becomes apparent, the roentgenogram is diagnostic. The zone of rarefaction is a linear break in



FIG. 96. "Slipped diaphysis" in scurvy. The epiphysis (E) of the humerus and calcified cartilage of the zone of primary calcification (ZPC) remained in place and in contact with the glenoid fossa. The diaphysis (D) was displaced laterally and separated from the epiphysis. The shadow (H) at the proximal end of the diaphysis represents beginning calcification of a subperiosteal hemorrhage.

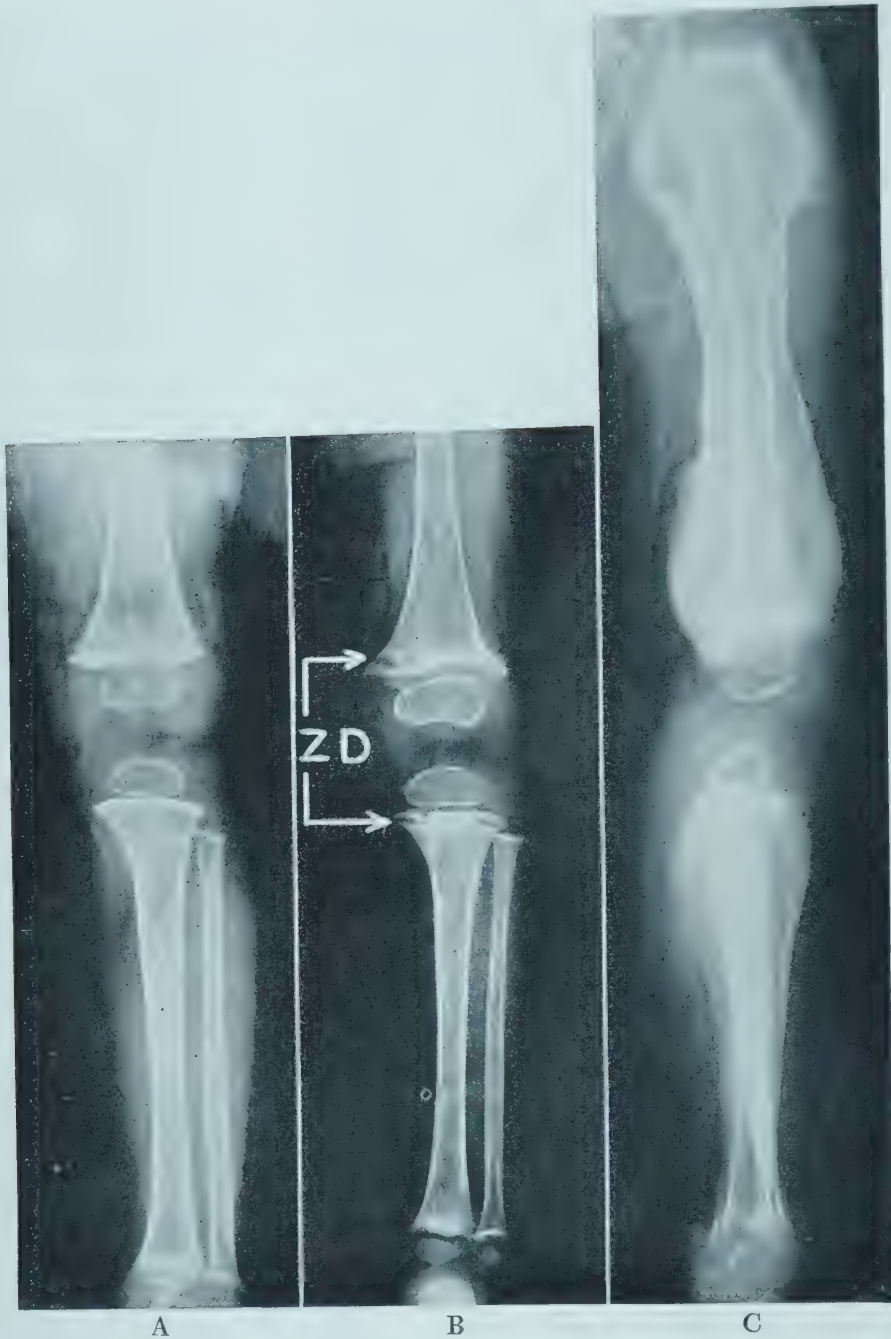


FIG. 97. Roentgenograms of lower extremity. A, Early scurvy: "white line" is visible on the ends of the shafts of the tibia and fibula; rings around epiphyses of femur and tibia. B, More advanced scorbutic changes; zones of destruction (ZD) in femur and tibia. C, Healing scurvy; calcification of subperiosteal hemorrhages.

the bone proximal and parallel to the white line. It often does not traverse the shaft in its entire width and may be seen only in its lateral parts as a triangular defect (Fig. 97, B). A spur, a lateral prolongation of the white line, may or may not be present. Epiphysal separation may occur along the line of destruction with linear displacement (Fig. 96) or compression of the epiphysis against the shaft. Subperiosteal hemorrhages are not visible roentgenographically in active scurvy.

During healing, however, the elevated periosteum becomes calcified and presents a striking picture. The affected bone assumes a dumbbell or club shape, since the hemorrhage occurs at the ends of the bone and elevates the periosteum more at this site than in the middle of the shaft (Fig. 97, C). As healing progresses, the shadow of the hemorrhage becomes more intense, but diminishes in width; the rings around the epiphysal centers of ossification become more distinct, and the



zone of destruction disappears and is replaced by calcified tissue.

**Differential Diagnosis.** The tenderness of the limbs and the pain elicited by movement have often led to a false diagnosis of arthritis. The age of the patient aids in differentiating scurvy and rheumatic fever, since the latter is rare in children under two years. Suppurative arthritis or osteomyelitis does, however, occur in young children and infants and should be considered in the differential diagnosis. The pseudoparalysis of syphilis usually occurs at an earlier age than does that of scurvy, and is often accompanied by other symptoms of syphilis. The roentgenogram aids in the differential diagnosis. Poliomyelitis causes a true flaccid paralysis, and in infants the exquisite tenderness found in the limbs in scurvy is absent. Diseases of the blood, dysentery or hemorrhagic nephritis are sometimes suspected in scurvy when the hemorrhagic tendency dominates the clinical picture.

The clinical diagnosis of latent scurvy is difficult. A fasting vitamin C level of the blood plasma of over 0.6 mg. per 100 ml. aids in the exclusion of scurvy; a lower vitamin C level does not, however, prove its presence. A better index of vitamin C deficiency is furnished by determination of the ascorbic acid concentration of the white cell-platelet layer (buffy layer) of centrifuged oxalated blood. A level of zero in this layer indicates latent scurvy, even in the absence of clinical signs of deficiency. The saturation of the tissues with vitamin C can be estimated by the amount of urinary excretion of vitamin C after a test dose of ascorbic acid. During the three to five hours after the parenteral administration of the test dose, 80 per cent of the total twenty-four hour excretion can be found in the urine. Children with vitamin C deficiency excrete less ascorbic acid under these conditions than normal children with well saturated tissues.

In general, the diagnosis of scurvy is based on other than chemical data, the roentgenographic appearance of the long bones being of greatest importance.

**Prognosis.** Recovery occurs rapidly in cases correctly treated. Pain ceases in a few days, but the swelling caused by subperiosteal hemorrhage may require months to disappear. Body growth is usually quickly resumed. In unrecognized and untreated cases death is liable to occur after a few months from malnutrition, exhaustion, some complication or intercurrent disease. Permanent deformity from scorbutic lesions is uncommon; even

when there has been metaphysial separation, reconstruction is usually good without orthopedic treatment.

**Prevention.** Scurvy may be prevented by administration of a diet adequate in vitamin C. All infants, even breast-fed ones, should receive ascorbic acid (25 to 50 mg.), orange juice (1 to 2 ounces) or fresh or canned tomato juice (2 to 3 ounces) daily, beginning at two to four weeks of age. Lactating mothers should take generous amounts of vitamin C; a minimum daily intake equal to 150 mg. of ascorbic acid has been recommended. There is no reason why boiled or pasteurized milk may not be used in artificial feeding, provided vitamin C is added to the diet. The diet of older infants and children is usually varied enough to contain sufficient vitamin C, although the diets of all children should be appraised from time to time to ensure their adequacy, since scurvy can develop at any time of life. A daily intake of 25 to 50 mg. of ascorbic acid for infants, 50 mg. for children, and 75 mg. for adults is considered adequate.

**Treatment.** The administration of 3 to 4 ounces of orange juice or tomato juice daily will quickly produce healing, but ascorbic acid is preferable. The daily therapeutic dose is 100 to 200 mg. or more, orally or parenterally.

JOSEF WARKANY

## REFERENCES

- Hess, A. F.: Scurvy, Past and Present. Philadelphia, J. B. Lippincott Company, 1920.
- McIntosh, R.: Infantile Scurvy. Barlow's Disease; in Brennemann, J.: Practice of Pediatrics. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. I, Chap. 35.
- Meiklejohn, A. P.: The Physiology and Biochemistry of Ascorbic Acid. Vitamins and Hormones. New York, Academic Press, Inc., 1953, Vol. XI.
- Park, E. A., Guild, H. G., Jackson, D., and Bond, M.: Recognition of Scurvy, with Especial Reference to the Early X-Ray Changes. Arch. Dis. Childhood, 10:265, 1935.
- Wolbach, S. B., and Bessey, O. A.: Tissue Changes in Vitamin Deficiencies. Physiol. Rev., 22:233, 1942.

## RICKETS OF VITAMIN D DEFICIENCY\*

**Etiology.** Rickets is a systemic disease resulting from an insufficiency of vitamin D.

Secretions of the human skin contain 7-dehydrocholesterol, a provitamin D. Under natural living conditions this provitamin is

\* Metabolic Bone Disorders Simulating Rickets are described on page 1221.

activated by ultraviolet rays of the sunlight (296 to 310 microns) and converted into vitamin D, which is absorbed by the blood and distributed throughout the body.

In the temperate zones, particularly during the winter months, the sunshine is rather limited. The dust, smoke and fog, as well as the shadows cast by high buildings in cities, reduce the antirachitic potency of the sunlight and skyshine by filtering out the effective ultraviolet rays before the light reaches the skin. Sunlight which has passed through ordinary window glass is deprived of its antirachitic potency. As a rule, infants in the temperate and arctic zones escape rickets only when they receive a protective amount of vitamin D in their diet.

The natural diet of infants contains only small amounts of vitamin D; breast milk is a poor source, and cow's milk contains only 5 to 40 I.U. per quart. Sugar, cereals, vegetables and fruits contain only negligible amounts. Egg yolk contains from 140 to 390 I.U. per 100 gm.

Many sterol derivatives have antirachitic value, but only two of them, 7-dehydrocholesterol and ergosterol, are of practical importance. The biologic properties of activated 7-dehydrocholesterol resemble those exhibited by vitamin D preparations of animal origin, and it is probable that the vitamin D in fish oil is principally activated 7-dehydrocholesterol, as is the provitamin D of the skin. Ergosterol is of plant origin and is the sterol found in fungi. Irradiation transforms ergosterol into vitamin D (calciferol) with certain by-products such as tachysterol and lumisterol. Irradiated ergosterol is sometimes called vitamin D<sub>2</sub>; irradiated 7-dehydrocholesterol, vitamin D<sub>3</sub>. There is no vitamin D<sub>1</sub>.

**Contributory Factors.** Several predisposing factors determine the extent and clinical pattern of rickets.

**Rapid growth.** Rapid growth is one of these contributory factors. It is often thought that vitamin deficiencies occur chiefly in undernourished persons, but this is not true of rickets. Signs of beginning rickets may be found in infants who appear well nourished. Premature infants are especially susceptible to rickets.

**Age.** Congenital rickets occurs only under rare conditions and is caused by a deficient maternal diet. Mild rickets is frequent in the first few months of infancy when no preventive measures have been taken. Well developed rickets occurs toward the end of the first and during the second year of life. In

the later years of childhood clinical rickets becomes rare, although rachitic changes may be found microscopically.

**Race.** Negro children are singularly susceptible to rickets. Whether this is due to the pigmentation of their skin or to their living conditions has not been determined.

**Genetic factors.** Genetic factors play a minor role in infantile rickets, although an inherited growth pattern may affect the development of rickets. Multiple cases of rickets in a family are usually caused by similar unfavorable living conditions or dietary faults. In vitamin D-resistant rickets (p. 1221) genetic factors are of great importance.

**Pathology. Normal bone development.** Proceeding from the cartilaginous or epiphysal end toward the osseous portion, several fairly well defined zones are encountered in normal bone. Adjoining the zone of resting cartilage is the zone of proliferating cartilage, the cells of which are arranged in orderly columns. This zone is followed by the zone of degenerating cartilage, where the cells are swollen and the intercellular matrix is impregnated with calcium salts (zone of preparatory calcification). Proceeding toward the osseous portion of bone, the spaces resulting from the degeneration and disappearance of cartilage cells are regularly invaded by capillaries, accompanied by osteoblasts, which deposit a layer of osteoid on the exposed calcified cartilaginous trabeculae. The zone of preparatory calcification appears as a straight line in roentgen films. The osteoid deposited upon the calcified cartilaginous trabeculae is rapidly mineralized, and the calcified cartilage is resorbed and ultimately replaced by bone.

**Development of bone in rickets.** Rickets is characterized by a defective growth of bone resulting from retardation or suppression of normal growth of epiphysal cartilage and of normal calcification. These changes are dependent upon a decrease in the calcium and phosphorus salts in the serum available for mineralization. In rickets the cartilage cells fail to complete their normal cycle of proliferation and degeneration along the epiphysal-metaphysal line. This failure of degeneration of cartilage cells and the subsequent failure of capillary penetration occur in a patchy manner, the result being a frayed, irregular epiphysal line at the end of the shaft. The width of the epiphysal cartilage continues to increase, but the columns of cartilage cells are irregularly arranged, and branching vessels penetrate between these clumps of cartilage.



In addition to the failure of normal maturation and degeneration of cartilage cells, there is failure of normal mineralization of osseous and cartilaginous matrix. The zone of preparatory calcification fails to mineralize, and newly formed uncalcified osteoid is deposited. As a result a wide, irregular, frayed zone of nonrigid tissue (the rachitic metaphysis), composed of noncalcified cartilage and osteoid tissue, is produced. This zone is responsible for many of the skeletal deformities in rickets. It becomes compressed and bulges laterally, producing flaring of the ends of the bones and the rachitic rosary.

Changes occur in the bone in sites other than the epiphysial-metaphysial region. Mineralization is lacking in the subperiosteal bone, and a shell of osteoid tissue is formed which surrounds the shaft over its entire length. Pre-existing cortical bone is resorbed in a normal manner, but is replaced by osteoid tissue which fails to mineralize. If this process continues, the shaft loses its rigidity. The result is a softened, rarefied, cortical bone which is readily disturbed by stress, and deformities and fractures result.

**Healing rickets.** With healing, degeneration of cartilage cells occurs along the diaphysial border of the cartilage, capillary penetration of the resultant spaces is resumed, and calcification takes place in the zone of preparatory calcification. This calcification occurs approximately at the line at which normal calcification would have occurred had the rachitic process not supervened, and produces a line clearly demonstrable in roentgen films. As healing progresses, the osteoid tissue between this line of preparatory calcification and the diaphysis also becomes mineralized.

Osteoid tissue in the cortex and about the trabeculae in the shaft rapidly becomes mineralized. Months or years may be required to repair the deformities, and in extreme instances complete repair may be impossible.

**Chemical Pathology.** The formation of the organic matrix of the bones continues during the pathologic process of rickets, but minerals are not deposited in the degenerating cartilage and in the newly formed bone. In healthy infants the inorganic serum phosphorus level is 4.5 to 6.5 mg. per 100 ml. of serum, whereas in rachitic infants it is usually reduced to 1.5 to 3.5 mg. Though the serum calcium is usually normal, under certain conditions it too is reduced, and the child may suffer tetany.

In active rickets absorption of calcium and phosphorus from the intestine is diminished, and reabsorption of phosphates by the renal tubules is also said to be decreased. The abnormal calcium and phosphorus metabolism is corrected by vitamin D.

The phosphatase level of the serum, which in normal children amounts to 5 to 15 Bodansky units per 100 ml., is elevated in rickets to 20 to 30 units per 100 ml. in mild cases and 60 units or more in severe cases. In healing rickets it returns slowly to normal levels. The level of serum citrate and the excretion of citrate in the urine are influenced by vitamin D. The citric acid content of bone is reduced in vitamin D deficiency and increased by administration of vitamin D.

Various dietary factors play a secondary role in the etiology of rickets. The anion-cation relationships of the diet influence the absorption of calcium to some extent. Citric and tartaric acid and their sodium and potas-

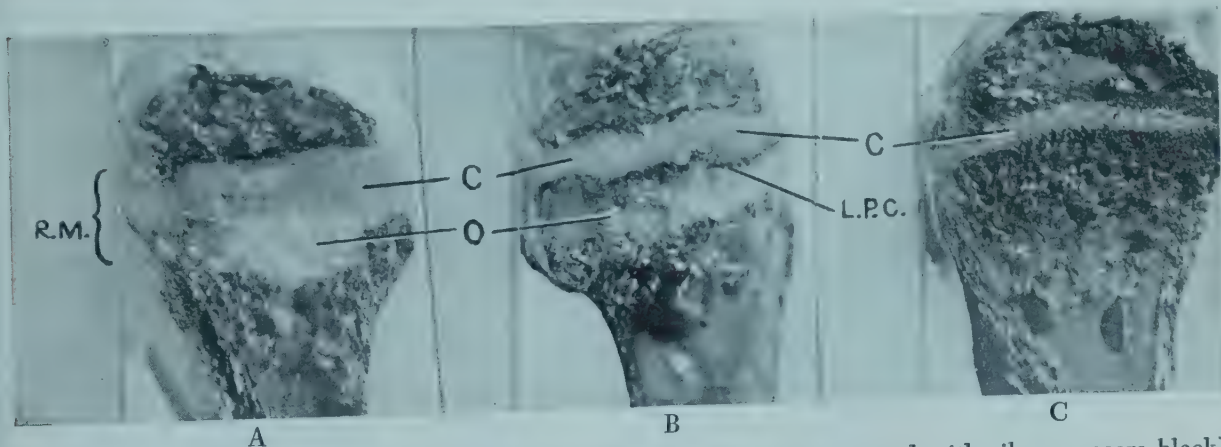


FIG. 98. Line tests in rats (proximal end of tibia) (calcified tissue stained with silver appears black). A, Active rickets. The light broad zone between epiphysis and shaft represents the rachitic metaphysis (R.M.); C, cartilage; O, osteoid. B, Healing rickets. Line of preparatory calcification (L.P.C.) between zone of cartilage (C) and osteoid (O). C, Healed rickets. Cartilaginous disk (C) between epiphysis and normal shaft.



FIG. 99. Rachitic rosary in a young infant. (Lyons and Wallinger: *Pediatrics and Pediatric Nursing*.)

sium salts have an antirachitic effect. A decrease in the alkalinity of the intestinal contents facilitates absorption of calcium. On the other hand, calcium deposition is hindered, and calcium may even be withdrawn from osseous tissue, by a decrease in the pH of the blood serum. In infants the absence of vitamin D is the basic factor responsible for rickets, and the disease is cured by vitamin D and not by the addition of calcium or phosphate to the diet.

**Clinical Manifestations. Early rickets.** The early recognition of rickets is important, but the early signs are difficult to evaluate. A history of inadequate intake of vitamin D is the best clue; the diagnosis can be established by roentgenographic examination.

Craniotabes, manifest as softening of the occiput or of the posterior parts of the parietal bones, may be found during the first few months of life when the rachitic process begins. Premature infants are particularly prone

to it. Palpation of the posterior half of the skull reveals soft spots of parchment-like consistency which may vary in size. There may also be softness of the borders of the large fontanel and along the sutures. Enlargement of the costochondral junctions and slight thickening of the wrists and ankles are suggestive of early rickets. The level of serum inorganic phosphorus usually falls below 3.5 mg. per 100 ml. at this time. In premature infants, however, rachitic changes may develop without hypophosphatemia.

**Advanced rickets.** Signs of advanced rickets are easily recognized, but the fully developed clinical case is rare, owing to widespread prophylactic treatment.

**HEAD.** Craniotabes may disappear before the end of the first year, although the rachitic process continues. The softness of the skull may result in flattening and, at times, permanent asymmetry of the head. The anterior fontanel is larger than normal; its closure may be delayed until after the second year of life, and the sutures remain soft and separated. The central parts of the parietal and frontal bones are often thicker than the corresponding areas of normal bones, forming frontal and parietal prominences or bosses, which give the head a boxlike appearance (*caput quadratum*). The head may be larger than normal, and may remain so throughout life. Eruption of the temporary teeth is sometimes delayed and out of the normal order. There may be defects of the enamel and extensive caries. The permanent teeth which are calcifying may be affected; usually the permanent incisors, canines and first molars show defects of the enamel, especially on the distal portion.

**THORAX.** In advanced rickets the enlargement of the costochondral junctions, the "rachitic rosary," becomes marked, and in



FIG. 100. Deformities in rickets, showing curvature of the limbs, potbelly and Harrison's groove.



many cases the beading of the ribs is not only palpable, but also visible. The costochondral junctions as well as the osseous part of the ribs gradually become softer. The sides of the thorax become flattened, and longitudinal grooves develop posterior to the rosary. The sternum with its adjacent cartilages appears to be projected forward, producing the so-called pigeon breast deformity. Along the lower border of the chest there develops a horizontal depression, Harrison's groove (Fig. 100), which corresponds to the costal insertions of the diaphragm. The chest may show a variety of other deformities, and the bones of the shoulder girdle may also be involved.

**SPINAL COLUMN.** Slight to moderate degrees of lateral curvature (scoliosis) are common, and a kyphosis may appear in the dorso-lumbar region in rachitic children who sit up (Fig. 101). Lordosis of the lumbar region may be seen in the erect position.

**PELVIS.** In children with lordosis there is frequently a concomitant deformity of the pelvis. The rachitic pelvis is not only small, but also continues to be retarded in growth. The pelvic entrance is narrowed by a forward projection of the promontory, and the exit by a forward displacement in the sagittal plane of the caudal part of the sacrum and the coccyx. In the female these changes, if they become permanent, add to the hazards of childbirth and may necessitate cesarean section.

**EXTREMITIES.** As the rachitic process continues, the epiphysal enlargements at the wrists and ankles become more noticeable. The enlarged epiphyses can be seen (Fig. 102) or palpated, but are not well visualized in roentgenograms, since they consist of cartilage and uncalcified osteoid tissue. There are various degrees and types of curving of the extremities, the legs usually being more deformed than the arms. Bending of the shafts of the femur, tibia and fibula results in bowlegs or knock knees, and the femur and tibia may also show an anterior convexity. Coxa vara is sometimes the result of rickets. If the rachitic metaphysis develops at an angle to the long axis of the shaft, bowing results which persists after healing. Bending may occur in the legs before walking is begun, although weight-bearing increases it. Greenstick fractures occur in the long bones, but seldom cause clinical symptoms.

Deformities of the spine, pelvis and of the legs result in reduction in height of the body, *rachitic dwarfism*.

**LIGAMENTS.** Relaxation of these structures, especially those of the spine and the larger joints, aids in producing deformities. This relaxation partly accounts for the production of knock knees, overextension of the knee joints, weak ankles, and scoliosis.

**MUSCLES.** The muscles are poorly developed and lacking in tone. As a result, children with well marked rickets are late in standing



FIG. 101. Rachitic spinal curvature well marked when the child is sitting.



FIG. 102. Curvature of arms, deformed "violin-shaped" chest, potbelly, enlarged epiphyses in a child 3 years of age.

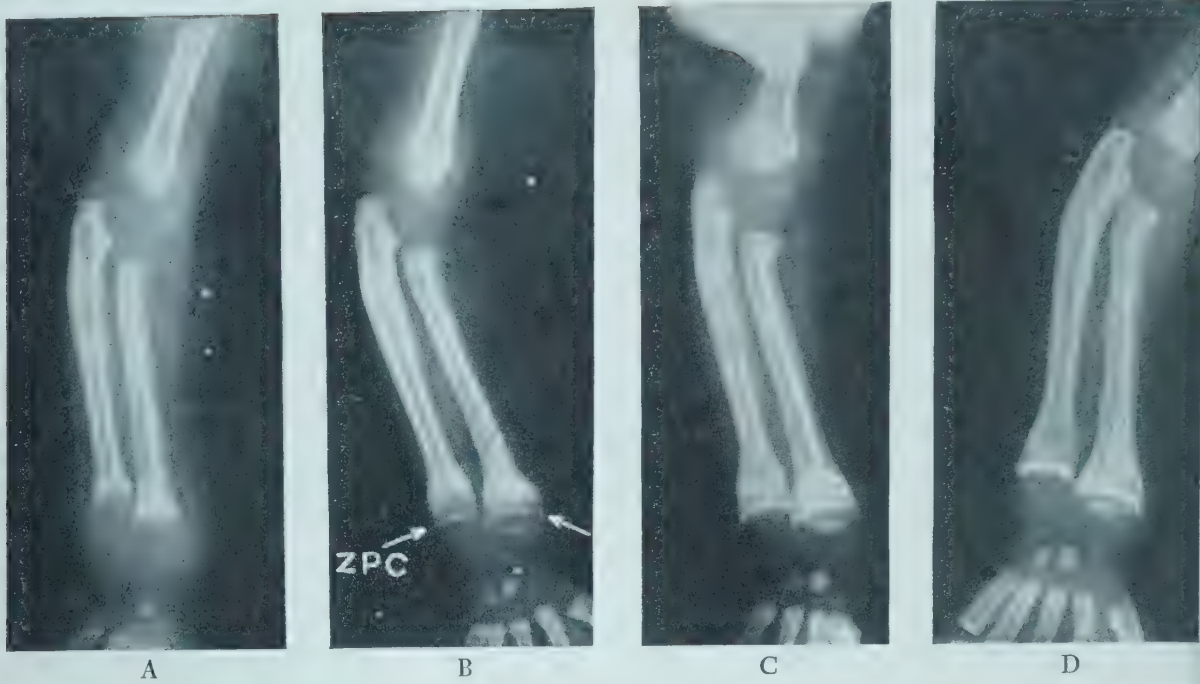


FIG. 103. A, Active rickets; cupping and fraying of distal ends of radius and ulna; double contour along lateral outline of radius (periosteal osteoid). The 2 dense zones in the shaft of the ulna are calluses of greenstick fractures. B, Healing rickets after 12 days of treatment with vitamin D. Zones of preparatory calcification (ZPC); above them in the rachitic metaphyses there is beginning calcification. C, Healing rickets after 18 days of treatment. The zones of preparatory calcification are well defined, and the rachitic metaphyses appear well calcified. The epiphysis of the radius has become visible. D, Healing rickets after 29 days of treatment. Zones of preparatory calcification, rachitic metaphyses and shafts have become united.

and walking. The common condition of pot-belly (Figs. 100, 102) depends to a large extent upon weakness of the abdominal muscles, although the weakness of the gastric and intestinal walls aids in its production.

**Diagnosis. Roentgenographic changes.** The diagnosis of active and healing rickets is usually based on evidence obtained from roentgenograms of the wrists.

**ACTIVE RICKETS.** In active rickets the distal ends of the radius and ulna appear widened, concave (cupping) and frayed, in contrast to the sharply demarcated and slightly convex ends observed in the roentgenograms of normal infants. The distance between the distal ends of the ulna and radius and the metacarpal bones is increased, since the large rachitic metaphysis, which is not calcified, does not appear on the roentgenogram. The shafts show decreased density, and the trabeculae are usually prominent. In Figure 103, A, two dense areas are seen in the ulna that represent callus formations at sites of healing fractures. The outer contour of the radius appears double and could be mistaken for "periostitis." The double contour, however, represents the layer of osteoid tissue formed

by the periosteum, and not an inflammatory process.

**HEALING RICKETS.** Beginning healing is indicated by the appearance of the line of preparatory calcification (Fig. 103, B). This line is separated from the distal end of the shaft by a zone of decreased calcification, the zone of the osteoid tissue. As healing progresses and the osteoid tissue becomes calcified, the shaft "grows" toward the line of preparatory calcification (Fig. 103, C) until it becomes united with it (Fig. 103, D). At this stage the roentgenogram somewhat resembles that in cases of lead poisoning or syphilis. In healing rickets, however, the line of increased density is concave, while it is straight or convex in poisoning with the heavy metals.

**Differential Diagnosis.** The diagnosis is based on a history of inadequate vitamin D intake, on clinical observation, on roentgenographic examination and on the calcium phosphorus and phosphatase levels of the blood. A roentgenogram of the wrist provides the best means of making an early diagnosis since characteristic cupping and fraying of the distal ends of the ulna and radius occur at an early stage. In chondrodystrophy there



may be irregular concave outlines of the distal ends of the bones, but there is no fraying.

Nonrachitic craniotabes is sometimes present in the immediate postnatal period, but it tends to disappear before rachitic softening of the skull becomes manifest (second to fourth months of life). Craniotabes also occurs in hydrocephalus and osteogenesis imperfecta, but it is not difficult to differentiate these conditions from rickets.

Delayed dentition, although a symptom of rickets, is not diagnostic and is often a familial characteristic. Enlargement of the costochondral junctions occurs in rickets, scurvy and chondrodystrophy. The enlargements in rickets are rounded knobs; whereas in scurvy there is a ledgelike depression with the chondral or sternal portion lower than the osseous. It is sometimes difficult to distinguish rachitic deformities of the chest from congenital deformities. Bowlegs can be the result of rickets, but may be due to osteogenesis imperfecta, or they may be a familial characteristic. Vitamin D-resistant rickets and other metabolic disturbances with osseous lesions resembling rickets must be differentiated (see p. 1221).

**Complications.** Respiratory infections, such as bronchitis and bronchopneumonia, are common in rachitic infants. Pulmonary atelectasis is not infrequently associated with severe deformities of the chest.

Chronic gastroenteric disturbances are common; there may be either diarrhea or constipation, or the two conditions may alternate in the same patient.

Anemia due to iron deficiency or accompanying infections often develops in severe rickets. The lymph nodes are frequently enlarged, and the spleen may be palpable.

**Prognosis.** Though "spontaneous" healing of mild rickets often occurs from exposure to sunshine, severe cases require more energetic treatment. If sufficient amounts of vitamin D are administered, healing begins within a few days and progresses until the normal bony structure is restored. Recovery, however, from the bony deformities is slow; in many instances the enlargement of the epiphyses and of the rosary and the deformities of the skull disappear only after months or years of treatment. In advanced cases, especially when treatment has been insufficient, there may be permanent osseous alterations in the form of bowlegs, knock knees, curvature of the upper arms, deformities of the chest and spine, rachitic pelvis, rachitic coxa vara, and even dwarfing.

Rickets in itself is not a fatal disease, but complications and intercurrent infections such as tetany, pneumonia, tuberculosis and enteritis are more likely to cause death in rachitic than in normal children.

**Prevention. Exposure to ultraviolet light.** Rickets can be prevented by exposure to ultraviolet light or by oral administration of vitamin D. Sunlight, as a prophylactic agent, can be considered effective in the temperate zones only during the summer months.

**Administration of vitamin D.** The daily requirement of vitamin D is estimated to be 400 I.U. per day. Oral administration of vitamin D in one of the many so-called concentrates is the practical means for the prevention and treatment of rickets. Such preparations can be obtained in fish oil and in water-miscible vehicles. Some preparations contain only vitamin D, and others, various combinations of vitamins. Prophylactic measures should be used in breast-fed as well as in artificially fed infants. The daily prophylactic dose of vitamin D recommended for premature infants and for twins of low birth weight is 1000 I.U. in a water-miscible vehicle.

Much of the whole milk available in urban areas and most, if not all, evaporated milk are fortified by the addition of vitamin D concentrate, so that 1 quart of fresh, whole milk or a reconstructed can of evaporated milk contains 400 I.U. of vitamin D. It would seem reasonable not to rely upon vitamin D milk alone, but to provide added protection by the administration of an additional 400 I.U. of vitamin D in a concentrate.

Vitamin D should be administered to the pregnant or lactating mother.

**Treatment.** Natural and artificial light is effective therapeutically, but the oral administration of vitamin D is preferred. The daily administration of 1500 to 5000 I.U. (6 to 20 drops of a preparation containing 10,000 units per gram) will produce healing demonstrable on the roentgenograms within two to four weeks except in the unusual cases of vitamin D-refractory rickets.

JOSEF WARKANY

#### REFERENCES

- Eliot, M. M., and Park, E. A.: Rickets, in Brenne-  
mann, J., ed.: Practice of Pediatrics. Hagerstown,  
Md., W. F. Prior Company, Inc., 1957, Vol. 1,  
Chap. 36.
- Follis, R. H., Jr., Jackson, D., Eliot, M. M., and Park,  
E. A.: Prevalence of Rickets in Children between  
Two and Fourteen Years of Age. *Am. J. Dis.*  
*Child.*, 66:1, 1943.
- Harrison, H. E., and Harrison, H. C.: Further Stud-

- ies of the Effects of Citrate Feeding on the Calcium Phosphorus and Citrate Metabolism of Rachitic Infants. *J. Pediat.*, 41:756, 1952.
- Hess, A. F.: Rickets, Including Osteomalacia and Tetany. Philadelphia, Lea & Febiger, 1929.
- Nicolaysen, R., and Eeg-Larsen, N.: The Biochemistry and Physiology of Vitamin D. Vitamins and Hormones. New York, Academic Press, Inc., 1953, Vol. XI.

## TETANY OF VITAMIN D DEFICIENCY (INFANTILE TETANY)

Formerly the most frequent cause of tetany was vitamin D deficiency. Tetany is associated with infantile rickets (vitamin D deficient) in less than half of the active cases, and is a rare manifestation of vitamin D-refractory rickets. The wide use of vitamin D prophylactically has eliminated tetany as a clinical problem. Occasionally it is observed in association with celiac disease, probably as a result of deficient absorption of both vitamin D and calcium. Tetany of vitamin D deficiency occurs most frequently between the ages of four months and three years; rarely is it observed before three months of age.

**Chemical Pathology.** When the serum calcium falls below 7 to 7.5 mg. per 100 ml., there is muscular irritability, resulting apparently from loss of the inhibitory control which the ionized calcium of the serum exerts upon the neuromuscular junctions. Why serum calcium is not consistently or even characteristically decreased along with serum phosphorus in rickets is not entirely clear. A possible explanation is that a compensatory hyperactivity of the parathyroid glands during the active stage of rickets maintains the serum calcium above the tetany level. Thus it is assumed that when the parathyroids do not compensate by secreting more hormone or cannot compete with extreme deficiencies in absorption, the serum calcium falls below the critical level and manifest tetany results. Tetany also occasionally occurs in infants with rickets shortly after vitamin D treatment has been started. This is assumed to be due to a rapid depletion of serum calcium secondary to increased deposition of calcium in the rachitic osteoid tissue and perhaps also to a decrease in parathyroid activity.

**Clinical Manifestations.** The symptoms are those of tetany, irrespective of the cause, and are described on page 1110. Vitamin D-deficient tetany may exist in either a latent or a clinically manifest stage. In practically

all instances there are clinical and roentgenographic manifestations of rickets.

**Latent tetany.** There are no evident symptoms, but they can be elicited by means of the Chvostek, Trousseau and Erb procedures (see p. 1112). The serum calcium level is less than 7 to 7.5 mg. per 100 ml.

**Manifest tetany.** Spontaneous clinical manifestations consist of carpopedal spasm, laryngospasm and convulsions. The serum calcium is often well under 7 mg. per 100 ml.

**Diagnosis.** The diagnosis is based on the combination of rickets, low serum calcium and the symptoms of tetany. The serum phosphorus may be low, normal or elevated; the serum phosphatase is increased. In the differential diagnosis other causes of tetany must be eliminated.

**Prognosis.** The prognosis is good unless treatment is delayed. Death is rarely due to tetany, although it may result from laryngospasm and possibly from cardiac dilatation, so-called cardiac tetany. Proper prophylactic treatment prevents subsequent attacks. The course need not be prolonged beyond that of the immediate attack.

**Prevention.** Prophylactic treatment is identical with that for rickets (p. 377).

**Treatment.** Active treatment is designed to raise the serum calcium above the tetany level. This may be attained by administration of calcium chloride in 10 per cent solution. For the first day or two, 4 to 6 gm. daily may be given in 1-gm. doses, the initial dose being 2 or 3 gm.; smaller doses of 1 to 3 gm. a day should then be continued for another week or two. When oral medication is impractical, calcium gluconate (5 to 10 cc. of a 10 per cent solution) can be administered intravenously, but not subcutaneously or intramuscularly, because of the dangers of necrosis.

Oxygen inhalation is indicated during convulsive seizures. When intravenous administration of calcium gluconate does not quickly control the attacks, sodium phenobarbital may be given intramuscularly (p. 1122). Parathyroid hormone in a dose of 10 to 30 units may be given in acute cases, but is rarely necessary and should not be repeated because of its rachitic effect. Dihydrotachysterol is contraindicated because of the slowness of its action and because it also is rachitic. Intubation is only occasionally necessary in prolonged attacks of laryngospasm, which is usually controlled by sedation and the administration of calcium salts. After the acute manifestations have been controlled vitamin



D administration in daily doses of 4000 to 5000 I.U. should be started and the oral administration of calcium continued (see above). When the rickets is healed, the dose of vitamin D should be decreased to the usual prophylactic one.

WALDO E. NELSON

## VITAMIN K DEFICIENCY

The exact function of vitamin K is uncertain; it is essential for the formation of prothrombin; absence of the vitamin or failure to absorb it from the intestinal tract results in hypoprothrombinemia.

Prothrombin may be measured by the two-stage method of Warner, Brinkhouse and Smith or by the simpler one-stage method of Quick. The latter technique measures in terms of "prothrombin time" the rate of clotting of oxalated blood after the addition of an excess of thromboplastin and calcium. Prothrombin with thromboplastin and calcium forms thrombin, which then joins with fibrinogen to form fibrin. With an adequate intake and absorption of vitamin K, prothrombin deficiency may occur in the presence of liver damage.

**Sources of Vitamin K.** Naturally occurring vitamin K is fat soluble and found in high concentrations in hog's liver, soy beans and alfalfa, and in smaller amounts in some vegetables such as spinach, tomatoes and kale. The natural vitamin, whose formula is 2-methyl-3-phytyl-1, 4-naphthoquinone, has been labelled vitamin K<sub>1</sub> to distinguish it from synthetic naphthoquinones with vitamin K activity, of which menadione (2-methyl-1, 4-naphthoquinone), a fat-soluble preparation, and Hykinone and Synkavite, water-soluble preparations, are examples.

Many bacteria, including normal intestinal flora, are capable of synthesizing quinones with vitamin K activity. Suppression of intestinal bacteria by various antibiotics may result in vitamin K deficiency with a diminution of prothrombin.

**Clinical Manifestations.** Deficiency of vitamin K, or hypoprothrombinemia, should be considered in all patients with a hemorrhagic disturbance. Such hemorrhages may be cutaneous or internal, or both. Since naturally occurring vitamin K is fat soluble, most instances of vitamin K deficiency in childhood are due to states affecting absorption or utilization of fat such as prematurity, chronic diarrhea, the celiac syndrome, sprue, and

obstructive lesions of the biliary tract. Diseases of the liver such as severe hepatitis, acute yellow atrophy, or cirrhosis giving rise to hypoprothrombinemia cannot strictly be listed as manifesting vitamin K deficiency, since intake of this vitamin may be normal, but damage to the liver prevents utilization of the vitamin in the production of prothrombin. Hemorrhagic disease of the newborn (p. 336) is considered to be due to vitamin K deficiency, but the exact role of liver insufficiency in this condition is undetermined.

Hypoprothrombinemia may also result from administration of certain drugs. Dicumarol, obtained from spoiled sweet clover, is used specifically for the production of hypoprothrombinemia in the prevention and treatment of venous thrombosis. It is thought that Dicumarol prevents the liver from utilizing vitamin K and has no direct effect on prothrombin. Blood prothrombin is continually destroyed in the body; since Dicumarol prevents its replacement, a fall in prothrombin occurs. If a dangerously low level results, massive doses of vitamin K<sub>1</sub> may be necessary to restore the prothrombin to the normal level. If the administration has been delayed too long, whole blood transfusions may be necessary.

Salicylic acid, a degradation product of Dicumarol, produces hypoprothrombinemia by similar action. The fall in prothrombin resulting from the use of salicylates, however, is only mild as compared with that brought about by Dicumarol. The hemorrhagic manifestations in acute rheumatic fever in some instances may be due to large doses of salicylates. Vitamin K is effective in neutralizing the action of salicylates, and its routine use in children receiving large doses of salicylates is recommended.

**Treatment.** Mild prothrombin deficiency may be corrected by oral administration of vitamin K, using the water-soluble preparations for patients who absorb fat poorly. One to 2 mg. daily for an infant will usually suffice. If prothrombin deficiency is severe and hemorrhagic manifestations have appeared, vitamin K should be given parenterally; the preparation of choice is the naturally occurring fat-soluble vitamin K<sub>1</sub> or its oxide. Both are equally effective and are superior to water-soluble synthetic preparations. In such instances 5 mg. should be administered daily. Larger doses should be avoided, especially in premature infants; synthetic vitamin K can produce hemolysis of red blood cells

containing low levels of glutathione and may be responsible for hyperbilirubinemia and kernicterus in premature infants. To date there has been no demonstration of hemolysis with administration of vitamin K<sub>1</sub>. When hypoprothrombinemia is due to liver damage, whole blood should be given; it need not be fresh, since prothrombin in stored blood is quite stable.

SYDNEY S. GELLIS

#### REFERENCES

- Almquist, H. J.: Vitamin K. *Physiol. Rev.*, 21:194, 1941.
- Bound, J. P., and Telfer, T. P.: Effect of Vitamin K Dosage on Plasma Bilirubin Levels in Premature Infants. *Lancet*, 1:720, 1956.
- Meyer, T. C., and Angus, J.: The Effect of Large Doses of Synkavit in the Newborn. *Arch. Dis. Childhood*, 31:212, 1956.
- Miller, R., Harvey, W. P., and Finch, C. A.: Antagonism of Dicumarol by Vitamin K Preparations. *New England J. Med.*, 242:211, 1950.
- Quick, A. J.: The Anticoagulants Effective in Vivo, with Special Reference to Heparin and Dicoumarol. *Physiol. Rev.*, 24:297, 1944.
- Warner, E. D., Brinkhouse, K. M., and Smith, H. P.: Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of the Newborn. *Am. J. M. Sc.*, 193:475, 1937.



# Infectious Diseases

## INFECTION, IMMUNITY AND ALLERGY IN RELATION TO PEDIATRICS

### *THE PHYSICIAN'S RESPONSIBILITY IN THE FIELD OF INFECTIOUS DISEASE*

The prevention and treatment of infections account for a large part of pediatric practice. The clinical pattern of different infections evolves with age, from the infantile response to the fully developed reaction of the adolescent or adult. Growth and development, which differentiate pediatrics from adult medicine, affect all the phenomena of infection, immunity and allergy in childhood; knowledge of these is vital to the pediatrician. He should also be familiar with the principles of epidemiology, since he must learn to look at a case of infectious disease in relation to its setting. Often the symptoms in his patient are only part of an epidemic pattern involving other members of the household or a larger group in the community. He should also appreciate the variability in clinical manifestations of many infections, such as those due to the poliomyelitis viruses or the meningococcus, in which mild or inapparent infection is the rule and the classic case of poliomyelitis or meningococcal meningitis is the occasional exception. The epidemiologic approach to a patient with infectious disease will not only assist in diagnosis, but also, if coupled with prompt reporting to the public health authorities, may play an important role in protection of the community.

### *GENERAL PRINCIPLES OF IMMUNOLOGY*

The responses of the organism to the stimulus of infection or of contact with certain foreign chemical substances are *specific* against the particular pathogenic agent and lead to a state of heightened resistance (*immunity*) and frequently to a state of hypersensitivity (*allergy*) as well.

Landsteiner's work demonstrated that the specificity of an immune response is determined by the chemical structure of the substance eliciting it, i.e., the antigen. Most

infectious agents call forth immune responses to the antigens they contain or secrete during the processes of growth. The capacity of antigens to induce the formation of antibodies or the development of hypersensitivity can be greatly enhanced by injecting them with adjuvants, such as mineral oil, killed tubercle bacilli or colloidal aluminum hydroxide, the substance used in the preparation of alum toxoids.

The clinical and pathologic manifestations of an infectious disease are the result of the interplay between the multiplying organism and the nonspecific and specific defenses of the host. During its growth the organism may release irritating substances from itself or from the tissues, giving rise to local and distant tissue changes, or it may act as little more than an inert foreign body until the allergic state develops and a more violent reaction takes place (tuberculosis, trichinosis). Certain types of infections call forth characteristic responses, such as the leukocytosis, polymorphonuclear exudate and elevated sedimentation rate of an acute pyogenic infection, or the normal leukocyte count, lymphocytic exudate and normal sedimentation rate of many viral infections. These can be important clinical guides to correct diagnosis and treatment.

The lymphoid tissues appear to be the principal source of the specifically modified serum gamma globulins, termed antibodies, which appear in the general circulation within a few days after antigenic stimulation. The antibody-producing cells retain an enhanced power of reaction to the same stimulus for a long time, so that a subsequent injection of antigen will call forth a more rapid appearance of antibodies, which will usually rise to a higher titer and persist longer than after the first injection. This is the basis for the use of "booster" doses of toxoids or vaccines.

The development of specific immunity is

closely related to the development of specific hypersensitivity or allergy, i.e., the property of reacting violently to ordinarily innocuous doses of an antigen. Two types of allergy may be broadly distinguished. The first or *anaphylactic* type, associated with the presence of antibody in the circulation, manifests itself by a histamine-like immediate skin reaction when the antigen is injected intradermally and by immediate and violent symptoms when it is injected intravenously. It is characteristic of the sensitivity to foreign proteins and the common allergens for constitutionally allergic persons (ragweed pollen, egg white, wheat, milk proteins, and so forth).

The second or *bacterial allergic* type of hypersensitivity (tuberculin) frequently develops as a response to an infection and is characterized by a lack of antibody in the serum, but may be passively transferred by lymphoid cells from a hypersensitive person. Intradermal injection of the antigen in a sensitized person results in a delayed (forty-eight hour) reaction with redness and induration; parenteral administration may result in fever and malaise and in focal reactions in areas of disease after a period of several hours. This type of sensitivity occurs in tuberculosis, brucellosis, tularemia and many other bacterial infections, in histoplasmosis, coccidioidomycosis and other fungus diseases, and in many viral diseases, notably lymphogranuloma venereum and mumps.

Although specific immune responses have been studied intensively, many nonspecific factors which play an important role in resistance to infection are poorly understood because they are difficult to study under controlled conditions. Animals can be bred for resistance or susceptibility to certain types of infection or anaphylactic sensitization. The low resistance of the premature infant is obvious, but not adequately explained. Nutritional and physiologic factors are hardest to evaluate. Clinically, undernutrition is associated with increased morbidity and mortality from many infectious diseases, but undernutrition usually occurs under crowded and unsanitary living conditions, which may be more important in the spread of infections.

The normal response of the adrenal cortex under the influence of the anterior lobe of the pituitary gland is important in protecting the individual against the metabolic stress of acute infections. However, large doses of cortisone may activate latent infection in experimental animals, and therapeutic doses in man may not only suppress the symptoms

of infection, but also render ordinarily mild infections such as varicella very severe.

## PEDIATRIC IMMUNOLOGY

Growth and development have an important influence on the reaction of the child to infection and on the evolution of the immune state.

### INFECTION

The incidence of different infections varies markedly at different ages. In large measure this is due to changes in immunity and to varying opportunities for exposure, but there is little doubt that tissues at various ages provide different conditions for the growth of microorganisms. During prenatal existence infection of the fetus is possible only if microorganisms invade the maternal blood stream and cross the placental barrier. In the early stages of pregnancy death of the fetus or congenital anomalies may arise either as indirect effects of maternal infection on the nutrition of the fetus or as the result of direct infection of fetal tissues. The agents of syphilis and toxoplasmosis can pass the placental barrier in the latter part of pregnancy; mumps, chickenpox and measles of the newborn resulting from intrauterine infection have also been described. Other infections are transmitted only during passage through the birth canal. During neonatal life certain bacterial infections, notably those due to *Staphylococcus aureus* and *Escherichia coli*, are far more prevalent than later.

Age influences the course and severity of infections. Bacterial diseases which may occur at any age, such as tuberculosis, vary characteristically in different age groups. In infancy they are likely to be severe and rapidly progressive, with a relatively high mortality and a decided tendency to hematogenous dissemination and the development of meningitis. Mortality and severity fall to their lowest points between the ages of three and ten years. With the approach of adolescence, severity and mortality begin to increase and rise steadily to reach their peak in later life. Many viral infections, notably chickenpox, measles, epidemic hepatitis and poliomyelitis, tend to be much more severe in the adult than in the child.

Part of the changing picture of infection at different ages is doubtless related to the development of hypersensitivity and immunity. The infant may suffer a generalized infection on initial contact with *Hemophilus*



*influenzae B* or herpes simplex virus; the immune adult has only local infection with these agents. Boisvert and his colleagues emphasized the contrasts between hemolytic streptococcal infections in infancy, childhood and adult life. They used the term "streptococcosis" to bring out the similarity between the over-all pattern of this infection and tuberculosis. In infants primary hemolytic streptococcal infection is characterized by a prolonged, irregular course, in which constitutional symptoms may be mild except for the occasional appearance of high fever, but in which fulminating bacteremia akin to miliary tuberculosis may develop. Later in childhood, scarlet fever becomes a more common form of disease caused by this organism; in adolescence and adult life it most often manifests itself as acute tonsillitis, with abrupt onset, severe constitutional symptoms and a relatively short course.

### IMMUNITY

The exchange of antigens and antibodies between mother and fetus in utero was clearly established by Levine in his work on erythroblastosis fetalis. He showed that this disease develops as a result of iso-immunization of the mother by antigenic material from the fetus, with subsequent passive transfer of the resultant antibodies from maternal to fetal circulation, where they react with fetal erythrocytes. Reversal of this process (iso-immunization of the fetus by maternal antigens) has never been demonstrated; perhaps this is a human counterpart of the phenomenon of acquired tolerance for tissue cells of another strain after injection of such cells during fetal life, as shown in mice by Billingham et al.

The fetus does not appear to synthesize antibodies or gamma globulins in contrast to most other serum proteins, but receives these from its mother by way of the placenta. The role of colostrum in the transfer of antibodies from mother to newborn infant, although essential in the cow, with its placental structure, has not been shown to be important in the human being.

The infant born at term has a level of serum gamma globulins and immune antibodies corresponding to those of the mother, from whom they were derived in utero. The quantities of certain of these antibodies, if present—for example, protective antibodies against measles and epidemic hepatitis—are sufficient to prevent or modify these infections in the infant for the first six to eight

months of life; levels of various antibacterial antibodies are only adequate to protect the child for a month or so. Synthesis of the child's own gamma globulins or antibodies does not ordinarily begin until the third or fourth week of life; consequently the serum levels of gamma globulin and antibodies normally decrease during the first month to values somewhat below one-half those at birth. Subsequently, as the capacity for gamma globulin synthesis increases, its serum level gradually rises to reach the normal adult range (800 to 1200 mg. per 100 ml.) at one to three years of age. The pattern of immune antibodies within the gamma globulins develops throughout life in response to a continuing succession of antigenic stimuli from infections and active immunizations.

Although the capacity of the young infant to form antibodies is less well developed than that of the older infant, this does not justify deferment of basic immunization, since a subsequent booster injection appears to be about as effective whether basic immunization was started at one month or six months of age.

### ALLERGY

Whether the ability to respond to antigens with the development of specific hypersensitivity varies greatly at different ages is not clear. In general, the incidence of hypersensitive reactions to therapeutic antisera or drugs is somewhat less in young children than in older children, adolescents and adults. Delayed hypersensitivity develops with great regularity in children of all ages in infections such as tuberculosis, although it may not be so intense in infants as in older persons. Late nonsuppurative complications of hemolytic streptococcal infections, rheumatic fever, acute glomerulonephritis, erythema nodosum, thought by many to be reactions of hypersensitivity to bacterial antigens, occur most frequently in childhood.

The responses of persons with inherited allergic (or atopic) tendencies follow a regular pattern as growth and development proceed. Passive transfer of allergens from mother to fetus by way of the placenta and to infant by way of the colostrum and milk has been suggested as a mechanism for early initiation of hypersensitivity. Although skin-sensitizing antibodies (atopic reagins) characteristic of hypersensitive individuals do not cross the placental barrier, so-called blocking antibodies induced by "hyposensitizing" injections of allergens do so. In infancy the skin is often the first organ to react, and atopic eczema serves

as an indicator of a highly atopic constitution. Many allergic responses, such as those of hay fever, asthma, gastrointestinal symptoms, chronic eczema, urticaria or angioneurotic edema, are likely to come and go or become chronic as the patient grows to adulthood. The allergic picture may be modified by endocrine, psychologic and infectious factors, but the allergic response represents an inherited tendency for exaggerated local responses to many antigens.

It is to be hoped that advances in such fundamental sciences as protein chemistry and enzymology will ultimately explain the underlying mechanisms of infection, resistance and allergy sufficiently to provide a rational interpretation of some of the confusing and complex biologic phenomena with which the pediatrician must deal.

CHARLES A. JANEWAY

## CLINICAL USE OF THE MICROBIOLOGY LABORATORY

Much of the responsibility for attaining satisfactory laboratory diagnosis and hence control of infectious diseases rests with the clinician. It is he, not the laboratory worker, who decides what specimens to collect, how to obtain them and which laboratory procedures to request. He must also see that specimens are preserved properly until they can be delivered to the laboratory. Finally, he should be competent to make the correct interpretation of the results. In institutional practice skilled laboratory personnel are usually available for consultation; otherwise the physician must rely upon his own knowledge and judgment.

**Choice of Specimens.** The choice of specimens to be examined often makes the difference between success and failure. The clinician, in many instances, will be guided by the patient's signs and symptoms as to the type of etiologic agent he should suspect. In other instances the signs and symptoms may be so nonspecific that he must ask the laboratory's help in ruling out a variety of agents. Material from the system of the body chiefly involved should be collected, e.g., cerebrospinal fluid from a patient with meningeal symptoms or blood from a patient with fever of undetermined origin. Consideration

## REFERENCES

- Billingham, R. E., Brent, L., and Medawar, P. B.: Actively Acquired Tolerance of Foreign Cells. *Nature*, 172:603, 1953.
- Boisvert, P. L., Darrow, D. C., Powers, G. F., and Trask, J. D.: Streptococcosis in Children. A Nosographic and Statistical Study. *Am. J. Dis. Child.*, 64:519, 1942.
- Janeway, C. A., and Gitlin, D.: The Gamma Globulins; in *Advances in Pediatrics*, IX, S. Z. Levine, Editor. Chicago, Yearbook Publishers, Inc., 1957, Vol. 9, p. 65.
- Landsteiner, K.: *The Specificity of Serological Reactions*. Cambridge, Harvard University Press, 1945.
- Levine, P.: The Pathogenesis of Erythroblastosis Fetalis. *J. Pediat.*, 23:656, 1943.
- McKhann, C. F., and Kapnick, I.: Immunity and Susceptibility to Disease in Early Infancy. *J. Pediat.*, 13:907, 1938.
- Osborn, J. J., Dancis, J., and Julia, J. F.: Studies of the Immunology of the Newborn Infant. I. Age and Antibody Production. *Pediatrics*, 9:736, 1952.

should also be given to possible portals of entry, such as the upper respiratory tract in patients with meningeal involvement.

In the choice of specimens one must decide whether an attempt should be made to isolate the etiologic agent, demonstrate the antibody response, or both. In bacterial infections the method of choice is the demonstration of the offending organism by smear and culture, provided the disease is of short duration. As the infection progresses, however, isolation technique may fail, and serologic tests should also be requested. In viral infections isolation is seldom practical, and the diagnosis usually rests upon demonstration of a rise in the specific antibody titer.

**Collection and Preservation of Specimens for Isolation of Etiologic Agent.** Care must be taken to avoid contamination from the skin, air or unsterile objects during the collection of body fluids; costly delay occurs when the laboratory identifies an unimportant contaminating bacterium or fungus. Superficial contaminants may be removed from skin lesions by swabbing the area with an alcohol sponge. It is rarely feasible to try to remove the normal flora from infected mucous membrane. Usually an almost pure culture of the offending organism can be ob-



tained by applying a dry cotton swab directly to the affected region.

The cotton swab is satisfactory for the collection of specimens from skin and mucous membranes. The preservation of swab specimens is too often neglected, however. They should be kept moist by placing them in a small amount of culture broth (see Fig. 104), since drying is rapidly destructive to many pathogenic bacteria and viruses. Specimens of body fluids and tissues obtained by biopsy or at autopsy should be secured aseptically and placed in sterile glass containers. All specimens should be delivered to the laboratory as promptly as possible. See Table 62 for special techniques applicable to the various types of infecting organisms.

**Bacteria, fungi and protozoa.** Fungal specimens do not require prompt attention, but immediate study of bacteriologic and parasitologic specimens is always desirable and in some instances essential. For example, darkfield examination for spirochetes is practically useless thirty minutes after the material has been collected. Whenever there is delay in transferring bacteriologic specimens to the laboratory, they should be stored in the refrigerator, but should not be permitted to freeze.

Purulent fluids, including cerebrospinal fluid, may coagulate on standing, so that accurate cell counts become impossible and detection of microorganisms is difficult. It is advisable, therefore, to add a few drops of anticoagulant at the time of collection.

**Viruses and rickettsiae.** These organisms may also be collected by means of swabs. However, in order to obtain viruses from the respiratory tract, throat washings with a buffered saline solution or a mixture of half saline and half broth can be collected. Cerebrospinal fluids from patients with viral infections of the central nervous system do not have a high protein content, so that, in contrast to the treatment of purulent specimens, anticoagulants should not be added, since they may affect the viability of any virus present. All viral specimens should be frozen as soon as possible and conveyed to the laboratory in the frozen state by means of dry ice, since preservation of viruses is facilitated by freezing.

**Collection and Preservation of Specimens for Serologic Tests.** Correct use of serologic tests for diagnosis requires at least two blood specimens. The first should be taken at the time of the first examination ("acute serum"), the second five to fourteen

days later or during convalescence ("convalescent serum"). Great care must be taken to avoid contamination and hemolysis. An aseptic venous puncture, removal of the needle before emptying the syringe into the tube, avoidance of air bubbles and early separation of serum are essential. Serum should be frozen for preservation, *but whole blood should never be*.

**General Consideration of Methods.** There are two principal types of diagnostic procedures in microbiology. The first is the direct method, whereby the infectious agent is identified in clinical material by direct microscopy, culture, injection into susceptible laboratory animals or by a combination of these methods. The second is the indirect approach through the detection of specific antibody either by skin tests or by serologic procedures. In general the direct method yields more reliable information for the diagnosis of bacterial, parasitic and mycotic infections in their early phase, whereas the immunologic response is more likely to provide diagnostic information when the infection is caused by viruses, rickettsiae and spirochetes, and when certain bacterial in-

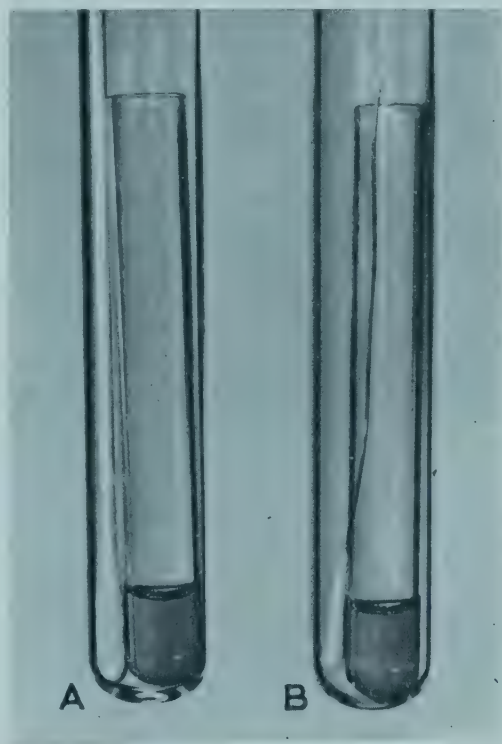


FIG. 104. Throat and nasopharyngeal swab outfit. A, Wooden swab for collection of material from the throat and tonsils or for general use. B, Wire swab for collection of nasopharyngeal specimens. Both are contained in sterile cotton-plugged test tubes. After the test material has been obtained the swabs are immersed in the broth in the inner tube.

fections are investigated late in their course. When the diagnosis depends on serologic methods, it may not be available until after recovery from the illness.

**Direct visualization.** In bacterial infections this method is limited to specimens derived from areas of the body which normally are sterile and to the recognition of bacteria that can be identified by their shape or by some unique staining property. For fungi and parasites direct microscopy, however, is a valuable step in the laboratory diagnosis. In viral infections this type of study may reveal characteristically altered host cells which are of immediate aid in making a differential diagnosis.

**Isolation procedures.** Laboratory culture is the mainstay of bacteriologic and mycologic diagnosis; precise identification of most pathogens is almost impossible in any other way. On the other hand, the parasitologist seldom uses this method.

Since viruses and rickettsiae cannot be cultured in the absence of living tissue, the virologist must make use of living hosts for isolation purposes; these include the chick embryo, various species of laboratory animals, and living cells of human or animal origin growing in tissue culture.

**Serologic methods.** The host produces antibodies in response to infection even when it is subclinical. The amount of antibody produced increases with severity, but varies with the kind of infection. Enteric gram-negative bacilli and exotoxins elicit the greatest immunologic responses. Fungi and animal parasites as a rule are poor antigens, whereas viruses generally produce good titers of antibody.

Antibody can be detected and specifically identified by serologic methods in vitro and in vivo by skin and neutralization tests. For most bacterial and leptospiral infections the method of choice is the agglutination test, using either the intact cell or a fraction of it adsorbed upon a particulate carrier such as type O human erythrocytes. The complement fixation test is used primarily for syphilis. The only important skin test for the diagnosis of bacterial infections is the tuberculin test, but other allergic skin tests could be developed if they were needed. Although the use of the complement fixation test is gradually increasing in the diagnosis of fungus and parasitic infections, the necessary antigens are not available to the average hospital laboratory. On the other hand, allergic skin tests are important in the diagnosis of

fungus and a few of the parasitic diseases, notably trichinosis.

Owing to the difficulties associated with the isolation of rickettsiae and viruses, much effort has gone into the development of satisfactory methods for the serologic diagnosis of these infections. The method most commonly used is the complement fixation test, for which a number of commercially prepared antigens are available. Certain viruses, such as those of influenza and mumps, have the capacity to agglutinate erythrocytes, a property that provides a means for measuring the corresponding antibodies by the extent to which a serum sample specifically inhibits hemagglutination. In a few viral, or presumably viral, infections for which no specific antigen is available certain nonspecific antigens are agglutinated by the serum of infected persons. For example, a rickettsial infection must be suspected when the patient's serum agglutinates one of the OX strains of *Proteus*. The presence of agglutinins for the MG strain of *Streptococcus* or cold agglutinins for type O human erythrocytes is formed in association with some types of so-called primary atypical pneumonia; in infectious mononucleosis there is usually a significant rise in the titer of a certain type of heterophile antibody.

The presence of viral antibody can also be demonstrated by the neutralization test: serum inactivation of live virus when mixed with the patient's serum. The neutralization test can be applied to all viral infections for which there is a suitable experimental host, e.g., chick embryo, mouse, tissue culture. Although it has a high degree of accuracy, the neutralization technique, when adequately controlled, is both tedious and expensive; therefore its use is limited to those viral infections which cannot be diagnosed by the complement fixation or hemagglutination inhibition tests.

**Interpretation of Results.** Interpretation of certain bacteriologic data is complicated by the presence of normal flora. Throat cultures constitute a particularly difficult problem because they usually contain many kinds of colonies. Occasionally the pathogen may be selected by means of its colonial and microscopic appearance, but often an identification made on such a basis is misleading. No informed person would conclude that all intestinal gram-negative bacilli are pathogenic simply because that class of bacteria includes some disease-producing types. Similarly, it

(Text continued on page 394.)



Table 62. Selection of Diagnostic Microbiologic Specimens

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Respiratory tract</b>			
Bacterial and fungus			
Streptococcus	Nasopharyngeal swab or throat swab	Place in 0.3 ml. of culture broth <sup>1</sup> . In case of delay, refrigerate until cultured	Culture <sup>2</sup> and antibiotic susceptibility tests Serologic typing of streptococci, pneumococci, <i>H. influenzae</i> and <i>Salmonellae</i> *
Staphylococcus			
Pneumococcus			
Meningococcus			
<i>H. influenzae</i>			
Coliform bacilli			
Proteus species			
<i>Pseudomonas aeruginosa</i>	Sputum	Collect in sterile glass containers. If stored, refrigerate	Same
Salmonella species	Bronchial aspirate*	Same	Same plus acid-fast smear
<i>Candida albicans</i>	Blood, whole, 10 ml.*	Add directly to culture broth at 37° C.	
Diphtheria	Laryngeal, pharyngeal, tonsillar or nasopharyngeal swabs	Smear on glass slides  Place one swab on Loeffler's slant; inoculate another to tellurite agar. Keep at 37° C.	Microscopic examination of special-stained smears  Culture (special method), animal toxigenicity tests and antibiotic susceptibilities
Pertussis and parapertussis	Nasopharyngeal swab	Inoculate directly to special agar plate or Place in 0.3 ml. of culture broth. <sup>1</sup> If stored, refrigerate	Culture on Bordet-Gengou agar containing 0.2 unit of penicillin
Tuberculosis	Sputum, first morning or a 24-hour specimen	Collect in sterile glass container. If stored, refrigerate	Direct smear (special stain) Culture (special method)
	Bronchoscopic aspirate*	Same	Same
	Gastric lavage (50-100 ml. of saline before breakfast)*	Same. If stored, adjust to pH 6.5-7.0 and refrigerate	Same, and inoculate guinea pigs with culture growth
Viral and rickettsial <sup>3</sup>			
Atypical pneumonia	Lung (autopsy)*	Collect in small portions in sterile tubes and freeze in dry ice	Virus or rickettsial isolation <sup>7</sup>
Psittacosis	Sputum, throat washings or throat swab*	Collect in sterile nutrient broth. Freeze in dry ice	Same
Q fever		Collect in sterile tube. Separate serum. Freeze and store for later test	Comparative complement fixation tests using appropriate respiratory viral antigens
Adenovirus	Blood, clotted, 5-10 ml. (acute phase)		
Myxovirus <sup>4</sup>			
CCA <sup>5</sup>			
ECHO			
"Cold viruses" <sup>6</sup>	Blood, clotted, 5-10 ml. in 14-18 days (convalescent)	Collect in sterile tube. Separate serum	Cold agglutinin and Streptococcus MG agglutinin tests with both serums

See page 394 for footnotes.

Table 62. Selection of Diagnostic Microbiologic Specimens (continued)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Gastrointestinal tract</b>			
Bacterial and fungus			
Shigellosis	Rectal swab (repeat if negative)	Culture at once or place in 0.3 ml. of buffer solution. <sup>8</sup> If stored, refrigerate	Culture <sup>2</sup> Sulfonamide and antibiotic susceptibilities Serologic typing of shigellae and enteropathogenic <i>E. coli</i>
With <i>Proteus</i> , <i>Pseudomonas</i> , <i>Aerobacter</i> , <i>Staphylococcus</i> or <i>Streptococcus</i>			
With enteropathogenic <i>E. coli</i>			
Moniliasis			
Salmonellosis	Blood, whole, 10 ml.	Add directly to culture medium. Place at 37° C.	Culture (special methods) and antibiotic susceptibilities
Typhoid fever	Blood, clotted, 5 ml. (repeat in 5-7 days)	Collect in sterile tube. Refrigerate	Agglutinin titer for groups B, C and D (preliminary, followed by repeat test with paired serums) Vi agglutination for typhoid <sup>7</sup> Culture and antibiotic susceptibilities
	Urine; voided if male, catheterized if female*	Collect in sterile tube or flask. If stored, refrigerate	
	Sputum*	Same	Same
	Swab of localized exudate*	Same	Same
<b>Parasitic</b>			
Amebiasis	Fresh stool after purgation and another after a saline enema	Collect in glass or waxed cardboard container. Examine at once. Keep at body temperature	Microscopic examination for trophozoites of <i>E. histolytica</i>
	Sigmoidoscopic aspiration (repeat at 5-7 days if negative)	Collect in test tube and place in glass of warm (37°-40° C.) water	Same
	Stool	Collect in waxed cardboard container	Microscopic examination for <i>E. histolytica</i> cysts
<b>Oxyuriasis</b>			
	N.I.H. cellophane swab (see p. 580) or	Collect by rolling swab over perianal and perineal skin in early morning	Microscopic examination for characteristic ova
	Scotch tape, 2-inch strip on wooden tongue blade	Same	Same
<b>Tapeworms</b>			
Hookworm	Stool	Collect in any suitable container. Examine at once or refrigerate	Examination for worm segments or ova in direct smears and concentration smears
<b>Viral<sup>3</sup></b>			
Enteroviruses	Stool	Collect in suitable container. Freeze in dry ice	Inoculation of suckling mice, tissue culture
Poliomyelitis			
ECHO			
Coxsackie	Blood, clotted, 5-10 ml. (acute phase)	Separate serum, freeze and store for later test	Comparative neutralization tests with both serums in tissue culture or suckling mice
	Same 10-14 days later (convalescent phase)	Separate serum	Comparative complement fixation tests

See page 394 for footnotes.



Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Nervous system</b>			
<b>Bacterial</b>			
<i>H. influenzae</i> Meningococcus Streptococcus Staphylococcus Pneumococcus Coliform bacilli Salmonella species Proteus species <i>Pseudomonas aeruginosa</i>	Nasopharyngeal swab	Place in 0.3 ml. of culture broth. <sup>1</sup> If stored, refrigerate <sup>9</sup>	Culture <sup>2</sup> and antibiotic susceptibilities Serologic typing*
	Cerebrospinal fluid	Sterile test tubes—in different tubes if there is a change in specimen. Examine at once or add 2 drops of 50% citrate if specimen is turbid	Cell count Microscopic examination of gram-stained smear. If clear, centrifuge first Sugar and protein estimation Culture of centrifuged specimen <sup>2</sup> and antibiotic susceptibilities Serologic typing*
	Blood, whole, 10 ml.	Add directly to culture medium. Place at 37° C.	Culture <sup>2</sup> and antibiotic susceptibilities Serologic typing*
Tuberculosis	Cerebrospinal fluid	Collect in sterile tubes—in different tubes if there is a change in specimen. If stored, refrigerate for fibrin web	Cell count Microscopic examination of Ziehl-Neelsen stained smear after centrifugation Sugar and protein estimation Culture (special method) of sediment
	See <i>Respiratory tract</i>		
Leptospirosis	Blood, whole, 2 drops from venipuncture needle	Add directly to 15 ml. of special culture medium. Do not refrigerate	Culture—special method (28°–30° C.)
	Cerebrospinal fluid	Add directly to special culture medium	Culture, as above Cell count Sugar and protein estimation
	Blood, whole, 5 ml.*	Collect in sterile bottle containing glass beads. Shake to defibrinate. Do not refrigerate	Culture as above, plus intraperitoneal injection of young hamsters
	Blood, clotted, 5 ml. (repeat in 4–7 days)	Collect in sterile tube and store in refrigerator	Antibody titer by agglutination-lysis method; <sup>10</sup> (preliminary, followed by repeat test with paired serums)
Fungus Cryptococcosis	Cerebrospinal fluid, tissue or exudate	Collect in sterile tube	Microscopic examination of wet India ink preparation of centrifuged sediment for <i>C. neoformans</i> Culture (special method) Inoculation of white mice

See page 394 for footnotes.

Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
Parasitic Toxoplasmosis	Cerebrospinal fluid	Collect in sterile tubes—different tubes if specimen changes. If stored, refrigerate	Cell count Microscopic examination of giemsa-stained smears of centrifuged material for <i>T. gondii</i> Intraperitoneal and intracerebral injection of mice and guinea pigs
	Blood, whole, 5 ml.	Collect in heparin. Examine at once or store in refrigerator	Intraperitoneal and intracerebral injection of young mice and guinea pigs
	Bone marrow or brain*	Collect in sterile tube. Refrigerate	Microscopic examination of stained smears and sections Animal inoculation
	Blood, clotted, 10 ml. (repeat in 1–2 weeks)	Collect in sterile tube	Complement fixation (paired serums). <sup>10</sup> Neutralization (dye) test <sup>10</sup>
Viral <sup>3</sup> Rabies Poliomyelitis Mumps ARBOR <sup>12</sup> viruses, including Eastern and Western equine, St. Louis, Japanese B, Murray Valley, Venezuela, California and many others Lymphocytic choriomeningitis (LCM) Herpes simplex Herpes zoster Coxsackie ECHO Cytomegalic inclusion disease	Brain or spinal cord	Take aseptically. Make contact smears. <sup>11</sup> Freeze small portions in dry ice	Examine for Negri bodies. <sup>11</sup> Virus isolation in animals or tissue culture
	Cerebrospinal fluid	Examine fresh. Freeze in dry ice	Cell count Sugar and protein estimation Virus isolation*
	Clotted blood, 5–10 ml. (acute phase)	Separate serum. Freeze clot in dry ice. Use some serum at once. Freeze and store remainder for later test	Virus isolation* Complement fixation test for mumps (See <i>Systemic infections</i> )
	Clotted blood, 5–10 ml. (convalescent 14–18 days)	Separate serum. Freeze and store remainder for later test	Comparative complement fixation tests with both serums against various neurotropic virus antigens
	Clotted blood, 5–10 ml. (late phase 6–8 weeks if indicated)	Separate serum	Comparative neutralization tests with all 3 serums in animals (especially for LCM)
Systemic infections Bacterial Typhoid fever Salmonellosis	See <i>Gastrointestinal tract</i>		
	Sputum*	Collect in sterile glass container. If stored, refrigerate	Culture (special methods) and antibiotic susceptibilities
	Swab of localized exudate*	Culture at once or place in 0.3 ml. of culture broth <sup>1</sup> and refrigerate	Same

See page 394 for footnotes.



Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
Brucellosis	Blood, whole, 10 ml.	Add directly to special culture medium. Place at 37° C.	Culture in 10% carbon dioxide Antibiotic susceptibilities Guinea pig inoculation*
	Lymph node biopsy*	Sterile tube. Divide into 2 portions, one for culture, the other for histologic examination. If stored, refrigerate	Same
	Blood, clotted, 5 ml. (repeat in 4-7 days)	Collect in sterile tube. Store in refrigerator	Agglutinin titers (preliminary, followed by repeat tests with paired serums)
Meningococcal, streptococcal, staphylococcal or pneumococcal With coliform bacilli, Proteus or Pseudomonas	See <i>Respiratory tract</i>		
Leptospirosis	See <i>Nervous system</i>		
Fungus Histoplasmosis	Peripheral blood, bone marrow aspiration and lymph node biopsy	Collect in sterile tubes containing heparin	Microscopic examination of thin and thick wright or giemsa-stained smears for intracellular parasites Culture—special method
	Swabs from ulcer, if available	Place in 0.3 ml. of sterile saline solution	Same
	Blood, clotted, 5 ml. (repeat in 1-3 weeks)	Collect in sterile tube	Complement fixation <sup>10</sup> (use paired serums for repeat test)
Parasitic Toxoplasmosis	See <i>Nervous system</i>		
Malaria	Blood, thin smears	Use thoroughly cleansed slides	Microscopic examination of giemsa-stained smears for plasmodia
	Blood, thick smears Sternal or splenic puncture*	Same Smear on clean glass	Same Same
Viral <sup>3</sup> Mumps Poliomyelitis Pleurodynia (Coxsackie B) Dengue Colorado tick fever Measles	Saliva	Freeze in dry ice	Virus isolation in eggs, suckling mice or tissue culture
	Stool		
	Blood, clotted, 5-10 ml. (acute phase)	Separate serum. Use some serum at once. Freeze and store remainder for later test	Complement fixation <sup>7</sup> test with soluble and viral mumps antigens
		Freeze clot in dry ice	Virus isolation in eggs, suckling mice and tissue culture
			Comparative complement fixation or neutralization test with both serums
	Blood, clotted, 5-10 ml. (convalescent 10-14 days)	Separate serum	
	Urine	Keep at 4° C.	Virus isolation in tissue culture
Cytomegalic inclusion disease			

See page 394 for footnotes.

Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Rickettsial</b>			
Typhus fever group	Blood, clotted, 5–10 ml. (acute phase)	Separate serum. Freeze and store for later test. Freeze clot in dry ice	Guinea pig inoculation with clot for rickettsial isolation
Epidemic, murine and scrub typhus			
Rocky Mountain spotted fever			
Rickettsialpox	Blood, clotted, 5–10 ml. (convalescent 14–18 days)	Separate serum	Comparative complement fixation and agglutination tests with specific antigens, and Weil-Felix tests with both serums
Q fever			
Nonspecific reaction to streptococcal infection. Rheumatic fever and acute glomerulonephritis	Blood, clotted, 5 ml. (repeat in 7–10 days)	Collect in sterile tube. If stored, refrigerate	Antistreptolysin titer. Repeat with paired serums  C-reactive protein
<b>Urogenital tract</b>			
<b>Bacterial</b>			
Gonococcal	Cervical, vaginal and/or urethral swabs	Smear one on glass slides  Inoculate second swab directly to culture medium, or place in 0.3 ml. of culture broth <sup>1</sup>	Microscopic examination of gram-stained smear Culture <sup>2</sup>
Enterococcus Coliform bacilli Proteus species <i>Pseudomonas aeruginosa</i> Staphylococcus		Place in 0.3 ml. of culture broth. <sup>1</sup> If stored, refrigerate	Culture Antibiotic susceptibilities
<b>Syphilis</b>	Chancre fluid or scrapings from superficial lesions Blood, clotted, 5 ml. (repeat for confirmation)	Place in a few drops of saline. Examine at once Collect in sterile tube. Store in refrigerator	Darkfield examination  Microflocculation and complement fixation tests with cardiolipin antigen Treponemal tests for confirmation
	Cerebrospinal fluid*	Collect in sterile tubes— different tubes if specimen changes	Treponemal tests for confirmation Cell count Flocculation and cardiolipin complement fixation tests Colloidal gold
<b>Viral<sup>3</sup></b>			
Lymphogranuloma venereum	Scraping of lesion	Smear on glass slide	Microscopic examination of giemsa-stained smear for giant cells or elementary bodies
Herpes simplex	Pus from lesion or contents of vesicle	Place in sterile tube	
	Blood, clotted, 5–10 ml. (acute phase)	Separate serum, freeze and refrigerate for later test	Inoculation into animals, eggs or tissue culture
	Blood, clotted, 5–10 ml. (convalescent 14–18 days)	Separate serum	Comparative complement fixation tests with antigens of psittacosis—LGV group, with herpes simplex virus and neutralization tests with both serums
Cytomegalic inclusion disease	Urine	Keep at 4° C.	Isolation in tissue culture

See page 394 for footnotes.



Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Skin and mucous membranes</b>			
<b>Bacterial</b>			
Streptococcal and staphylococcal	Swabs from lesions.	Smear one on glass slide	Microscopic examination of gram-stained smear
With coliform bacilli, enterococci, <i>Proteus</i> and <i>Pseudomonas</i>	Cleanse skin with alcohol first	Place other in 0.3 ml. of culture broth. <sup>1</sup> If stored, refrigerate	Culture and antibiotic susceptibilities
<i>Fusospirochetal</i>	Swabs from lesions	Smear on glass slides	Microscopic examination of dilute carbolfuchsin-stained smears for <i>many</i> fusiform bacilli and spirochetes
<b>Fungus</b>			
Moniliasis	Swabs from surface of infected area	Use one swab to make smears on glass slide	Microscopic examination of gentian violet-stained smear for yeast cells
		Place other in sterile tube. If stored, refrigerate	Culture <sup>2</sup>
Blastomycosis Sporotrichosis	Swabs or scrapings from cleansed lesions	Place in sterile tube. Keep moist	Microscopic examination of wet lactophenol cotton blue mounts Culture (special methods)
Ringworm	Hairs or skin scrapings	Place in dry container	Microscopic examination of unstained preparation after clearing with 10% potassium hydroxide Culture (special methods)*
<b>Viral</b>			
Herpes simplex Herpangina (Coxsackie A) Variola Vaccinia Varicella Herpes zoster Molluscum contagiosum <sup>13</sup>	Vesicle fluid or swab	Place in nutrient broth and freeze in dry ice	Virus isolation in eggs, tissue culture or suckling mice
	Blood, clotted, 5-10 ml. (acute phase)	Separate serum. Freeze and store for later test	Comparative neutralization and/or complement fixation tests with appropriate antigens with both serums Histologic examination for inclusion bodies Microscopic examination of giemsa-stained smear for elementary bodies or giant cells
	Blood, clotted, 5-10 ml. (convalescent 10-14 days)	Separate serum	
	Biopsy	Fix in Zenker's acetic solution	
	Scraping of lesion	Smear on clean slide	
<b>Eye</b>			
<b>Bacterial</b>			
Streptococcal, staphylococcal, pneumococcal or gonococcal	Swabs of exudate from site of infection	Smear one on glass slide	Microscopic examination of gram-stained smear
		Place other in 0.3 ml. of culture broth. <sup>1</sup> If stored, refrigerate	Aerobic and anaerobic cultures on blood agar. Antibiotic susceptibilities

See page 394 for footnotes.

Table 62. Selection of Diagnostic Microbiologic Specimens (*continued*)

<i>Suspected Infection</i>	<i>Specimen</i>	<i>Handling of Specimen</i>	<i>Laboratory Tests</i>
<b>Viral<sup>3</sup></b>			
Trachoma <sup>13</sup>	Conjunctival scrapings	Smear on clean slide	Microscopic examination of giemsa-stained smear for inclusion bodies
Inclusion blennorrhea <sup>13</sup>			
Herpes simplex			
Epidemic keratoconjunctivitis (adenovirus type 8)	Swab	Place in nutrient broth and freeze in dry ice	Virus isolation in eggs, tissue culture or suckling mice
Variola			
Molluscum contagiosum <sup>13</sup>			
Varicella			
Herpes zoster	Blood, clotted, 5-10 ml.	Separate serum. Freeze and store for later test	Comparative complement fixation tests with various antigens and both serums
Newcastle disease	(acute phase)		
Pharyngoconjunctival fever (adenoviruses types 3, 7, 1)			
	Same after 10-14 days (convalescent phase)	Separate serum	Comparative neutralization tests with both serums*
<b>Wounds</b>			
<b>With</b>			
Pyogenic cocci	Swabs from infected	Smear one swab on glass slide	Microscopic examination of gram-stained smear
Anaerobic streptococci	wound		
Coliform bacilli		Place second swab in 0.3 ml. of culture broth. <sup>1</sup>	Culture <sup>2</sup> and antibiotic susceptibilities
Proteus species		If stored, refrigerate	
<i>Pseudomonas aeruginosa</i>			
Gas gangrene	Swabs from infected wound	Smear one swab on glass slide	Microscopic examination of gram-stained smear
		Place second swab in a tube of milk or thioglycolate medium and seal	Culture anaerobically
			Do toxigenicity tests in laboratory animals
	Pieces of débrided tissue	Place in sterile tube and refrigerate in case of delay	Examine ground-up tissue by stain and culture

\* Optional or not routinely indicated.

1. See Figure 104 (N-P culture outfit).
2. Aerobic and anaerobic blood agar plates are routine. Special culture media for coliforms, Salmonella and *Candida albicans*. Chocolate agar is the preferred medium for gonococci and meningococci; the cultures are incubated in 10 per cent carbon dioxide.
3. Incomplete list—includes viruses most likely to be encountered.
4. Myxoviruses include influenza A, B, C, D; mumps; Newcastle disease; hemabsorption viruses; and croup-associated virus (C.A.).
5. Respiratory syncytial virus or agent (chimpanzee-coryza agent—C.C.A.).
6. Include J.H. and 2060 viruses.
7. Valuable in an epidemic.
8. Sodium chloride, 0.45 gm.; K<sub>2</sub>HPO<sub>4</sub>, anhydrous, 0.3 gm.; potassium dihydrogen phosphate, anhydrous, 0.1 gm.; para-aminobenzoic acid, 5 mg.; glycerol, U.S.P., 30 cc.; distilled water, 70 cc.
9. Meningococcal and gonococcal specimens should be examined at once.
10. Tests carried out in specialized laboratories only.
11. For diagnosis of rabies.
12. Arthropod-borne virus.
13. Antigens not available.

should not be assumed that all hemolytic streptococci and staphylococci in a throat culture are pathogenic. Thus it is the responsibility of the laboratory to indicate, if possible, whether a potentially significant organism in some large heterogeneous category is likely to be pathogenic.

Under most circumstances isolation of a virulent bacterium or a virus from the patient provides highly suggestive evidence of an etiologic relationship and is usually accepted as sufficient for diagnostic purposes. Such a finding does not in itself, however, actually establish the organism as the cause of the



infection, and when there may be some doubt, further proof should be sought by serologic methods.

The demonstration of specific antibodies against the recovered agent in a single sample of convalescent serum, however, is not diagnostic. Unless it can be established that a rise in antibody titer occurred during the illness, the possibility must be considered that the patient is only an immune carrier who is suffering from an infection by a different pathogen. An antibody titer in convalescent serum (taken as a rule fourteen days or later after the onset of illness) which is at least fourfold greater than that found in the serum taken at the beginning of the illness is usually considered to be diagnostic.

Certain limitations of serologic methods should be mentioned. With most infections antibody is not detectable by ordinary methods during the first few days. When it does appear in blood, it may be directed toward a group or common antigen shared by many related microorganisms. This is the case with the psittacosis-lymphogranuloma group of viruses, the salmonellae, the rickettsiae of Rocky Mountain spotted fever and rickettsialpox, *Treponema pallidum* and *Histoplasma capsulatum*. Even a fourfold rise in titer in successive specimens may in reality be a booster or anamnestic response to an antigenically related but biologically unrelated organism.

Nevertheless serologic tests still provide val-

uable aid in establishing the etiology of infections. For example, a tentative diagnosis may be made on a *single* serum specimen under the following circumstances: (1) a high antibody level as compared with that of the population in general; (2) the presence of antibodies in the serum of a young infant which are not present in the mother's blood; (3) in mumps, antibodies to the soluble ("S") fraction of the virus, which often can be demonstrated as early as the second or third day of the disease, and before those to the viral ("V") antigen; (4) in typhoid fever the presence of Vi antibody.

T. F. McNAIR SCOTT  
EARLE H. SPAULDING

#### REFERENCES

- Conant, N. F., and others: Manual of Clinical Mycology. 2nd ed. Philadelphia, W. B. Saunders Company, 1954.
- Diagnostic Procedures for Virus and Rickettsial Diseases. 2nd ed. New York, American Public Health Association, 1790 Broadway, 1956.
- Kolmer, J. A., Spaulding, E. H., and Robinson, H. W.: Approved Laboratory Technic. 5th ed. New York, Appleton-Century-Crofts, Inc., 1951.
- Maxted, W. R.: The Use of Bacitracin for Identifying Group A Haemolytic Streptococci. J. Clin. Path., 6:224, 1953.
- Rivers, T. M., and Horsfall, F. L., Ed.: Viral and Rickettsial Infections of Man. 3rd ed. Philadelphia, J. B. Lippincott Company, 1958.
- Smith, D. T., and Conant, N. F.: Zinsser's Textbook of Bacteriology. 11th ed. New York, Appleton-Century-Crofts, Inc., 1957.

## SELECTION OF ANTIMICROBIAL AGENTS BY LABORATORY MEANS

**General Considerations.** The great majority of bacterial infections can be cured without the use of the laboratory. For the remainder an effective therapeutic program requires the assistance of microbiologic procedures consisting of culture, identification of potential pathogens and determination of their susceptibility to chemotherapeutic agents.

Infections that need laboratory aid fall into three categories: (1) fulminating infections requiring hospitalization; (2) those which fail to respond to initial therapy; (3) those which relapse. For patients who are hospitalized for infections, bacteriologic specimens should be collected upon admission so

that, if clinical response to initially prescribed therapy is not satisfactory twenty-four hours later, the results of culture and susceptibility tests are available.

During recent years there has been a steady increase in the incidence of infections due to such bacteria as staphylococci, *Proteus*, *Pseudomonas* and enterococci which are often comparatively resistant, and sometimes completely so, to the commonly used chemotherapeutic agents. Whenever infections fail to respond to prescribed antimicrobial therapy, it is likely that the causative organism is resistant to the drug being used.

Relapses despite sustained medication result from the emergence of highly resistant

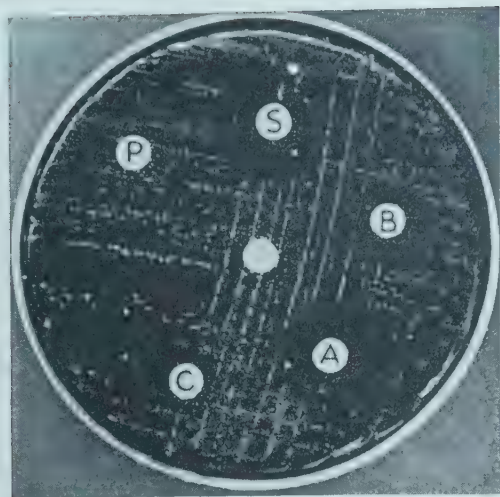


FIG. 105. Antibiotic susceptibility disk test on a nasopharyngeal culture containing a coagulase-positive *Staphylococcus* (large colonies) and a group A *Streptococcus* (small colonies). P, Indicates penicillin; S, dihydrostreptomycin; B, bacitracin; A, Aureomycin; C, Chloromycetin. Saline control disk is in the center. The *Staphylococcus* is resistant to penicillin and Chloromycetin, slightly susceptible to bacitracin, very susceptible to Aureomycin. Note streptomycin zone containing resistant colonies, indicating that this drug would probably be ineffective. The *Streptococcus* is very susceptible to Aureomycin, moderately so to penicillin and dihydrostreptomycin, and slightly so to bacitracin and Chloromycetin.

mutants or represent superinfections by secondary invaders, the most common of which are the four kinds of bacteria just mentioned. Relapses, whether due to resistant mutants or secondary invaders, constitute new infections which require further laboratory guidance.

Individual strains within the same species may vary greatly in susceptibility to a chemotherapeutic drug. This is true especially of strains of *Staphylococcus aureus* and members of the *Proteus* and *Pseudomonas* groups, so that susceptibility tests offer the only reliable basis for selecting the proper medication.

**Susceptibility Tests in Vitro.** These tests may be carried out in several ways, but the most useful methods are the disk-agar diffusion and the test tube-broth dilution tests. The latter is more accurate and can be applied to the evaluation of antibiotic combinations for synergism, but the test organism must first be isolated in pure culture, so that there is a delay of two or three days. Therefore its usefulness is mainly limited to subacute and chronic infections.

The disk test, on the other hand, can be carried out at the time of the primary culture; thus the results are available as soon as the

culture grows out. Disks may consist of compressed commercially prepared tablets, or pieces of impregnated paper (Fig. 105). Wet disks, soaked in a standard solution at the time of use, should be used only by laboratories qualified to establish adequate controls; on the other hand, commercial dry disks are satisfactory for use in any laboratory capable of culturing clinical material. Although the disk procedure is qualitative rather than quantitative, it selects the antimicrobial agents most likely to be effective. Disks carrying penicillin, streptomycin and a tetracycline should be used regularly. If further tests are indicated, pure cultures of the important isolated bacteria are used as inocula.

Commercial disks are available not only for antibiotics, but also for sulfonamides, isonicotinic acid hydrazide, p-aminosalicylic acid, Furadantin, Mandelamine and many other antimicrobial chemicals. The antimicrobial properties of the important chemotherapeutic agents appear in Table 63. Summarizations such as these, however, tend to be misleading because they imply that all members of a morphologic tinctorial category behave in the same way. One should keep in mind that important exceptions do occur. For example, the *Salmonella*, *Proteus* and *Pseudomonas* groups are generally resistant to the tetracyclines, although they are all gram-negative bacilli; and *Staphylococcus aureus* constitutes a group of gram-positive cocci for which susceptibility patterns vary in response to past exposure to antibiotics. *The need for susceptibility testing grows in proportion to the number of antibiotics being used.*

**Validity of susceptibility results in vitro.** Although the results as a whole correlate well with clinical experience, discrepancies occur. Many factors in the host, such as absorption, diffusion and excretion rate, may operate to diminish or increase effectiveness in vivo. The following factors may be responsible for clinical failure in a situation when "susceptible bacteria" had been reported by the laboratory: (1) absence of the causative organism among those isolated; (2) inadequate dose of the drug; (3) presence of resistant bacterial mutants; (4) replacement of the original susceptible flora by a more resistant one; (5) mechanical or anatomic barriers limiting access of the drug to the site of infection, such as a walled-off abscess or the valvular vegetations of subacute bacterial endocarditis.

Conversely, bacteria which appear to be resistant to a drug by the disk method, especially penicillin, may be rapidly destroyed



Table 63. Antimicrobial Properties of the Important Therapeutic Agents

	<i>Gram-Pos. Organisms and Gram-Neg. Cocci</i>	<i>Gram-Neg. Bacilli</i>	<i>Spirochetes</i>	<i>Tubercle Bacillus</i>	<i>Rickettsiae and Large Viruses</i>	<i>Fungi</i>	<i>Protozoa</i>	<i>Bactericidal Activity</i>	<i>Development of Resistance</i>
Sulfonamides	B	B							Fairly rapid
Penicillin	A		A					+	Slow
Erythromycin	A				B				Fairly rapid
Novobiocin	A								Fairly rapid
Streptomycin		B		A (PAS, INH)				±	Rapid
Neomycin*	B	A					B	+	Slow
Chloramphenicol	A	A	B		A				Slow
Tetracycline	A	A	B		A		B		Slow
Nystatin						A (Candida)			Very slow
Bacitracin*	A						B		Slow
Polymyxin B*		A						+	Very slow

\* Usually limited to oral or local application.

A = Drug of choice.

B = Usually effective.

in the patient's tissues. Clinical cures under such circumstances have become more frequent with the prescription of large doses of penicillin. The disk method measures only the bacteriostatic and not the bactericidal concentration, so that the effectiveness of penicillin, which, unlike other antibiotics, is rapidly bactericidal for many bacteria, is not completely reflected. The test tube-broth dilution test can be adapted to measure the bactericidal capacity of an organism, but the technique is not suitable for routine application.

Finally, microorganisms are not ordinarily destroyed in vivo by bacteriostatic drugs, whose role in clinical cure is to inhibit growth and thus increase the effectiveness of phagocytosis and other immune mechanisms; tests

in vitro do not measure the immunologic factor which operates in favor of the host.

EARLE H. SPAULDING

## REFERENCES

- Dowling, H. F., Lepper, M. H., and Jackson, G. C.: Clinical Significance of Antibiotic Resistant Bacteria. *J.A.M.A.*, 157:327, 1955.
- Kempe, C. H.: The Use of Antibacterial Agents: Summary of Round Table Discussion. *Pediatrics*, 15: 221, 1955.
- Power, E. E.: The Use and Abuse of Antibiotic Sensitivity Tests. *Canad. J. Med. Tech.*, 17:2, 1955.
- Spaulding, E. H., and Anderson, T. G.: Selection of Antimicrobial Agents by Laboratory Means. *J.A.M.A.*, 147:133, 1951.
- Welch, H.: Principles and Practice of Antibiotic Therapy. New York, Medical Encyclopedia, Inc., 1954.

## ISOLATION MEASURES FOR INFECTIOUS DISEASES

The care of a patient with a communicable disease involves measures to prevent others from contracting it, as well as treatment of the acute condition. Certain legal quarantine requirements, which vary somewhat in different localities, have been set up for the protection of the community (Table 64). Quarantine regulations have at best a limited value in control of the spread of contagious diseases. In many places "placarding" is no longer practiced for the so-called minor con-

tagious diseases, being used only for diphtheria, scarlet fever, smallpox, poliomyelitis and meningococcal meningitis. There are substantial arguments in favor of permitting children to contract such diseases as measles, German measles, chickenpox and mumps during the preadolescent years, provided they are in a state of good health at the time. For the control of diphtheria, smallpox and pertussis, artificially induced immunity is of greatest importance. However, a patient with

Table 64. Suggestions for Quarantine Regulations\*

<i>Disease</i>	<i>Patient Is Released from Isolation and May Return to School</i>	<i>Susceptible Contacts May Re-enter School</i>	<i>Immune Contacts May Re-enter School</i>
Diphtheria.....	On recovery, and after 3 successive negative cultures; or if avirulent. Not less than 16 days after onset if unable to obtain culture	When cultures of nose and throat are negative, but not for at least 7 days after last exposure	If bacteriologically negative
Scarlet fever.....	Upon recovery and cessation of purulent discharges; but not until at least 7 days from onset	Not less than 7 days after last exposure	If there is not continued exposure
Measles.....	On recovery; 9 days minimum (5 days after appearance of rash)	Exclusion from school of no practical value; when practised, at least 14 days must elapse after last exposure	No restriction
German measles..	Quarantine is usually not imposed. Period of infectivity estimated from 3 to 5 days after onset of catarrhal symptoms	Exclusion from school of no practical value; when practised, at least 21 days must elapse after last exposure	No restriction
Smallpox.....	On recovery and disappearance of scabs and crusts; usually 3 to 6 weeks	18 days after successful vaccination	If there is not continued exposure and if successfully vaccinated within 5 years. The person should be vaccinated whenever exposure occurs even if there has been a previous successful "take"
Chickenpox.....	On recovery and when crusts have formed; at least 7 days after onset	Exclusion from school of no practical value; when practised, at least 21 days must elapse after exposure	No restriction
Pertussis.....	Not before 3 weeks after onset of typical paroxysms	14 days after exposure	No restriction
Poliomyelitis.....	One week after onset of symptoms or after defervescence, whichever is longer	2 weeks	2 weeks
Mumps.....	When swelling has disappeared	Usually no exclusion. Regular, daily inspection advised	No restriction

\* Adapted from several sources, principally from The Control of Communicable Diseases, The American Public Health Association, New York, 1945, and Report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases, American Academy of Pediatrics, 1952.

a contagious disease should be isolated, not only to limit distribution of the disease, but also to protect him from secondary infection.

Isolation technique necessitates cooperation of physician, nurse and family, and, in hospitals, of all personnel, including orderlies and maids, who come in contact with the patient or his environment. An error in technique by any one of these persons may defeat the efforts of all the others.

The patient is regarded as a contaminated unit, and the area in which he is—whether a room in home or hospital, a cubicle or space in a ward—as a contaminated unit area. The space between beds in an open ward should be at least 6 feet. Anything which comes in contact with the unit area must be consid-

ered contaminated. Isolation precautions for persons entering and leaving the unit area are based on "hand and gown technique"; all physicians and nurses should be familiar with an approved method. When the child is to be cared for by a nonprofessional attendant at home, as, for example, the mother, adequate instruction should be given by the physician.

Infectious agents may also be transferred to another person by air conduction. The control of air-borne infection has received considerable attention, but is still not adequately solved for practical application. Oiling of floors and of bed blankets would appear to be as useful a method as any; air sterilization with ultraviolet irradiation or an aerosol has a limited effectiveness in reducing the



spread of infection in institutions. Antibiotic treatment of bacterial infections is the most effective means for limiting their spread.

The unit area must be properly equipped to care for the patient, and nothing should be taken into it that is not necessary or cannot later be destroyed or sterilized in some manner. The trays and dishes—or the bottles for infants—should be sterilized after each use by boiling or autoclaving.

A bedpan should be provided for each patient, or bedpans should be sterilized. In the home a special bathroom reserved for the isolated area is a great convenience.

Bed linen and clothing, including diapers, should be sterilized in an autoclave; in the home they should be boiled before being sent to the laundry.

Secretions from the eyes, nose, mouth and throat should be received on soft paper squares or small pieces of cloth which are placed in a paper bag and later burned.

All attendants should be in good health and free of infection of the respiratory tract.

The patient should be discharged from the unit area only after thorough bathing with soap and warm water, including a shampoo.

He should not, of course, return to the contaminated area.

Other materials, as well as the floor and furniture of the room, should be thoroughly washed with soap and water, and the room aired for at least twenty-four hours before again being occupied.

Material in the unit area which cannot be burned is cleansed as follows: all clothing and linen, as already described; mattresses and pillows are aired for six to eight hours, preferably on two successive days; all glass, rubber, chinaware, enamelware and any instruments which permit it are boiled for five to ten minutes, or autoclaved, or put into 2 per cent cresol solution or 1:5000 Zephiran for eighteen hours.

When a patient is to be taken to an operating room or x-ray room, or is transferred to another unit area, the accompanying attendant must wear a clean gown, and the patient should wear a mask and must be wrapped in a clean sheet. Equipment in the operating or x-ray room which has been contaminated should be cleaned in the manner described for the unit area.

WALDO E. NELSON

Table 65. Résumé of the Common Contagious Diseases Having an Exanthem or Enanthem

	Diphtheria	Scarlet Fever	Measles	German Measles	Smallpox	Chickenpox
Etiology	<i>Corynebacterium diphtheriae</i>	Hemolytic Streptococcus (Group A; some symptoms perhaps allergic)	Virus	Virus	Virus	Virus
Transmission	Usually direct contact; by carriers	Usually direct contact; occasionally indirect or by contaminated milk, etc.	Usually direct contact	Direct contact	Direct or indirect contact; probably air-borne	Direct or indirect contact; probably air-borne
Incubation	2-5 days	2-7 days	10-14 days	14-21 days	8-16 days	14-21 days
Mouth and throat	Pseudomembrane spreads beyond tonsillar area and is difficult to remove	Punctate scarlet enanthem; tonsillar exudate; strawberry tongue early; raspberry tongue later	Koplik's spots	Macular eruption on soft palate (Forchheimer's spots)	Lesions on mucous membranes	Vesicular enanthem
Eruption	None	Bright red, punctate; face little involved; first on neck and chest, then spreads downward; later (after a week), desquamation, especially of hands and feet	Reddish maculopapules, centrally grouped, appear first on face; later (after a week), branny desquamation	Pale rose macules, variable in size, discrete; first on face, spreads rapidly (24 hours) over body. At times scarlatiniform rash	Macules, then papules, then vesiculation of papules, then (by sixth day) pustules. Attacks first face and wrists, then hands and arms, then trunk and legs (chiefly on exposed parts of body)	Macules, papules, then vesicles, then some become pustules; lesions superficial, and found simultaneously in all stages of development. Attacks first face and back, then spreads rapidly downward (chiefly on covered parts of body)
Important constitutional symptoms	Fever often not high; marked prostration	At onset: sore throat, fever, nausea or vomiting and headache	Photophobia; catarrhal symptoms. Fever may subside about third day of invasion, then recur within 24 hours when the rash appears	Mild catarrhal symptoms; slight fever; may be none	At onset: vomiting, headache, high fever. Improvement at onset of rash; fever again in pustular stage	Fever; usually slight general reaction
Blood	Polymorphonuclear leukocytosis usually not very marked	Leukocytosis even if not marked, always a polymorphonuclear increase	Absence of leukocytosis; neutropenia common	Absence of leukocytosis	May be leukopenia in prodromal stage; later leukocytosis, often with mononuclear increase	Slight leukocytosis
Important complications	Bronchopneumonia; cardiac failure; postdiphtheric paralysis	Otitis; adenitis; arthritis; nephritis; enditis	Bronchopneumonia; otitis media; sinusitis; laryngitis; encephalomyelitis	Occasionally bronchopneumonia; encephalomyelitis	Laryngitis, bronchopneumonia; gangrene; encephalomyelitis	Pustular skin lesions; encephalomyelitis
Diagnosis: Technical aids	By culture from membrane	Culture; Schultz-Charlton test				
Other features	May be nasal or laryngeal involvement, etc.	"Surgeal" scarlet fever	Risk to fetus in first trimester	May be modified by previous vaccination		



# BACTERIAL INFECTIONS

## STREPTOCOCCAL INFECTIONS

### GENERAL CONSIDERATIONS

Most human and animal streptococcal infections are caused by beta-hemolytic streptococci, which produce a brilliant, complete hemolysis of blood. The viridans and non-hemolytic streptococci are of relatively low virulence and most often exist in the throat or feces, unassociated with disease. When they produce infection, it is usually subacute or chronic.

The beta-hemolytic streptococci are divided into groups, designated A through N, and these groups have distinct host associations. Group A streptococci are most commonly associated with infections in man, group B with cattle, and group C with cattle, horses, guinea pigs and other animals. Groups C, D and G are occasionally and groups B and F rarely pathogenic for man. Table 66 shows these and other host relationships.

**Cellular Antigens of Group A Streptococci.** The various groups of beta-hemolytic streptococci are differentiated in the laboratory by means of a precipitin test involving the C-substances, which are complex polysaccharides immunologically distinct in each group. The group A streptococcal cells contain protein antigens designated by the letters M, T, P and R. Of these, the M-substance is most important, since it determines the type-specificity of group A strains.

More than forty streptococcal types have been described. The streptococci that cause acute infections of the throat and elsewhere, including the infections associated with scarlet fever and those preceding rheumatic fever, may belong to any of the types. Rammelkamp and his associates have presented evidence that certain strains of streptococci, particularly type 12, produce infections complicated by acute glomerulonephritis more frequently than do strains of other types.

The M-substance appears to be related to the virulence of the organism; the antibodies it evokes are responsible for type-specific immunity. The T-substance is a type antigen of secondary importance, since it is not involved in virulence or protection. The P-antigens are nonspecific, being present in many gram-positive organisms. Little is known of the significance of the R-antigen, which is present in only a few streptococcal strains.

**Extracellular Antigens of Group A Streptococci.** The *erythrogenic toxin*, produced by about 90 per cent of group A streptococci, is responsible for the rash and possibly for other toxic manifestations of scarlet fever. Only strains producing erythrogenic toxin are capable of causing scarlet fever. Streptolysins O and S are the two hemolytic toxins of group A streptococci. They are distinct chemical entities with distinct toxic properties. Most strains of group A streptococcus produce both

Table 66. Serologic Groups of Hemolytic Streptococci\*

Animal Source	Chief Pathogenic Group	Occasionally Pathogenic Group	Groups Apparently Nonpathogenic
Man.....	A	B, C, D, F, G, H	K, L
Cattle.....	B, C	A, G	D, E, H, L, N
Horse.....	C		
Monkey.....		A, G	C
Dog.....	G, L, M		
Chicken	C	A?	G
Swine		E, L	
Goat			
Sheep			
Ferret		A, B	
Rabbit			
Guinea pig	C, M	A, B, C	
Mouse			
Fox.....			

\* From R. C. Lancefield, Harvey Lecture, 1940-41.

lysins, but occasional strains fail to produce one or the other. Streptolysin O causes myocardial damage in experimental animals and also has an injurious effect on leukocytes. Streptokinase (fibrinolysin) activates a proteolytic enzyme, plasminogen, normally present in blood, which causes dissolution of fibrin clots. It is not pharmacologically toxic, but may play a part in the spread of streptococci through tissues by activating the destruction of fibrin barriers. The *proteinase* of Elliott is an enzyme produced by certain strains of group A streptococci which digests many proteins, including the type-specific M protein in culture. Streptococcal *hyaluronidase* attacks the hyaluronic acid of the capsule of group A streptococci as well as the same polysaccharide found in such tissues and fluids as Wharton's jelly, joint fluid and connective tissue; other streptococcal enzymes include *desoxyribonuclease* and *diphosphopyridinenucleotidase*, the latter possibly being responsible for the leukotoxic action of certain streptococci.

**Antibodies to Streptococcal Antigens.** In natural and experimental infections, antibodies directed toward the various intracellular and extracellular antigenic constituents of streptococci appear in the blood. Of the cellular antigens of the group A *Streptococcus*, those provoked by the M-antigen are the most important. They are type-specific and constitute a main factor in immunity to reinfection of the human host. Infection with a particular type of *Streptococcus* is believed to produce type-specific immunity which lasts for many years. Antibodies for the M-antigen in serum cannot be measured by the precipitin reaction, but indirect evidence of their presence is provided by a phagocytic test. Anti-M bodies appear in the human host as early as three weeks after the onset of natural infections and persist as long as three years. Watson showed that after infection with a particular type of group A *Streptococcus*, a monkey was immune to reinoculation with the same type for at least a year, but could readily be infected with strains belonging to other types.

Antibodies for the T-, P- and R-substances are not practicably measurable in human serums after infection.

Antibodies for the erythrogenic toxin are responsible for lasting immunity to the rash of scarlet fever. Their presence in the human host is measured by the Dick test. Antibodies for streptolysin O, antistreptokinase and hyaluronidase have been widely used, because they indicate a previous streptococcal infection, even though the infecting organisms may

have disappeared from the host. Antibodies to these three substances usually reach higher levels in the blood of rheumatic fever patients than in the blood of patients having uncomplicated streptococcal disease, and their presence is one of the strongest pieces of evidence supporting the streptococcal etiology of rheumatic fever.

**Drug Susceptibility and Resistance.** With the exception of group D organisms, most beta-hemolytic streptococci are susceptible to low concentrations of the sulfonamides, penicillin, tetracycline, chloramphenicol and erythromycin. Penicillin is at present the drug of choice for streptococcal infections. Some strains of group D streptococci are sensitive to streptomycin.

The acquisition of resistance to these drugs has been a problem only with the sulfonamides, and such evidence is largely limited to experience in military camps during World War II. Sulfonamide-resistant strains are rare in the general population. Recently tetracycline-resistant group A strains have been encountered.

**Epidemiology.** Climate influences the prevalence of streptococcal disease, the colder climates generally showing a higher incidence; in any climate streptococcal infections are most common in the winter and in spring. Strains isolated during epidemics almost always belong to group A, contain large amounts of M-substance and are mucoid and encapsulated. However, many strains with these same characteristics show little tendency to spread at epidemic rates. It is impossible to distinguish epidemic from nonepidemic strains with certainty by laboratory tests.

In some instances the mode of dissemination of the infecting organism influences an epidemic. The chief natural reservoir of group A streptococci is the human upper respiratory tract, and spread from infected persons or carriers to susceptible persons is largely by direct contact or through air. It is likely that spread in the course of relatively intimate human contact, by either direct mechanical transfer or the transmission of large infected droplets, is more dangerous than spread over longer distances by small infected particles. Streptococci in dust are incapable of inducing infections in human volunteers.

Epidemics resulting from milk-borne spread of cocci were once common, but have not been encountered recently in this country. This may largely be attributed to widespread pasteurization of milk. Only rarely do epidemics result from direct contamination of



raw milk by a dairyman or food handler, because milk contains a substance, lactenin, which prevents the growth of group A streptococci. Streptococci grow well in reconstituted, dried or canned milk and in milk sterilized by heat, since the lactenin is thus destroyed; epidemics have occurred after direct contamination of such milk. Thus, since the presence of only group A organisms is of significance in milk, the importance of serologic grouping of streptococci from a suspect milk supply during an epidemic of streptococcal disease is obvious.

The composition of the community affects the course of epidemics. In a large urban area where the number of susceptible persons may be relatively small and widely scattered and intimate human contacts are limited, the increase in number of cases may be slow and irregular and may continue at a fluctuating low epidemic level for a long time until immunity becomes general or until seasonal influences interrupt the course of the epidemic. In a closed or semiclosed community, such as a boarding school or an orphanage, where contacts are close, the attack rate rises rapidly to a peak and tends to terminate rapidly.

In military training centers a different epidemic situation may exist. Here the transfer of infection is facilitated by close contact and by the introduction of new susceptibles at frequent intervals. After the initial rise the attack rate continues to be irregularly high instead of falling off.

An important and familiar type of epidemic is that which occurs in hospitals (nosocomial infections). They may be epidemic, but more often are sporadic. Premature infants and other malnourished, debilitated, eczematous, syphilitic or mentally defective infants who remain in the hospital for prolonged periods are most prone to acquire nosocomial infections. The sources of infection are hospital personnel, visitors and fellow patients.

Another hazardous situation exists in the waiting rooms of busy physicians, although the period of exposure is relatively brief.

#### CONTROL MEASURES

Measures for the control of streptococcal infections are (1) attempts to prevent exposure of susceptibles, (2) avoidance of environmental conditions which favor epidemic spread of infection, (3) attempts to render the host insusceptible to the organism.

To prevent exposure of susceptibles it is customary to isolate known infected persons.

Isolation and quarantine procedures are inadequate because many infections are transferred by mild or undiagnosed cases and by carriers, whom it is not feasible to isolate. The arbitrary periods of isolation of seven to twenty-one days for patients with scarlet fever have no sound basis. The segregation of patients with scarlet fever in so-called group isolation is to be decried, since patients infected with one serologic type can acquire infection of a different type from a neighboring patient.

Because patients may carry streptococci for months and sometimes for more than a year, it is not practical to isolate all convalescent patients carrying streptococci until negative cultures are consistently obtained. Only patients carrying group A streptococci are potentially dangerous, but some carriers of group A organisms are more efficient disseminators of infection than others. Patients with large numbers of streptococci in their anterior nares are especially dangerous. In such cases it might be advisable to try to eradicate the carrier state with massive doses of penicillin.

To minimize the occurrence of cross infections in hospitals, McKhann makes the following recommendations: Infants and other particularly susceptible patients should be hospitalized only when absolutely necessary, and the stay should be as short as possible. Infected patients should be isolated from non-infected ones and from one another. Open cubicles with walls not reaching to the ceiling are less satisfactory for this purpose than cubicles with walls extending to the ceiling; these in turn are less effective than separate rooms with individual outside ventilation. Visiting should be restricted to the immediate family. "Hand and gown" technique and the use of deflecting or filtering masks help to reduce spread from one patient to another and from attending personnel to the patient; but no matter how diligently they are used, they are inadequate to prevent all cross infection.

The pasteurization of milk, the proper preparation and handling of food and the elimination of infected persons and carriers from the kitchen are measures used to prevent food-borne streptococcal infections.

Vaccines for immunization against streptococcal infections have not been successful; this fact is not surprising, since immunity to streptococci is largely type-specific. Because of the large number of serologic types, active immunization could be profitably used only in epidemics in which the infecting strains would be typed early and immunity to these

particular types conferred. Immunization with the Dick toxin has been used under special circumstances—for instance, among student nurses. It prevents only the rash of scarlet fever and not the acquisition of streptococcal infection. As a general procedure it is not recommended.

*Chemoprophylaxis* with a sulfonamide or penicillin has been used for the prevention of streptococcal infection in individuals and for the interruption of streptococcal epidemics in groups. Its use in the individual patient has been studied most extensively in children who have had an attack of rheumatic fever and for whom streptococcal infections constitute a serious hazard (see p. 910 for details).

Because of the hazard of subacute bacterial endocarditis developing when teeth are extracted or tonsils removed, penicillin should be given to patients with rheumatic heart disease before and after such operations.

ARMINE T. WILSON

#### REFERENCES

- Lancefield, R. C.: Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci. *The Harvey Lectures*, 36:251, 1940–41.  
 McCarty, M., ed.: *Streptococcal Infections*. New York, Columbia University Press, 1954.  
 Swift, H. F.: The Streptococci, in Dubos, R. J., ed.: *Bacterial and Mycotic Infections of Man*. 2d ed. Philadelphia, J. B. Lippincott Company, 1952, pp. 265–323.

#### SCARLET FEVER

(SCARLATINA)

**Definition.** Scarlet fever is an acute infection caused by a member of the group A beta-hemolytic *Streptococcus*. The clinical picture is a combination of septic and toxic manifestations. The primary site of infection is usually the pharynx, from which the organism may invade surrounding tissues and even the blood stream. The organism produces a potent soluble toxin, which, after absorption into the blood stream, causes such symptoms as fever, headache, delirium, rapid pulse, vomiting and the rash. Some of the clinical manifestations have been regarded as allergic. The hemolytic *Streptococcus* is responsible for a variety of clinical diseases, such as tonsillitis, otitis media, meningitis and erysipelas, which from an epidemiologic standpoint should be considered on the same etiologic basis.

**Etiology** (see also p. 401). Any erythrogenic toxin-producing strain of beta-hemolytic *Streptococcus* may cause scarlet fever. Actually these are all members of group A with the

exception of a few in groups C and G. Strains of the organism are serologically assigned to a group on the basis of their group antigen, the C-substance, which is a carbohydrate. Within a group many different types exist, recognized on the basis of their M-substance, which is a protein.

One or more types of the group A organism may be identified as the causative agent in a given outbreak of the disease. In one outbreak twenty-two different types were encountered among 228 patients. Of these, the most frequently observed types were 14, 18, 28 and 3.

Group A organisms elaborate a number of soluble substances, some of which are important in pathogenesis. These are the erythrogenic toxin, streptolysins (O and S), fibrinolysin (streptokinase), leukocidin and hyaluronidase. The rash-producing toxin is one of the most important and may exist in the blood in a concentration of 30 to 300 units per milliliter within eighteen hours of the onset of illness. During convalescence, or after active immunization with toxin, specific antitoxin develops and the Dick test reverses from positive to negative.

**Epidemiology.** Serologic typing and grouping have greatly enhanced knowledge of factors influencing the existence and spread of streptococcal infections. Within a given community the flora may consist of many different types, constantly changing in occurrence and dominance. Obviously, the carrier state is important and causes the major portion of infection by direct contact. In close quarters air-borne transmission is highly probable.

The carrier rate and the incidence of scarlet fever are influenced by season. Late fall, winter and early spring are the seasons of highest incidence. The disease is common in temperate and cold climates; rare in tropical areas, although the Dick-negative distribution within age groups in tropical areas resembles that in the temperate areas. Negroes, Eskimos and the yellow race appear to possess natural immunity. In the United States the disease is most common in the North, including the Rocky Mountain States, and least frequent in the South.

About half of the cases of scarlet fever occur between the ages of two and eight years, although other types of streptococcal infection in early infancy are not unusual. Certain families appear to be particularly susceptible, but the family communicability rate is only 5 to 10 per cent.

Both the morbidity and mortality rates in the United States have markedly decreased



in the last twenty years. For example, in New York City there were 50,622 cases reported during the period 1935–1939 with a fatality rate of 0.4 per cent. During the period of 1951–1954, 9430 cases were reported with a fatality rate of 0.01 per cent.

**Immunity.** Resistance to scarlet fever is both antibacterial and antitoxic. Antitoxic immunity is the more important, since it provides protection, usually permanent, against the erythrogenic toxin, which is responsible for the rash. Antibacterial immunity is type-specific. Though immunity to a given strain of *Streptococcus* may be of long duration, repeated streptococcal infections such as tonsillitis, sinusitis and otitis media are the rule, each possibly being an infection with a different strain. The presence of antitoxic immunity (negative Dick reaction) would seem to account for the occurrence of "scarlet fever" without an eruption (*scarlatina sine exanthemata*).

Immunity to the erythrogenic toxin is measured by titrating the serum and is reflected within limits by the Dick test.

This skin test consists in injecting 0.1 cc. of standardized streptococcal toxin intradermally. The amount of toxin injected is the amount which will produce within eighteen to twenty-four hours an area of erythema at least 1 cm. in diameter in the susceptible subject. This is known as one skin test dose (S.T.D.). The test is usually positive during the first few days of the disease and negative during convalescence. The test is more dependable with the heat-

labile toxin than with the ordinary Dick toxin. The heat-labile toxin is obtained from ordinary toxin by precipitation with alcohol (Ando). The heat-stable fraction accounts for the occurrence of a number of the Dick-positive reactions observed during convalescence.

The relation of the incidence of positive Dick reactions to age is similar to that of the Schick test (Fig. 106). During the first three to six months of life the Dick test is negative in the majority of infants, but this finding is not explained by the presence of demonstrable antitoxin in the blood.

*Passive immunity* may be conferred in a susceptible person by the injection of suitable amounts of convalescent serum, of whole blood from an immune donor or of antistreptococcal serum. It is difficult to assess antitoxic immunity, which probably fluctuates. Moreover, there is evidence that erythrogenic toxins are heterogenic, a fact that may explain variations observed in skin testing.

*Active immunity* is conferred by an attack of the disease or by a series of injections of toxin. It is probably also produced by repeated unrecognized infections by toxigenic strains of hemolytic streptococci.

**Pathology.** The local lesions result from bacterial invasion and consist of acute tonsillitis and pharyngitis. The tonsils are enlarged and hyperemic, and their crypts are filled with exudate. The mucous membrane of the pharynx is hyperemic and edematous. An

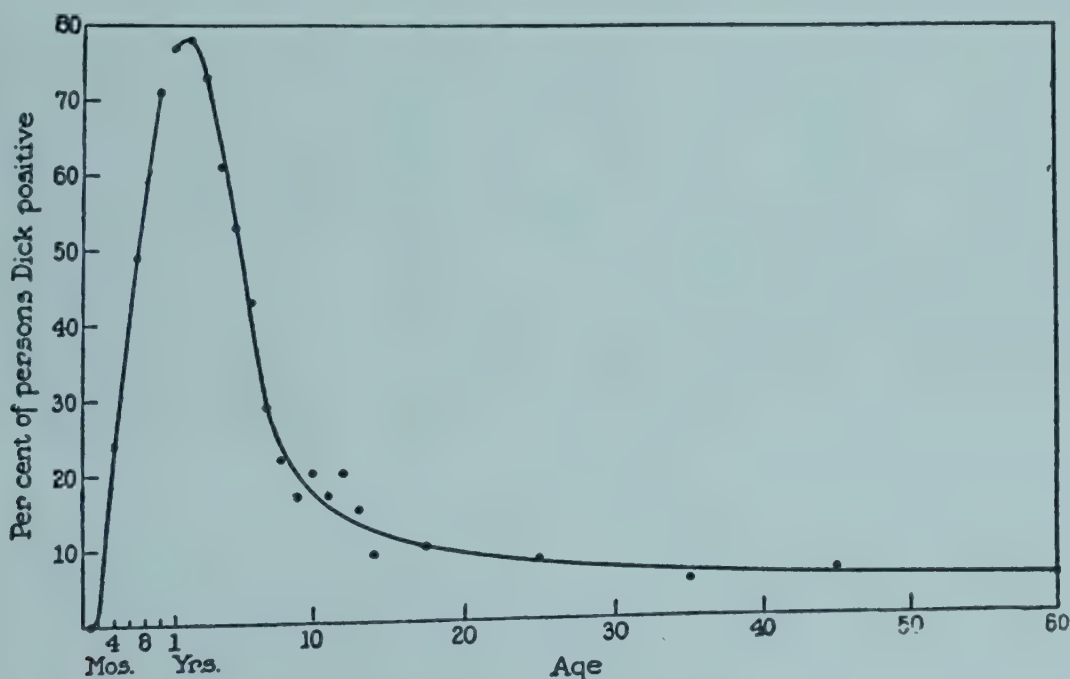


FIG. 106. Relation of age to the incidence of positive Dick reaction. (F. F. Schwentker, J. H. Janney and J. E. Gordon: *Am. J. Hyg.*, Vol. 38.)

infiltrate of polymorphonuclear leukocytes is present in the edematous submucosa as well as within the epithelium; the latter is covered by patches of mucopurulent or fibrinopurulent exudate. The regional lymph nodes are enlarged and reveal toxic hyperplasia or sup-puration.

The exanthem and enanthem are the result of bacterial toxins. Hyperemia of the corium is responsible for the diffuse redness. In addition, there is edema of the skin with a lymphocytic and monocytic infiltrate around the hair follicles. The cellular and fluid exudate accumulates in the midzone of the epidermis, where an accelerated keratinization (pseudo-keratosis) occurs. Separation of the outer layers of the epidermis from the intermediate keratinized zone is responsible for the des-quamation. The "strawberry" appearance of the tongue results from erythematous papillae projecting from a gray-coated background; with desquamation a beefy red appearance ensues.

Visceral involvement consists in general-ized hyperplasia of lymphoid tissue and perivascular and diffuse infiltration of lymphocytes and monocytes. These infiltrates are especially prominent in the heart, liver and kidney; in renal interstitial tissue they may rarely lead to uremia, which usually appears within a week after the eruption.

**Clinical Manifestations.** The incubation period is usually two to four days, with an upper limit of six to seven days.

The primary infection, which occurs in the pharynx, is responsible for the toxic mani-festations and for the septicemia. The toxic manifestations include headache, fever, vom-iting, rapid pulse, delirium, exanthem, enan-them, generalized lymphadenitis, myocarditis, nephritis and perhaps arthritis. The septic manifestations resulting from bacterial inva-sion of the tissues and blood stream, in addi-tion to cellulitis of the pharynx and neck, and cervical adenitis, may include otitis media, sinusitis, mastoiditis, pyelonephritis, endocarditis, meningitis and other metastatic lesions.

The typical case of scarlet fever begins with headache, fever, sore throat and vomiting, followed within twenty-four to seventy-two hours by the appearance of the rash.

The onset is sudden, with a temperature of 101° to 104° F., reaching its height about the second day and gradually subsiding to normal by the seventh to the tenth day. The pulse rate is increased out of proportion to the temperature. Nausea is common, and

vomiting occurs in approximately 80 per cent of the cases in children. Headache is often severe, and prostration is common.

The throat is deeply injected (Fig. 107), and petechiae are present on the uvula and soft palate. Edema of the soft tissues may be present. Mucopurulent exudate may be dis-tributed over the surface of the tonsil, re-sembling the early lesion of diphtheria. In severe cases a serosanguineous nasal discharge may be present. The cervical lymph nodes are usually palpable, often definitely enlarged and tender. There is also a generalized en-largement of the superficial lymph nodes.

The eruption is a diffuse, finely papular, bright red erythema which blanches on pres-sure. It begins twelve to seventy-two hours after the onset of symptoms about the base of the neck, in the axillae and groins, and later appears on the trunk and extremities. The cheeks are flushed, and a ring of pallor corresponding to the topical area of the orbic-ularis oris muscle encircles the mouth (cir-cumoral pallor). Invasion of this area by a true exanthem does not occur, and frequently the remainder of the face is also spared. When there is a rash over the cheeks, it is of less degree than elsewhere. In the creases on the flexor surface of the elbow are deeply injected transverse lines of hyperemia which do not fade on pressure (Pastia's sign, Fig. 108). Petechiae are frequent in the more toxic cases and may occur in mild cases; the Rumpel-Leede test is positive.

The toxic eruption may be locally blanched by the intradermal injection of 0.2 ml. of convalescent serum or diluted commercial antitoxin. This reaction, considered to be a local neutralization of the erythrogenic toxin by specific antitoxin, is known as the Schultz-Charlton blanching phenomenon (Fig. 109). A circumscribed area of blanching appears within eight to twenty-four hours at the site of injection. A positive reaction is strongly indicative of scarlet fever; a negative reaction does not rule out the disease, possibly be-cause of the existence of more than one type of erythrogenic toxin. The test is rarely posi-tive after the fourth day of the disease.

After three to seven days the rash fades and is followed by a branny type of desquama-tion (Fig. 110) which is most noticeable in the axillae, groin, finger tips and at the base of the nails, but may occur anywhere on the body. The degree of desquamation is propor-tional to the intensity of the rash. In mild cases it may be absent.

The so-called strawberry tongue is observed





FIG. 107.

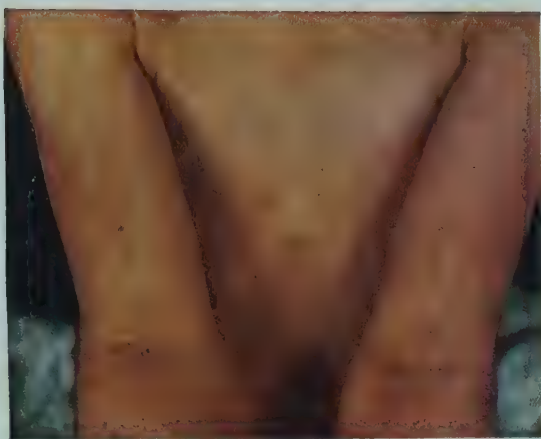


FIG. 108.



FIG. 109.



FIG. 110.

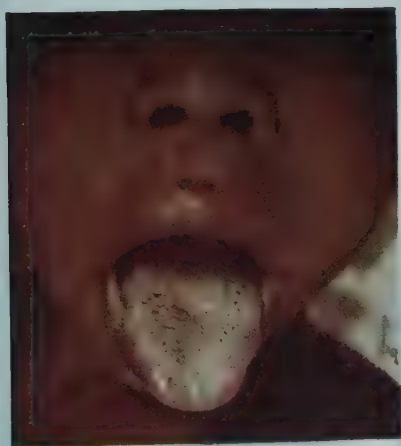


FIG. 111.

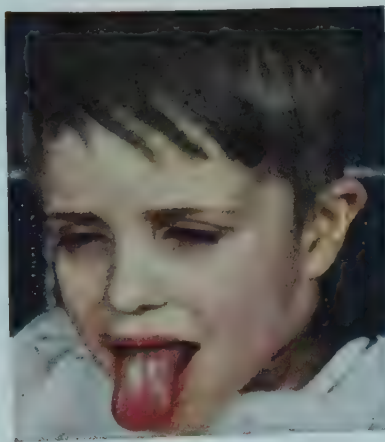


FIG. 112.



FIG. 113.

FIG. 107. Enanthem of throat in scarlet fever. (Courtesy of Dr. P. F. Lucchesi.)

FIG. 108. Rash of scarlet fever, showing Pastia's sign.

FIG. 109. Rash of scarlet fever, showing positive blanching test.

FIG. 110. Desquamation of scarlet fever.

FIG. 111. White strawberry tongue of first day of scarlet fever. (Courtesy of Dr. P. F. Lucchesi.)

FIG. 112. Partial desquamation of scarlet fever, approximately third day of disease.

FIG. 113. Denuded tongue (red strawberry tongue) of scarlet fever, fifth to seventh day of disease.

(Courtesy of Dr. P. F. Lucchesi.)

in more than half of the cases and is an important clinical sign. Early in the disease the tongue is coated and somewhat swollen, the borders and tip are deeply injected, and the papillae are prominent (white strawberry tongue, Fig. 111). By the third or fourth day the coating desquamates, leaving a beefy red tongue with swollen papillae (red strawberry tongue) (Figs. 112, 113). This type of tongue is frequently observed in streptococcal infections without eruptions.

The clinical patterns of scarlet fever vary markedly in severity. The more toxic or septic the initial reaction is, the more frequent and numerous are the complications and the more grave is the prognosis.

There is usually a secondary anemia, albuminuria and leukocytosis. The white blood cell count is 10,000 to 20,000, of which 75 to 90 per cent are polymorphonuclear cells. Eosinophilia (4 to 20 per cent) may be observed after the fourth day of the rash. It diminishes during the second week and often increases again during the third week.

Relapses occur in about 0.5 per cent of cases in the third to sixth week of the disease and are now generally regarded as representing infection with a new strain of *Streptococcus*. They are usually of shorter duration and less severe than the original attack, and their occurrence may be influenced by such factors as inadequate antibiotic therapy and failure of the host to develop antitoxic immunity.

Second attacks are rare and require clinical and bacteriologic proof. The few instances of suspected second attacks observed by the author usually occurred in allergic persons, and confirmatory evidence of one of the attacks was incomplete. Diagnosis of second attacks on clinical evidence alone is not reliable.

**Differential Diagnosis.** The typical case offers little difficulty in diagnosis. The characteristic onset with fever, sore throat and vomiting followed within one to three days by a diffuse erythematous rash constitutes a presumptive diagnosis of scarlet fever. In mild, atypical cases and in infants the diagnosis may be exceedingly difficult.

In *German measles*, which is perhaps most frequently confused with the mild type of scarlet fever, the intensity of the eruption is out of proportion to the symptoms. Enlargement of the occipital nodes and the rapidly changing and fading eruptions are characteristic. The throat symptoms are mild, and desquamation is rare.

*Measles* can usually be identified by the catarrhal symptoms, the morbilliform erup-

tion with involvement of the face, the presence of Koplik's spots, and leukopenia. The modified type of measles may offer considerable difficulty in diagnosis.

*Exanthema subitum* may on occasion present an eruption more scarlatiniform than morbilliform. The course of the disease and leukopenia are characteristic.

*Infectious mononucleosis* may be differentiated by serologic and hematologic data.

*Drug rashes*, particularly those caused by belladonna, the coal-tar derivatives, sulfonamides and irritants to which the patient is allergic, are common causes of error. Drug rashes are usually more intense on the extremities. The history of drug administration is helpful. The scarlatiniform type of eruption associated with serum disease is easily identified by its pruritic quality and its relation to an injection of serum.

When the throat symptoms in scarlet fever are severe and the eruption is not characteristic, the throat culture, history of active immunization and the Schick test may assist in ruling out *diphtheria*.

In general, the following evidence may assist in the positive diagnosis of a questionable case of scarlet fever: (1) history of exposure within one week; (2) concurrent streptococcal infections in siblings or close contacts; (3) subsequent desquamation or development of nephritis; (4) many hemolytic streptococci in the throat culture; (5) positive rash-extinction test; (6) reversal of the Dick reaction during the illness.

**Complications.** The complications fall into two general groups: (1) those caused by septic infection by the hemolytic *Streptococcus* or other secondary invading organism, and (2) those caused by the toxin.

The incidence of the septic complications, suppurative cervical adenitis, sinusitis, otitis media, mastoiditis, lateral sinus thrombosis, epidural abscess, meningitis and endocarditis, has been greatly reduced by early treatment with effective antibacterial agents.

*Sinusitis* probably occurs in most cases, varying from a mild ethmoidal infection to severe pansinusitis. Definite cellular reaction of the orbital tissues is commonly associated with ethmoidal infection. Persistent purulent rhinitis is indicative of sinus infection, which often remains as a focus in the carrier state. The tonsils and adenoids are always infected and frequently are responsible for persistence of the nasal infection. The presence or absence of tonsils and adenoids has little to do with the incidence of scarlet fever. Retro-



pharyngeal and peritonsillar abscesses are also complications.

The pain of acute *mesenteric adenitis* may resemble that of appendicitis.

*Laryngitis* is occasionally an early manifestation and may be obstructive. It may progress to diffuse laryngotracheobronchitis.

*Bronchopneumonia* is not common and is usually interstitial in type; empyema develops in about one third of untreated cases.

*Cardiac disorders*, which are of several types, occur in less than 1 per cent of cases. One of the most common is acute toxic myocarditis, which occurs early and is not unlike that of diphtheria. It is often transient. Bacterial endocarditis and pericarditis are septic in origin. If rheumatic carditis occurs, it usually does so during the second or third week.

*Albuminuria* with only an occasional cast or red blood cell occurs early in most severe cases. It usually disappears when the temperature subsides.

Clinically manifest acute *glomerulonephritis* occurs in about 1 per cent of cases in the second or third week of the disease. As shown by Lyttle, an increase of urinary protein and cellular components may be found in the majority of cases at this time, if studied by the Addis method.

*Arthritis*, usually involving the smaller joints, may occur in older children during the second or third week of the disease. It is probably caused by the toxin and subsides within a week or more. It resembles rheumatic fever, which may also occur at this time. Suppurative arthritis of pyemic origin is usually multiple and involves the large joints.

*Paronychia* is a common minor infection.

**Prognosis.** The mortality rate in the United States is now under 1 per cent. It is somewhat higher in infants, in whom septic features of the disease are more common. These complications should be controlled by early and adequate antimicrobial therapy. Late complications such as rheumatic fever and glomerulonephritis may occur regardless of the severity of the disease.

**Prevention.** Isolation measures have in general failed to control the spread of scarlet fever, owing to the many sources of group A beta-hemolytic streptococci. The carrier rate appears to be little affected by quarantine.

Patients adequately treated with penicillin for ten days rarely become carriers. If the mucous membranes of the nasopharynx appear normal and there are no purulent com-

plications, isolation of the patient may be discontinued after seven days.

Exposed persons, especially family contacts, may be effectively protected by oral administration of 200,000 units of penicillin night and morning for a week after exposure. Exposed persons who have had rheumatic fever should receive adequate prophylactic therapy.

Since active immunization with toxin results only in prevention of the rash, but not of the infection, it is not recommended.

**Treatment.** Rest in bed, adequate fluids, and a liquid, soft or regular diet, as the child desires, are the general measures indicated in the acute stage. Codeine and aspirin may be required to relieve headache, sore throat and general discomfort.

Daily examinations of the patient and frequent urinalyses should be made during the febrile period. Inhalation of moist air is indicated when there is severe infection of the upper respiratory tract. Cold or hot local compresses may be applied to painful, swollen cervical lymph nodes; incision should be made only when fluctuation is obvious.

The pain of otitis media is relieved by codeine and aspirin and the local application of heat. Early myringotomy is indicated if the drum is bulging. The treatment of toxic myocarditis is identical with that described under Diphtheria (p. 419). The management of acute glomerulonephritis is discussed elsewhere (p. 1041). The secondary anemia quickly responds to administration of an adequate diet, iron and cobalt.

Penicillin is the antibiotic of choice. Daily intramuscular injections of 300,000 to 600,000 units of an aqueous suspension of procaine penicillin for ten days is ideal. One or two daily injections followed by suitable oral therapy for a week are satisfactory and more practicable.

Although penicillin does not neutralize the toxin, it rapidly eliminates the organism and inhibits the development of streptococcal antibodies such as antistreptolysin, thus reducing the incidence of complications. However, such early effective therapy probably also interferes with the development of acquired immunity (Strom, 1955).

If penicillin cannot be used, one of the tetracycline drugs is a second choice. They are effective against the septic manifestations, but do not so readily eliminate the organism or prevent a rise of the antistreptolysin titer. Sulfonamides should be given only if penicillin and the tetracyclines cannot be used.

Since antibiotic therapy is highly effective and toxic features of the disease are seldom marked, there is little, if any, need for serum therapy. However, when indicated, gamma globulin, which contains from three to five times the amount of erythrogenic antitoxin as does the average human immune serum, may be injected intramuscularly in doses of 20 to 60 cc.

**Surgical Scarlet Fever.** In this type of the disease the focus of infection is somewhere other than the throat. It may be a traumatic or operative wound or a burn. It may follow any surgical operation, but particularly those of the ear, mouth or nose; the onset is usually within two to four days. The symptoms are usually mild, and complications are infrequent. The pharynx is not involved, and hemolytic streptococci can usually be cultured from the suspected focus.

WILLIAM L. BRADFORD

#### REFERENCES

- American Academy of Pediatrics: Report of the Committee on the Control of Infectious Diseases. Revised, 1957, p. 61.
- Cooke, J. V.: Scarlet Fever. *Ann. Int. Med.*, 11:484, 1937.
- Dick, G. F., and Dick, G. H.: A Skin Test for Susceptibility to Scarlet Fever. *J.A.M.A.*, 82:265, 1924.
- Schwentker, F. F., Janney, J. H., and Gordon, J. E.: The Epidemiology of Scarlet Fever. *Am. J. Hyg.*, 38:207, 1943.
- Stimson, P. M., and Hodes, H. L.: *Common Contagious Diseases*. 5th Ed. Philadelphia, Lea & Febiger, 1956, p. 161.
- Strom, J., and Turnevall, G.: Long-acting (DBED) Penicillin and Procaine Penicillin in the Treatment of Scarlet Fever. A Clinical and Serobacteriological Follow-up Study. *Acta paediat.*, 44:527, 1955.
- Zingher, A.: The Dick Test and Active Immunization with Scarlet Fever Streptococcus Toxin. *Am. J. Pub. Health*, 14:955, 1924.

#### ERYSIPELAS

(ST. ANTHONY'S FIRE)

Erysipelas is an acute streptococcal infection of the skin and occasionally of the mucous membranes. It is characterized locally by a painful erythematous induration with sharply demarcated serpiginous borders and generally by constitutional symptoms.

**Etiology.** A number of the subgroups of group A hemolytic streptococci may be the cause of erysipelas.

**Epidemiology.** The disease exists endemically in all communities where streptococcal

infections occur. Since the introduction of the sulfonamides and antibiotics it is relatively infrequent.

**Immunity.** The newborn infant is highly susceptible. An attack of the disease confers no immunity against subsequent ones. Certain persons appear to be predisposed to the disease and have repeated attacks. In this respect erysipelas differs from scarlet fever, in which immunity to the erythrogenic toxin (rash) is conferred. Thus it would seem that antitoxic immunity is relatively ineffective in erysipelas.

**Pathology.** Streptococci are found in great numbers in and about the lymphatics of the skin near the border of the spreading infection. The surrounding area is hyperemic and edematous. Infiltration of mononuclear cells is marked, extending into the corium and subcutaneous fatty area. Suppuration is rare except in the subcutaneous region, where it may occur in infants. The regional lymph nodes are enlarged. In young infants septicemia is frequent and results in multiple metastatic purulent lesions which may include parenchymal lesions of the liver, kidneys, brain, heart and other organs.

**Clinical Manifestations.** The local lesion is often the first evidence of infection, although at times fever, malaise, irritability, vomiting, loss of appetite or other general symptoms may precede it. The portal of entry is a wound of the skin which may be trivial or may be a surgical incision, or the lesions of such conditions as eczema, impetigo, varicella and vaccinia. The sites most frequently involved are the periumbilical area (newborn), the genitals, face and extremities. When the face is involved, the infection may extend from one cheek across the nose to the other cheek (the familiar "butterfly" type). The inflamed area is red, hot and tender, and there may be vesiculation. The border is elevated and spreads in an irregular manner, avoiding areas of the skin where tension normally exists, such as bony prominences. The disease may be self-limited or may spread over a large portion of the body, fading in one area while extension occurs in another. The fading area becomes brawny and desquamates.

Erysipelas of the mucous membranes is relatively rare. It may occur as a hard, painful, swollen inflammation of the pharynx, nose, larynx or vulva. Extension into the larynx may lead to suffocation.

The temperature usually reaches a level of



104° or 105° F. It may be intermittent, but more often remains at a high level. The fever may last only a few days or may persist for one or more weeks. Occasionally it is of a low grade type; in overwhelming infections, especially in newborn infants, the temperature may be subnormal.

Leukocytosis is usually present, the white blood cell count ranging from 12,000 to 40,000 per cubic millimeter, with a preponderance of polymorphonuclear cells. Except in infants, blood cultures are usually sterile.

Relapses are common, usually beginning in areas of skin most recently infected. The course of a relapse is usually shorter and the symptoms are less severe than in the original attack.

**Diagnosis.** The fully developed case of erysipelas offers little diagnostic difficulty.

*Diffuse cellulitis*, or infection of the subcutaneous tissue, is the condition most commonly confused with erysipelas. The constitutional symptoms are usually less pronounced, and the characteristic elevated border of erysipelas is absent. Orbital cellulitis, secondary to ethmoidal sinus infection, is occasionally misdiagnosed as erysipelas.

*Dermatitis medicamentosa*, particularly that due to mercurial ointment, may be differentiated by history and by lack of fever, as may eczema of the erythrodermic type. Severe sunburn should offer little difficulty in differential diagnosis.

**Complications.** In infancy, septicemia, bronchopneumonia and peritonitis are the most important complications. Abscess formation occurs in 10 to 15 per cent of all cases. Sloughing with ulceration results most frequently in areas subject to pressure.

Suppurative lesions of the accessory nasal sinuses sometimes occur. More extensive forms of such infections may lead to thrombosis of the cavernous sinus or other dural sinuses, meningitis or brain abscess.

**Prognosis.** The general mortality was formerly 5 to 10 per cent, and in infants as high as 80 per cent. When treatment is instituted early, recovery can be expected in practically all instances, even in infants.

**Treatment.** Although the infection is relatively noncommunicable, the patient should be in strict isolation. Erysipelas responds dramatically to the systemic administration of penicillin or other antibiotics effective against the beta-hemolytic *Streptococcus* (see p. 402). Local treatment is not effective.

## DIPHTHERIA

**Definition.** Diphtheria is a specific infectious disease caused by *Corynebacterium diphtheriae*. In its classic form it is characterized by a local pseudomembranous lesion, usually on the tonsils, pharynx and adjacent tissues, from which a powerful toxin is absorbed. This toxin produces the constitutional symptoms. The location of the lesion, its extent and the degree of toxemia vary greatly.

**History.** The modern concept of the disease began with the classic clinical description by Bretonneau in 1826, who called it *diphtherite*. Diphtheria, however, was known to the Hebrews before Christ. It is not known when the disease reached America; Samuel Bard (1771) probably described an epidemic in New York City and the Colony.

Klebs in 1883 demonstrated diphtheria bacilli in the pseudomembrane, and Loeffler in 1884 identified them in pure culture. In 1888 Roux and Yersin described the toxin, and in 1894 von Behring discovered its antitoxin. Theobald Smith suggested toxin-antitoxin for active immunization, and it was widely popularized by Park and Zingler (1913). Schick introduced the intracutaneous test for determining susceptibility in 1913, and in 1922 Ramon described the preparation of formalized toxin (toxoid). The introduction of tracheotomy (1825) by Bretonneau and of intubation (1895) by O'Dwyer were also important contributions.

**Etiology.** The diphtheria bacillus is polymorphous, but characteristically is a slender, slightly curved, sometimes clubbed organism. In smears prepared from cultures the bacilli tend to group themselves in parallel (palisade) or V-shaped formations. The stained protoplasm of the organism may appear uniform in consistency or may be granular or barred. Dark-staining polar bodies at or near the ends of the organism are characteristic. Smears for diagnosis are usually stained with methylene blue, toluidine blue or Ljubinsky's stain. Characteristic bacilli may be found on smears made directly from lesions in the majority of instances, but they cannot be differentiated by this means from nonpathogenic diphtheroid bacilli. A negative smear does not rule out the presence of the organism in the lesion.

The bacillus is gram-positive, nonmotile and nonspore-forming. It is easily destroyed by heat (60° C. for ten minutes) and is susceptible to weak antiseptics. It survives in ice for several weeks. In water, milk or dried mucus it may remain viable for several weeks.

Three types of the organism, *gravis*, *mitis* and *intermediate*, may be identified by the type of colony formed on a blood-agar me-

Table 67. Death Rates for Diphtheria by Age\*; All Races, Both Sexes: Death Registration States 1920-1953

Year	Total	Under 1 Year	1-4 Years	5-14 Years
1920.....	15.3	49.8	90.5	28.0
1930.....	4.9	22.1	33.5	8.1
1940.....	1.1	7.1	9.0	1.7
1950.....	0.3	0.7	1.6	0.5
1953.....	0.1	0.2	0.5	0.2

United States Department of Health, Education, and Welfare, Public Health Service. National Office of Vital Statistics Special Reports 43, #6, May 18, 1956.

\* Rate per 100,000 population of age group.

dium containing potassium tellurite. The gravis and intermediate forms are thought to be associated with a high fatality rate and the mitis type with the milder forms of the disease. Frobisher, however, found no constant relation between the gravis form and malignant diphtheria.

The diphtheria bacillus produces a powerful toxin. Guinea pigs die when injected with doses as small as 0.02 ml. Approximately one fiftieth of this amount of toxin is used for intradermal injection to determine susceptibility of man to the disease (Schick test). If no reaction occurs at the site of injection, the person is considered immune and to have at least 1/30 unit of antitoxin per milliliter of blood serum. (Some evidence suggests that as little as 1/250 unit may neutralize the skin test.)

The toxin, a heat-coagulable protein, accounts for practically all the clinical manifestations. It is a potent tissue poison which, within a few hours after absorption, produces characteristic cellular changes, especially in the cardiac, renal and nervous tissues.

**Epidemiology.** Diphtheria occurs endemically and epidemically throughout the world, particularly in the temperate zones, and is more frequent during the winter. Though the incidence is slightly greater among females, there is no significant difference in mortality between the sexes. Negroes are said to have greater immunity than white persons.

Diphtheria has a characteristic age incidence, corresponding to the lack of humoral antitoxin. The disease is rare during the first six months of life; the incidence reaches its peak between the second and fifth years, and it declines rapidly beyond the age of ten. In the United States about 65 per cent of cases have occurred in children under five years of age. There is, however, evidence of a rising

age incidence, which may be the result of extensive active immunization among the younger age groups. Such evidence indicates the continued use of "booster injections," at least throughout the school years (see p. 141).

The morbidity and mortality from diphtheria have declined rapidly in the United States, particularly since 1920, when active immunization became widely established (Table 67).

Diphtheria is particularly apt to be spread in schools and other places where children of susceptible ages are grouped together. One or more chronic carriers may account for its persistence within a particular community. The recent discovery that, in the presence of a specific bacteriophage, certain avirulent strains can become permanently virulent adds importance to the role of the carrier.

Infection is due to contact with a person with the active disease or with a carrier of virulent organisms. Fomites and animals play an unimportant role in the transmission of the disease, as do water and milk. Chronic sinusitis and diseased tonsils and adenoids are important predisposing factors.

**Immunity.** Resistance to *C. diphtheriae* is of two types: passive and active.

*Passive immunity* may be obtained by the newborn infant transplacentally from an immune mother. It is almost absolute for the first three months of life and partial until about the sixth month. If the mother is susceptible to diphtheria, her baby is also susceptible. Passive immunity for about three weeks may be artificially obtained by subcutaneous injection of 1500 units of antitoxin.

*Active immunity* is acquired by having the disease or by receiving inoculations of one of several types of suitable antigens. Not all persons recovering from the disease become immune; hence secondary attacks are not uncommon. It is probable that the early injection of antitoxin, though curative, interferes with the patient's power to generate antibodies. Conversely, not all persons immune to diphtheria have had the classic disease. Active immunity is presumably induced by subclinical diphtheritic infections. Occasionally a susceptible person lacking demonstrable humoral immunity as reflected by a positive Schick reaction fails to contract diphtheria in spite of repeated exposures to virulent organisms. This suggests that resistance may depend upon cellular as well as humoral immunity.

**Schick test.** The minimal lethal dose



(M.L.D.) of diphtheria toxin is defined as that amount which, injected subcutaneously, causes the death of a 250-gm. guinea pig within four days. The Schick test consists in intracutaneous injection of 1/50 M.L.D. of toxin contained in 0.1 ml. of a proper diluent. If the tested person is susceptible, an area of reddish-brown discoloration appears at the site of injection within twenty-four hours. In persons who have practically no antitoxin, vesication often occurs. After five to seven days the reaction begins to fade, leaving a scaling, wrinkled area with brownish pigmentation which may last four to six weeks. If the tested person is immune, no local reaction occurs unless he is allergic to the auto-lyzed substance of the diphtheria bacillus or to other protein components of the culture medium or diluent solution. In this case a pseudoreaction manifested by a diffuse erythema with or without an urticarial wheal develops within a few minutes or hours. It usually disappears within seventy-two hours. A control test has been devised consisting of a material identical with that used for the test except that the toxin has been destroyed by heat. In some clinics the control test is omitted, and the interpretation is made at the end of the fifth day, when pseudoreactions have usually disappeared.

Four types of Schick reactions are commonly observed (Fig 114).

About 15 per cent of newborn infants have positive Schick reactions. In such instances the mother's reaction is almost always positive. The incidence of positive reactions gradually increases until the sixth month of age, when about 50 per cent are positive. At one year fully 90 per cent of nonimmunized infants have a positive reaction; after this age the incidence until recent years gradually diminished, until at seventeen years only about 15 per cent remained positive. Surveys, however, indicate that 50 to 60 per cent of adolescents and adults now have positive reactions.

**Pathology.** An exotoxin elaborated by the organisms tends to inhibit the local inflammatory response. As this response is overcome the bacteria multiply rapidly and produce more toxin, resulting in edema, hyperemia and necrosis of the epithelium. A pseudo-membrane, consisting of fibrin, leukocytes, necrotic tissue and bacteria, is formed and becomes adherent to the underlying tissue. Removal of it exposes a raw, bleeding surface. The membrane is less adherent to columnar epithelium than in the trachea, and is more

readily separated from its attachment. Pseudomembranes may be absent in early or mild forms of the disease and may be present in diseases other than diphtheria.

Pharyngeal membranes may extend to the nasopharynx into the larynx, or the lesion may be localized to the latter site. Primary tracheal diphtheria is rare, involvement of the larynx almost always being present. Since the tracheal membrane is easily detached, not being in contact with an extensive vascular bed, the toxemia may be much less than in the pharyngeal type. The tracheal membrane often becomes loose except at its point of attachment in the larynx and may cause obstruction in the lower respiratory tract. Rarely an almost perfect cast of the bronchial tree may be formed by an extensive membrane.

Lymph nodes draining the affected area, and at times more remote ones, reveal reactive hyperplasia. The malpighian corpuscles of the spleen and of the lymph nodes contain large toxic reaction centers.

In patients dying with toxic myocarditis, the heart is soft and flabby, and the chambers, especially the left ventricle, are dilated. Scattered petechiae may be present. Histologically, there are interstitial edema and multiple areas of necrosis associated with an inflammatory infiltrate consisting predominantly of polymorphonuclear leukocytes. In less severely involved areas droplets of fat may be demonstrable within the myocardial fibers.

Paralysis results from the effects of the toxin on the peripheral nerves. There is degeneration and even destruction of myelin sheaths, and the axons may be swollen. Rarely does irreparable axonal damage occur.

Cloudy swelling and occasionally focal necrosis may be present in the liver and kidneys; rarely is there acute interstitial nephritis.

Death may result from peripheral vascular collapse, respiratory obstruction, cardiac failure, respiratory paralysis or secondary bronchopneumonia.

**Clinical Manifestations.** The incubation period is from two to seven days.

**Faucial diphtheria.** The disease may be so mild that it is overlooked, or discovered only by bacteriologic examination, since only a catarrhal inflammation may occur. Infection without membrane formation is particularly likely in partially immune persons.

In the moderately severe case there may or may not be soreness of the throat, but malaise and headache are usually present. Fever is usually of the low grade type, 101° to 103° F. Inspection during the first day reveals con-

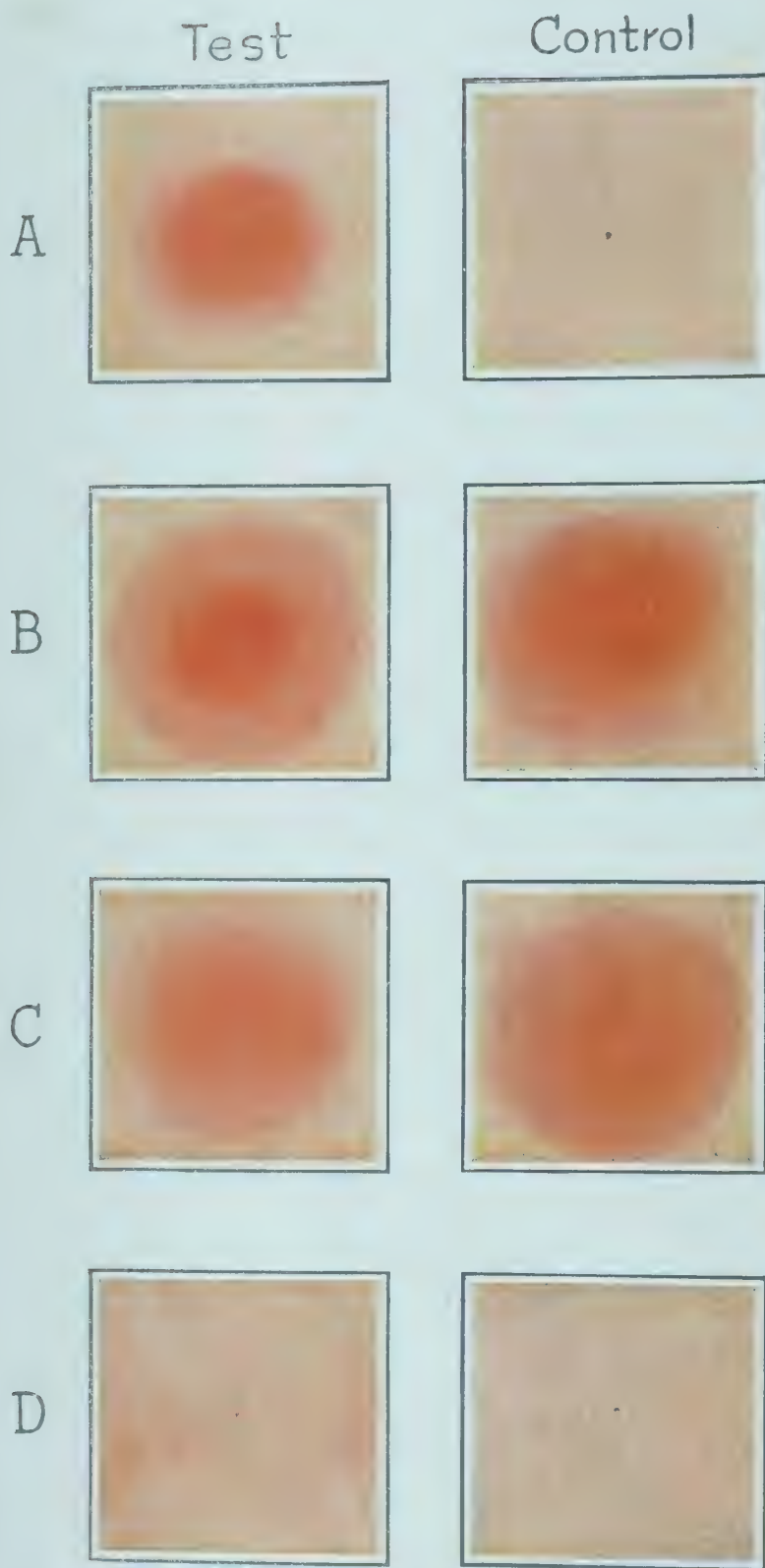


FIG. 114. Schick test and control reactions 24 to 48 hours after injections (see text for more complete description). A, Positive reaction: patient susceptible to diphtheria and not allergic to protein material in test solution. B, Positive combined reaction: patient susceptible and also allergic to protein in test solution. C, Pseudoreaction: patient immune, but allergic to protein in test solution. D, Negative reaction: patient immune and nonallergic to protein material in test solution.



gestion and slight swelling of the tonsillar and pharyngeal tissue, with slight enlargement of the cervical lymph nodes. Within twenty-four hours small yellowish-white spots appear upon the surface of the tonsils. They closely resemble those of follicular tonsillitis and are removed with difficulty. The spots coalesce and spread rapidly from the tonsillar surface to the pillars, uvula, soft palate and posterior pharyngeal wall. The membrane may extend upward into the nares and cause a bloody, serous nasal discharge. The odor is offensive, but not characteristic. Swelling of the soft tissues and cervical lymph nodes develops. Constitutional symptoms increase in severity, and the pulse becomes rapid and of less volume. The blood pressure falls, and prostration becomes pronounced. Difficulty in swallowing increases, and noisy breathing becomes evident even without laryngeal obstruction. A nasal voice or regurgitation of liquids through the nose during the act of swallowing suggests palatal paralysis. The patellar reflexes may be diminished or absent. In severe cases there is rapid reduction of erythrocytes and hemoglobin. Polymorphonuclear leukocytosis develops. The urine usually contains albumin, and often hyaline and epithelial casts.

The more malignant type of the disease is usually a combined faucial and nasopharyngeal lesion. Toxemia in this form is extreme, and the sensorium is frequently disturbed. The local infection is extensive, and there may be secondary infection, frequently with the hemolytic *Streptococcus*. Hemorrhages from the mouth and nose are common, and petechiae, resulting from capillary fragility, may appear in the skin and mucous membranes. The cervical lymph nodes may become greatly swollen and, with the firm, non-pitting edematous changes in the surrounding skin and subcutaneous tissue, create a characteristic "bullneck" appearance. The face becomes edematous and has a waxy pallor. Death usually occurs within a week from toxic myocarditis or bronchopneumonia.

**Laryngotracheal diphtheria.** In about one fourth of all cases the infection invades the larynx and trachea, the laryngeal lesion being an extension from a pharyngeal focus about three times as often as it is primary. It is more common in infants and has a high mortality rate. There is less toxemia in the primary form.

Hoarseness, a brassy cough and noisy breathing are the initial symptoms. Laryngeal obstruction is soon apparent and is progres-

sive with stridor that is both inspiratory and expiratory. Restlessness, anxiety and retractions of the episternal and subcostal regions increase; if the obstruction is not relieved, cyanosis develops, and death occurs from suffocation or cardiac failure.

Laryngoscopic examination reveals edema, congestion and the pseudomembrane.

**Nasal diphtheria.** In about 2 per cent of all cases, more often in infants, diphtheria may occur primarily in the nose, where the infection may remain localized or extend to the nasopharynx, throat and larynx. When the lesion is limited to the nose, constitutional symptoms are usually absent or slight, and the fever tends to be low. The only evidence may be a nasal discharge which characteristically is sanguineous and has a foul odor. Obstruction to breathing may be present. Nasal diphtheria, because of its chronicity, constitutes a continuous source of contagion if not discovered.

**Cutaneous diphtheria.** Cutaneous infection is not unusual in the tropics, as was observed in the armed forces during World War II in Africa and in the Pacific theatre. It is said to be common in New Guinea, where faucial diphtheria has not been reported. In a series of 1423 cases of diphtheria (Los Angeles County Hospital, 1945-50) there were six instances of cutaneous infection and ten of infection in the ear, conjunctiva, umbilicus or vagina.

The skin infection may be primary or secondary to lesions of the mucous membranes. A common form consists of a gray membrane around the swollen edge of a wound. Other lesions may be eczematous, impetiginous, pustular or bullous. Constitutional reactions range from none to a fatal toxemia. The lesions usually respond promptly to specific treatment.

**Other types of diphtheria.** Primary infection may occur in unusual regions of the body, or these areas may become secondarily infected from a diphtheritic lesion in the upper respiratory tract. The vulva, vagina, umbilical cord, conjunctivas and cutaneous wounds are some of the unusual sites. Lesions on the lips and face may also occur. Wounds, especially those resulting from tonsillectomy, are at times infected. Tonsillectomies should be performed only on children known to be Schick-negative.

**Diagnosis.** There is nothing typical about the early tonsillar lesion, except the manner and rapidity of extension of the membrane. A throat swab should be obtained for culture

and smear at the initial examination. If dependable bacteriologic facilities are not available, antitoxin should be administered immediately in each suspected case.

Bacteriologic diagnosis of diphtheria requires (see also p. 387) (1) good culture medium, (2) proper technique of taking the culture, and (3) expert interpretation of stained smears. The mediums should be fresh and moist. A drop of water of condensation at the bottom of the slant is desirable. The swab should be made from the base of the exudate or membrane. Direct smears are important only when positive and diphtheroid organisms cannot be differentiated; a negative culture does not rule out diphtheria.

In doubtful cases, particularly in patients under observation in a hospital, the following routine may prove helpful: (1) an accurate history concerning previous active immunization and Schick reaction, (2) incubation of a culture from the lesion, (3) performance of a Schick test, (4) careful, regularly repeated examination of the throat lesion, and (5) immediate therapy with penicillin. If the membrane spreads, antitoxin should be administered even if the culture is negative. A rapid method of culturing the organism consists in the use of a swab impregnated with horse serum, the surface of which is coagulated by passing the swab through a flame. Charged swabs prepared in this manner, when incubated, often show growth of *C. diphtheriae* within two to four hours.

**Differential Diagnosis. Nasal diphtheria.** This lesion may be confused with any condition responsible for a persistent bloody nasal discharge. Ulcers produced by constant picking of the nose, foreign body and congenital syphilis are the more common conditions that require consideration.

**Faucial diphtheria.** Faucial diphtheria is most likely to be confused with follicular tonsillitis, in which the temperature is usually high, swallowing is painful, and the follicular exudates, though they may coalesce, do not usually extend beyond the surface of the tonsils. In early syphilis primary or secondary ulcerative lesions may resemble those of diphtheria. They are more frequent in adults, and the specific serologic reaction is positive. Severe pharyngeal reactions to herpes virus occasionally suggest diphtheria; but characteristic herpetic lesions of the tongue, cheeks, lips and gums are usually present or soon develop. In severe or septic cases of scarlet fever, tissue swelling, ulceration and heavy mucoid exudate over the tonsil, soft palate

and posterior pharyngeal wall may occur. The throat lesion of *infectious mononucleosis* may be confusing. *Thrush*, usually encountered during infancy, occurs in other areas of the oral cavity as a rule, and the exudates are whiter than that of diphtheria and characteristically arranged as small linear (filaments) membranes. The membranes which characteristically form in *post-tonsillectomy wounds* have been mistaken for diphtheria. In certain *blood dyscrasias*, such as agranulocytosis and leukemia, necrotic lesions occur in the throat which may resemble those of diphtheria.

**Laryngeal diphtheria** (see also p. 778). This lesion is most frequently confused with *acute laryngitis* and *laryngotracheobronchitis*. Clinical differentiation of these conditions is often not possible. Direct laryngoscopic examination offers the best assistance both for direct visualization and for obtaining material for culture. *Spasmodic croup* produces an intermittent rather than progressive stridor. It often occurs in a child known to have had previous attacks and frequently responds to ipecac, sedatives and a moist atmosphere. *Bronchopneumonia* in infants may be characterized by dyspnea, hoarseness and stridor with retraction; this is especially true of acute bronchiolitis (p. 795). The stridor of *bronchial asthma* is principally expiratory and usually responds to a test dose of epinephrine. Retropharyngeal or peritonsillar abscess, mediastinal tumor, edema of the glottis, papilloma of the larynx, and tetany are other conditions which at times must be considered. The patient with an acute stridor should be examined with the direct laryngoscope and a culture taken from the upper trachea.

**Complications.** Complications vary in epidemics and with the promptness with which specific antitoxin therapy is instituted.

**Respiratory complications.** *Bronchopneumonia* is common, particularly in infants and especially in conjunction with the laryngeal form of diphtheria. It is usually caused by other organisms than *C. diphtheriae*. It occurs in over half of the fatal cases.

*Atelectasis* is associated particularly with laryngeal and tracheal lesions.

**Circulatory complications.** Circulatory failure is one of the most important complications. Early circulatory failure is the result of toxemia. Late circulatory failure occurs during apparent convalescence and is due to changes in the peripheral vasomotor mechanism. Cardiac failure is due to acute toxic myocarditis with or without superimposed damage to the intrinsic conduction system. It may occur at



any time during the disease, but most commonly between the fifth and twelfth days. The symptoms are fatigue, dyspnea and a weak, rapid pulse. At times the pulse rate is very slow, in some, but not all, instances caused by heart block. The heart sounds, particularly the first, become feeble, and often there is an associated gallop rhythm. Enlargement of the liver, epigastric pain, vomiting, cardiac dilatation, pallor and diminished blood pressure are characteristic findings. The electrocardiogram reveals an increased P-R interval and inversion of the T wave in the first and second leads.

**Renal complications.** *Albuminuria* is common during the febrile stage of the disease. It is due to toxic degenerative changes in the renal epithelium. In the more severe cases there is usually a mild generalized edema. The urine is diminished in volume and contains leukocytes, epithelial cells and hyaline casts, but seldom erythrocytes. Clinical evidence of *nephritis* exists in about 10 to 15 per cent of all cases; postmortem studies reveal renal changes in the majority of fatal cases.

**Paralysis.** Paralysis occurs in 10 to 15 per cent of all cases as the result of a toxic peripheral neuritis which is painless, usually persists for several days or weeks and may involve any muscle or group of muscles. The time of onset and the extent of the paralysis depend upon the severity of the disease and the time when antitoxin is given.

**Palatal paralysis** is the most frequent and usually the first type to appear. This usually appears during the first or second week of the disease. The patient cannot elevate the palate, the voice becomes nasal, and regurgitation of fluids through the nares occurs upon attempts at swallowing. Palatal paralysis occasionally is recurrent.

**Paralysis of the ocular muscles** is the second most frequent type, usually involving the muscles of accommodation. Inability to read may be the first evidence. Strabismus, dilatation of the pupils and ptosis of the eyelid may occur. Ocular palsy occurs usually during the third week or later.

Progressive **general paralysis**, involving the face, neck, trunk and extremities, may follow the palatal or ocular type. It usually occurs after the fourth week of the disease. Inability to raise the head is characteristic. The deep tendon reflexes, especially the patellars, become diminished or absent, though at first they may be increased. The superficial reflexes are frequently obtainable. The Guillain-

Barré syndrome has been observed in association with diphtheria.

**Paralysis of the phrenic nerve** occurs in the severest cases. Cough, dyspnea, thoracic breathing and cyanosis are present. The forced respiratory efforts induced by the patient's fear of suffocation are impressive. Respiratory paralysis usually occurs during the fourth to the eighth week of illness and may be fatal. It is often associated with pneumonia or myocarditis.

Paralysis of the pharyngeal and laryngeal muscles usually occurs during the third week and often results in accumulation of secretions and liquids in the lower respiratory tract. Aphonia obviously results.

Except for the unusual occurrence of monoplegia or hemiplegia resulting from thrombosis of a cerebral artery, there is complete recovery from diphtheritic paralysis. Though marked involvement usually lasts but one or two weeks, complete recovery may not occur for several months.

**Unusual complications** include pleurisy, arthritis, septicemia, empyema, thrombosis and embolism. Chronic laryngeal stenosis may follow tracheotomy, particularly when the incision is made too near the larynx (p. 780).

Occasionally there are relapses and recurrences of diphtheria, the latter usually being less severe than the original attack.

**Prognosis.** The fatality rate from diphtheria is 3 to 5 per cent. In general the prognosis depends on the stage of the disease when an adequate and properly administered amount of antitoxin is injected. When specific treatment is carried out on the first day of the disease, the mortality rate is about 0.3 per cent; on the third day, 4 per cent; on the fourth day, 12 per cent; and on subsequent days, 25 per cent. In young infants the fatality rate is higher, owing to the frequency of laryngeal involvement and of bronchopneumonia. Septic symptoms, cardiac involvement and hemorrhagic manifestations are unfavorable complications. The virulence of the organism and the location and extent of the membrane are important prognostic factors. Secondary infections obviously may influence the outcome.

**Prevention.** Immediate contacts should be subjected to Schick tests, nose and throat cultures and daily inspection. Penicillin should be given intramuscularly or orally.

Previously immunized contacts should receive a booster injection of fluid toxoid. Those with negative Schick tests and positive cultures should be treated as carriers. Those

with positive Schick tests and positive cultures should be treated as active cases with antitoxin (2000 units) and with either penicillin or erythromycin. Contacts not previously immunized, but showing positive Schick reactions, should later be actively immunized with toxoid.

When the foregoing regimen is not possible, it may be safer to provide passive immunity for the immediate contacts with a subcutaneous injection of 2000 units of antitoxin after proper testing for sensitivity. They should also receive penicillin.

Isolation of the patient should be maintained until two negative cultures on consecutive days have been obtained from the nose and throat. The first culture should not be taken until one week after the onset of the disease. If the second culture is positive, five days should elapse before another culture is taken. The child should not return to school for at least three weeks after the onset of illness.

**Active immunization** (see p. 139). The most important preventive measure is active immunization during infancy. Four types of antigenic substances have been successfully used for this purpose: toxin-antitoxin, toxoid, alum-precipitated toxoid and floccules.

**TOXIN-ANTITOXIN.** Although toxin-antitoxin is a good antigen, it has the following disadvantages: It is difficult to prepare; the mixture has a tendency to dissociate under certain conditions; and there is the possibility of sensitization to horse serum.

**TOXOID.** Ramon showed that diphtheria toxin is rendered nontoxic, but remains highly antigenic, when treated with a small amount of formalin. This product, known as anatoxin or toxoid, is widely used for active protection. It is more stable, easier to prepare, and is probably more effective than toxin-antitoxin.

**ALUM-PRECIPIATED TOXOID.** The precipitated toxoid is absorbed more slowly from the site of injection, thereby resulting in prolongation of the antigenic stimulus.

**FLOCCULES.** Floccules consist of the precipitate formed by a mixture of toxoid and antitoxin. It is widely used in England.

The practice of combining diphtheria and tetanus toxoids in the precipitated form has become common, and a "triple vaccine" which includes pertussis vaccine is also frequently used (see p. 139).

Early administration of antitoxin may interfere with production of immunity during an attack of diphtheria, a factor probably accounting for many of the second attacks. Hence it is advisable to Schick test the patient convalescing from the disease after the anti-

toxin administered therapeutically has been eliminated (six to eight weeks). If the reaction is positive, he should receive active immunization.

**Management of the carrier.** Diphtheria is one of the classic "carrier diseases." In about three fourths of the cases of diphtheria the organisms disappear from the upper respiratory tract within three weeks after the acute phase. In the remaining fourth, organisms may be retained for months. This type of carrier, known as the convalescent carrier, and the contact carrier, who has been closely associated with an active case, are epidemiologically important because they can be assumed to harbor virulent organisms. Only about 10 per cent of the carriers discovered by surveys harbor virulent organisms.

The incidence of convalescent carriers is decreased when treatment during the acute stage includes antitoxin and either penicillin or erythromycin.

The nonconvalescent carrier should be treated with penicillin or erythromycin. In persistent carriers foci of infection in tonsils, adenoids and sinuses should be eliminated. If the carrier is Schick positive, the operation should be deferred until he has been actively immunized. Penicillin should be given immediately before and after the operation.

Carriers should be isolated until virulent organisms are no longer demonstrated by culture.

**Treatment. General care.** The patient should be kept absolutely quiet in bed for at least two weeks. If the membrane extends beyond the surface of the tonsils or if antitoxin was not given until late in the course of the disease, this period should be extended. Daily physical examinations are essential. If there is the slightest doubt about the status of the circulatory system, an electrocardiographic tracing should be obtained. Intravenous injections of 10 per cent glucose solution (about 1 gm. per kilogram per day) are indicated to counteract the tendency to hypoglycemia associated with toxemia. A fluid or soft diet ample in vitamin content should be given. Saline throat irrigations may prove helpful, and an ice collar is comforting when the cervical lymph nodes are swollen. Codeine and aspirin may relieve suffering from sore throat or headache.

*Penicillin should be administered in addition to antitoxin, not as a substitute.*

**Specific treatment.** This consists in the early injection of an adequate amount of antitoxin. From 10,000 to 20,000 units of



antitoxin may be injected intramuscularly in cases of average severity. In the toxic, the complicated or the laryngeal case 20,000 to 40,000 units should be administered, one half intramuscularly and one half intravenously. If improvement in the local or general condition of the patient is not apparent within twenty-four hours, more antitoxin may be administered. Injected antitoxin neutralizes only the toxin free in the circulatory system and that which will be absorbed later; it has no effect upon that which is already bound by the body cells.

**SENSITIVITY TEST.** Preliminary testing of the patient for sensitivity to horse serum should always be made before antitoxin is administered. This is done by injecting 0.05 cc. of a 1:20 dilution of horse serum intracutaneously, or a similar amount of the antitoxin.

**DESENSITIZATION.** In the event of a local reaction (a wheal with an area of erythema appearing within ten to thirty minutes) or general reaction to the preliminary test, careful desensitization of the patient should be carried out.

Serial injections of diluted antitoxin as indicated below may be made at intervals of fifteen minutes, provided no reaction occurs. If a reaction occurs after an injection, one should wait an hour and then repeat the last dose which failed to cause a reaction.

1. 0.05 cc. of a 1:20 dilution of antitoxin, subcutaneously
2. 0.05 cc. of a 1:10 dilution of antitoxin, subcutaneously
3. 0.1 cc. of undiluted antitoxin, subcutaneously
4. 0.2 cc. of undiluted antitoxin, subcutaneously
5. 0.5 cc. of undiluted antitoxin, intramuscularly
6. 0.1 cc. of undiluted antitoxin, intravenously
7. The remainder of the therapeutic dose is slowly injected intravenously.

In a person known to be allergic to horse emanations extreme care should be used, or bovine antitoxin should be substituted. A syringe containing epinephrine chloride solution should always be available when antitoxin is being injected.

**Complications.** The management of complications, especially circulatory failure and paralysis involving the mechanisms of swallowing and respiration, is often difficult. The therapeutic principles for the management of diphtheritic myocarditis are the same as those in other types of acute myocarditis. Absolute rest is essential, and intravenous therapy is often necessary. Though once considered to

be contraindicated, digitalis is now thought to be of value in diphtheritic myocarditis and should be given if possible before there is evidence of decompensation. Oxygen, sedatives, a salt-poor diet and diuretics are indicated in cardiac insufficiency.

For shock and peripheral circulatory collapse, measures, such as the use of plasma, blood and ephedrine, designed to raise the blood pressure and to restore blood volume should be instituted. Cortisone should be used as recommended for circulatory failure in meningococcemia (p. 428).

Paralyses or weakness of the extremities requires rest, splinting and appropriate physical therapy. A polyethylene tube is useful for gastric feeding when muscles concerned with swallowing are involved. The respirator should be used early for respiratory paralysis, and maintenance of an adequate airway should be ensured. The emotional problems of both child and parent must be taken into account.

**Laryngeal diphtheria.** In addition to the general and specific measures, relief of obstruction to breathing is necessary. This is accomplished by aspiration, intubation or tracheotomy. When, and which method to use are often difficult decisions. If the patient can rest and sleep quietly in a moistened atmosphere, intervention may not be required. However, increasing restlessness, anxiety and increasing retractions of the suprasternal and substernal structures indicate increasing obstruction which needs relief. Cyanosis indicates that relief is urgent. Sedatives should be withheld during this period of observation, for they may conceal important symptoms.

In certain instances aspiration of the membrane by direct laryngoscopy may provide an adequate airway, but has the disadvantage that more edema and further obstruction may result from the manipulation.

Intubation, now seldom used, has obvious technical difficulties, and the intubated patient requires constant and skillful care.

Tracheotomy is now regarded as the most effective and safest method. It can be performed under local anesthesia, with slight risk of pneumomediastinum if no dissecting is done during the procedure (p. 780). One of its greatest advantages is the ease with which suction may be carried out. The tube can usually be removed after seven to ten days. During this period antibiotic therapy should be maintained.

## REFERENCES

- Beach, M. W., Gamble, W. B., Zemp, C. H., Jr., and Jenkins, M. Q.: Erythromycin in the Treatment of Diphtheria and Diphtheria Carrier State. *Pediatrics*, 16:335, 1955.
- Collins, S. D.: Diphtheria Incidence and Trends in Relation to Active Immunization with Some Comparable Data for Scarlet Fever. *Pub. Health Rep.*, 61:203, 1946.
- Committee on the Control of Infectious Diseases: Evanston, Ill., American Academy of Pediat., 1957.
- Edmond, D. G., and Allison, V. D.: Diphtheria in the Immunized, with Observations on a Diphtheria-Like Disease Associated with Non-toxigenic Strains of *C. Diphtheriae*. *J. Hyg.*, 49:205, 1951.
- Livingood, C. S., Perry, D. J., and Forrester, J. S.: Cutaneous Diphtheria: Report of 140 Cases. *J. Invest. Dermat.*, 7:341, 1946.
- Murphy, W. J., Maley, V. H., and Dick, L.: Continued High Incidence of Diphtheria in a Well Immunized Community. *Pub. Health Rep.*, 71:481, 1956.
- Schick, B.: Die Diphtherietoxin-Hautreaktion des Menschen als Vorprobe der prophylaktischen Diphtherieheilseruminjektion. *Munch. med. Wchnschr.*, 60:2608, 1913.
- Stimson, P. M., and Hodes, H. L.: *Common Contagious Diseases*. 5th ed. Philadelphia, Lea & Febiger, 1956, p. 90.
- Updyke, E. L., and Frobisher, M., Jr.: A Study of Bacterial Synergism with Reference to the Etiology of Malignant Diphtheria. *J. Bact.*, 54:619, 1947.

## PERTUSSIS

## (WHOOPIING COUGH)

**Definition.** Pertussis is an acute infection of the respiratory tract caused by *Hemophilus pertussis*. In its typical form the disease is characterized by a series of repeated spasmodic coughs ending in a forced inspiration (the whoop) and at times followed by vomiting. In mild cases neither the whoop nor the vomiting may be present.

**History.** De Baillou in 1578 wrote the first classic description of the disease. Bordet and Gengou (1906) described a small, coccoid bacillus, which they found in the sputum of active cases. Since then Shipley, Holt and others have experimentally reproduced the disease in the chimpanzee, and the MacDonalds, in susceptible children. Goodpasture and Gallavan, by an ingenious method of inoculating the chorio-allantoic membrane of the developing chick embryo, produced a pathologic lesion of the bronchial epithelium which is essentially that found in the human disease. Leslie and Gardner (1931) demonstrated the differences between the antigenic properties of the smooth (phase I) and the rough (phase IV) types of organism.

**Etiology.** *Hemophilus pertussis* is regularly present in the upper respiratory tract

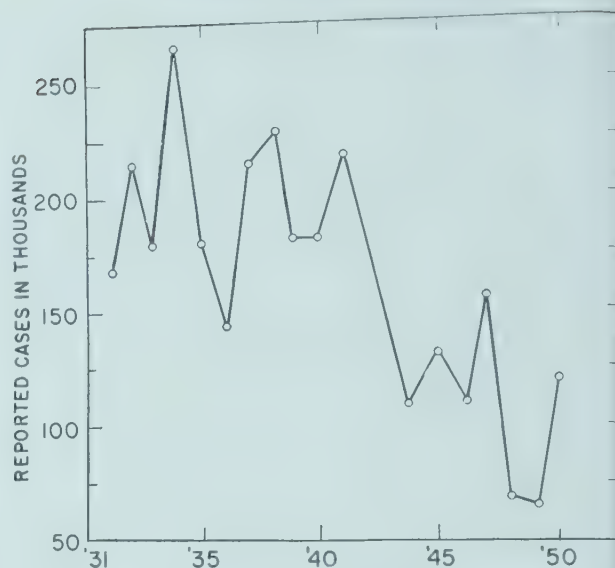


FIG. 115. Reported incidence of pertussis in United States (1931-50). (From Vital Statistics-Special Reports, Vol. 37, June 15, 1953.)

during the early stage of the disease. It is seldom found in persons without symptoms, but is occasionally recovered from immediate contacts of an active case.

**Epidemiology.** Worldwide in distribution, pertussis exists in most of the thickly populated communities, where it prevails epidemically at intervals of two to four years. Although it occurs throughout the year, the peak incidence occurs in May in the southern states, and during January and February in the northern ones. The communicability rate is high, approaching that of measles and of chickenpox. In family exposures it is between 75 and 90 per cent.

Pertussis may occur at any age. The youngest patient observed by the author was two weeks of age, the oldest seventy-seven years, but about 50 per cent of all cases occur under four years of age. Since 1935 there has been a definite decrease in the number of reported cases (Fig. 115). The incidence varies in different regions of the country and is higher in the female, especially above the age of ten years.

**Immunity.** Susceptibility to the disease is great. In contrast to the temporary immunity to measles and diphtheria, the newborn infant is usually highly susceptible to pertussis. Proved second attacks are rare, though they are often suspected clinically. Humoral antibodies, as demonstrated by the agglutinin titer and by complement fixation and mouse protective tests, appear during convalescence from an attack and after active immunization with a suitable antigen. The organism appar-



ently possesses more antigens in common with *H. bronchisepticus* than it does with *Hemophilus parapertussis*. Bacterial immunity to these three organisms appears to be more specific than does that to the toxin.

**Pathology.** The lesions are located principally in the bronchi and bronchioles, although changes are present in the trachea, larynx and in the nasopharyngeal mucosa. Numerous bacilli are entangled within the cilia of the columnar ciliated epithelium, which may be covered by a mucopurulent exudate. The essential lesion consists in necrosis of the basilar and midzonal epithelium, with a focal infiltrate of neutrophils and macrophages. An infiltrate of lymphocytes and, to a smaller extent, of neutrophils is present in the walls of the respiratory passages and extends outward into the interalveolar septums to produce a peribronchial interstitial pneumonitis. Plugs of mucus are occasionally present in the small bronchi, with resultant obstructive emphysema and atelectasis. Little exudate is found in the alveoli unless secondary infection has occurred. Bronchiectasis may result from the pulmonary lesions. Small foci of hemorrhage may be found in the brain, but whether a true encephalitis occurs is not established.

**Clinical Manifestations.** The incubation period varies from seven to fourteen days. The course of the typical disease is about six weeks, representing three stages: catarrhal, spasmodic and convalescent, each lasting approximately two weeks.

The clinical course of pertussis is extremely variable. The disease may exist in an extraordinarily mild form and may occur without vomiting, whoop or even spasmodic coughing. In two proved cases in nonimmunized persons the duration of cough was one week, and in a previously immunized patient only four days.

**Catarrhal period.** The onset is usually insidious with a mild cough, often nocturnal. During the next ten days the cough becomes progressively intense, spasmodic and diurnal. Coryza, sneezing and anorexia are frequently present, and hoarseness occasionally. In rare instances the disease resembles acute obstructive laryngitis.

**Spasmodic period.** Near the end of the second week the cough becomes aggravated. In the typical severe paroxysm a series of explosive efforts occurs, and the patient appears to strangle; the face becomes red and in some instances cyanotic; it temporarily appears swollen, and anxiety is apparent. The

paroxysm ends with a sudden forceful inspiratory crow or whoop, often followed by vomiting or by the coughing up or swallowing of large amounts of thick, tenacious, mucoid sputum. Sweating, congestion of the neck and scalp veins, mental confusion, convulsions and exhaustion may follow the spells of violent coughing. Infants may become so cyanotic that artificial respiration and oxygen inhalation are necessary. In small infants choking spells may replace the characteristic whoop. Activity, excitement, sudden changes in temperature or inhalation of irritating fumes tend to provoke paroxysms. Epistaxis often occurs, and subconjunctival hemorrhages and puffiness of the lower eyelids are common in severe cases.

**Convalescent period.** About the fourth week the number and severity of the paroxysms decrease, vomiting becomes less frequent, and the appetite returns. The hilar and basilar rhonchi disappear. An intercurrent infection, such as the common cold, may cause return of the major symptoms even to the point of resembling a new attack.

**Diagnosis.** Typical severe pertussis is readily recognized during the paroxysmal

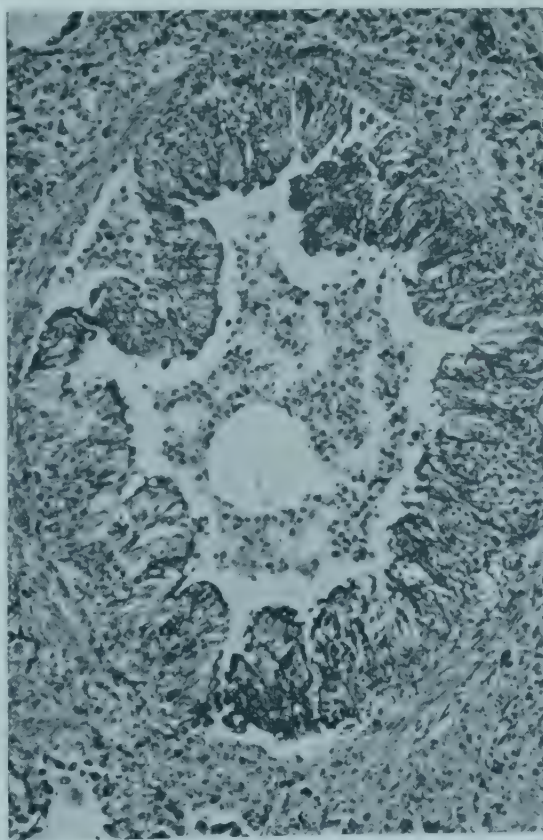


FIG. 116. Small bronchus from a case of human pertussis, showing necrosis, desquamation and inflammation in and beneath epithelium.  $\times 120$ . (Gallavan and Goodpasture: *Am. J. Path.*, Vol. 13.)

stage. In the early stage and in the atypical forms, however, it may be difficult to diagnose. The disease may be suspected when a progressive nocturnal cough becomes diurnal and continues in a spasmodic form, and when the physical examination reveals no obvious explanation of its cause. Since a history of exposure is often not elicited, it may be necessary to defer diagnosis until the cough becomes more characteristic. In such an instance the patient should be isolated and a culture taken.

The characteristic lymphocytosis appears during the late catarrhal or early paroxysmal stage. Average leukocyte counts range from 15,000 to 45,000 cells per cubic millimeter of blood, with a progressive increase in the number of lymphocytes; infrequently the count may be as high as 250,000. On occasion the lymphocytes may appear late, or the percentage of them may be equivocal.

The causative organism may be isolated from the upper respiratory tract by the cough-plate culture method or, preferably, by the nasopharyngeal swab method (see p. 387). Bacteriologic diagnosis is particularly helpful in the catarrhal stage and in the atypical case. A negative culture does not eliminate the possibility of pertussis.

Serologic tests for the presence of humoral antibodies include determination of the agglutinating titer, the complement-binding power or the mouse protective value. Since these all appear at the height or during the convalescent stage of the disease, they are of no value in early diagnosis.

**Differential Diagnosis.** A spasmodic cough similar to that of pertussis may be observed in tracheobronchitis, bronchiolitis and interstitial pneumonitis caused by a variety of agents. On occasion, epidemics of respiratory infection in infants and small children have so closely resembled pertussis clinically that it could be excluded as a diagnosis only by failure to isolate *H. pertussis* and by absence of the usual changes in the white blood cells.

Other clinical conditions which may resemble pertussis include sinusitis or adenoiditis with postnasal discharge, allergic rhinitis and bronchitis, endobronchial tuberculosis, foreign bodies in the larynx or trachea, the combination of tetany and upper respiratory infection and the respiratory infection associated with cystic fibrosis of the pancreas.

*Parapertussis*, caused by *Hemophilus parapertussis*, resembles mild pertussis so closely that it can be differentiated only by culture.

An attack of one disease does not protect against the other.

**Complications. Respiratory tract.** The most frequent complications are in the respiratory tract. *Otitis media* is common, especially in infants, and is usually caused by secondary invading organisms. *Bronchitis* is so common that it may really be considered a part of the disease. *Bronchopneumonia* is by far the most important complication and is usually interstitial in type. Atelectasis is common, resulting from blocking of a bronchus with mucus. Vesicular or interstitial emphysema occurs in practically all severe cases. Air may reach the cellular tissues of the mediastinum and extend into the soft tissues of the neck. Cases in which there is widespread subcutaneous emphysema are often fatal. Pneumothorax and empyema are infrequent complications. *Bronchiectasis* is more frequent than is generally recognized. A pre-existing *primary tuberculous* infection may be disseminated. *Persistent pneumonia*, *atelectasis* or *pulmonary fibrosis* are not uncommon sequels. Cardiac dilatation involving chiefly the right side of the heart is most commonly associated with a diffuse pneumonic lesion.

**Digestive tract.** Severe and prolonged vomiting may result in emaciation. Prolapse of the rectum and hernia may be secondary to straining. Diarrhea and abdominal distention occur occasionally and are difficult to manage. Ulceration of the frenum of the tongue may result from biting the tongue during the violent coughing spells; stomatitis may develop.

**Nervous system.** Convulsions are relatively common in infants. Tetany may occur when there is coexisting rickets and occasionally when there is alkalosis produced by loss of hydrochloric acid from excessive vomiting. Intracranial hemorrhages occur, but probably are infrequent as a cause of convulsions. Cerebral congestion and edema are common postmortem findings. Neurologic complications of pertussis include epilepsy, mental retardation, personality changes, spastic paralysis, myelitis, temporary or permanent visual disturbances, hemiplegia, monoplegia and aphasia. If caused by edema or congestion, they are temporary; if by hemorrhage or encephalitis, they may be permanent.

**Hemorrhages.** Hemorrhage is usually mechanical in origin, and occurs most often as epistaxis, hemoptysis and subconjunctival extravasations. The most serious type is intracranial.



**Prognosis.** From 1920 to 1953 the mortality rate from pertussis fell from 12.5 to 0.2 per 100,000 population (Table 68). Although this decrease began before the introduction of effective active immunization and antibiotic therapy, there is little doubt that these factors now play important roles.

Pertussis is conspicuous in that its mortality rate is higher among females than males. Pulmonary and cerebral sequels may constitute serious handicaps.

**Prevention.** (See also p. 138.) The infant should be carefully protected from exposure, but, when exposed, should receive passive immunization. This may be accomplished by the intramuscular injection of 2.5 cc. of gamma globulin prepared from hyperimmune human serums (Hypertussis). Prophylactic doses of one of the broad-spectrum antibiotics may also be given.

The exposed subject should be isolated for two weeks, and active immunization should be started.

During the active phase the child should be isolated for four to six weeks to protect susceptibles and to protect him from possible secondary infections responsible for many of the serious complications.

Active immunization of all infants should be started by the third month of age or earlier. This can be accomplished by the intramuscular injection of a triple vaccine (D.P.T.) (see p. 141). Because *H. pertussis* has certain allergic attributes, and encephalopathy has occasionally followed injection of the vaccine, care should be observed in immunizing infants subject to seizures. In such instances small doses of vaccine should be given.

**Treatment.** Good nursing care is essential, especially of the seriously ill infant. When vomiting is frequent, feedings should be given at shorter than usual intervals and should be reduced in quantity. Sudden changes in temperature should be avoided.

Patients with convulsions or persistent dyspnea should be placed in an oxygen tent, even though acyanotic. Strangling from excess mucus may be relieved by gentle suction and by placing the infant on his abdomen with the head lowered to facilitate drainage.

On occasion, sedation with phenobarbital may be indicated, but excessive sedation should be avoided. When convulsions occur, phenobarbital should be given intramuscularly (see p. 1122), and oxygen should be administered. Magnesium sulfate in doses of 0.05 ml. of a 50 per cent solution per pound

Table 68. Death Rates per 100,000 for Whooping Cough of Stated Ages; All Races, Both Sexes

Death Registration States, 1920-1953

Year	Total	Under 1 Year	1-4 Years	5-14 Years
1920.....	12.5	321.6	57.7	2.9
1930.....	4.8	163.5	23.4	0.9
1940.....	2.2	99.7	9.7	0.3
1950.....	0.7	23.7	2.5	0.2
1953.....	0.2	5.4	0.5	0.0

Vital Statistics: Special Reports, U.S. Department of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, 43, No. 7, May 21, 1956.

of body weight (0.1 ml. per kilogram) may be injected intramuscularly for its sedative effect, but not more often than twice a day.

Hyperimmune human serum (20 to 40 ml.), administered intravenously, or hyperimmune gamma globulin (5 to 10 ml.), injected intramuscularly, may be of benefit during the early stage of the disease. Immune rabbit serum (15 to 30 ml.) may also be used if the child is not sensitive to it.

The administration of pertussis vaccine or other antigens during the catarrhal period to a child previously immunized may be of limited value.

The tetracyclines and chloramphenicol are about equally effective against *H. pertussis* in doses of 25 mg. per pound of body weight per day (50 mg. per kilogram) divided into three or four doses. Chloramphenicol is not recommended for routine use because of its potential toxic effect on the bone marrow.

WILLIAM L. BRADFORD

#### REFERENCES

- Bradford, W. L.: The Pertussis Group; in Dubos: Bacterial and Mycotic Infections of Man. 2nd ed. Philadelphia, J. B. Lippincott Company, 1952, p. 536.
- Byers, R. K., and Moll, F. C.: Encephalopathies Following Prophylactic Pertussis Vaccine. *Pediatrics*, 1:437, 1948.
- Felton, H. M.: Pertussis: Current Status of Prevention and Treatment. *Pediat. Clin. North America*, 4:271, 1957.
- Scherp, H. W., Bradford, W. L., Day, E., and Allen, R. M.: Humoral Antibodies and Intradermal Reactions to Chemical Fractions of *Hemophilus Parapertussis*. *Am. J. Dis. Child.*, 87:724, 1954.
- Vital Statistics: Special Reports. U.S. Dept. of Health, Education, and Welfare, Public Health Service, National Office of Vital Statistics, 43, #7, May 21, 1956.

## PARAPERTUSSIS

**Definition.** Parapertussis is an acute infection of the respiratory tract caused by *Hemophilus parapertussis*. The disease resembles mild pertussis, from which it can be distinguished only by bacteriologic methods.

**History.** Eldering and Kendrick, and Bradford and Slavin, independently isolated the causative organism in 1937 from patients clinically suspected of having pertussis. The organism was isolated in 1933 in Copenhagen, though its clinical relationship was not recognized at the time.

**Etiology.** *Hemophilus parapertussis* is a small nonmotile, gram-negative coccobacillus, morphologically indistinguishable from *Hemophilus pertussis*. It has common antigenic fractions with both *H. pertussis* and *Brucella bronchiseptica*, but is identical with neither. *Hemophilus parapertussis* is virulent for mice, producing pulmonary lesions after intranasal inoculation that resemble those of experimental murine pertussis. A similar, though less potent, toxin is produced.

Specific humoral antibodies develop during the course of the disease, and may be demonstrable for at least three years. Second attacks have not been reported. An attack of either pertussis or parapertussis affords no immunity against the other disease. Active immunization against pertussis gives no protection against parapertussis.

**Incidence.** Bacteriologic and serologic evidence indicates that the disease is a common one, which is usually overlooked clinically. From a random sample of routine hospital admissions in Rochester (1954) 7 per cent of the children had agglutinative titers of 1:320 or higher, compared to 34 per cent against *H. pertussis*. The disease has been reported from widely separated areas, the greatest outbreak being reported by Lautrop, Copenhagen, 1954.

**Clinical Manifestations.** The incubation period is not definitely known, but is probably six to fifteen days. The onset is similar to that of pertussis, though it may be more abrupt. The cough is less severe, but is spasmodic and is sometimes followed by a whoop and less often by vomiting. The entire course of the disease is one to three weeks. The infection sometimes resembles tracheitis.

Complications are rare, though otitis media and bronchitis have been observed. Two deaths have been reported, in which the organism was isolated at autopsy.

**Treatment.** Active cases should be isolated. Therapy is usually only symptomatic.

Experimentally, polymyxin B, Terramycin and chloramphenicol are effective, though treatment with them is rarely indicated because of the usually mild course of the disease.

WILLIAM L. BRADFORD

## REFERENCES

- Bradford, W. L., and Slavin, B.: An Organism Resembling *Hemophilus Pertussis*, with Special Reference to Color Changes Produced by Its Growth upon Certain Media. *Am. J. Pub. Health*, 27: 1277, 1937.
- Eldering, G.: A Study of the Antigenic Properties of *H. Pertussis* and Related Organisms. II. Protection Tests in Mice. *Am. J. Hyg.*, 36:294, 1942.
- Lautrop, H.: Parapertussis: Bakteriologiske, Epidemiologiske og Kliniske under so gelser (with an English summary). Koberhavn, Ejnar Munksgaard, 1954.
- Zuelzer, W. W., and Wheeler, W. E.: Parapertussis Pneumonia: Report of Two Fatal Cases. *J. Pediat.*, 29:493, 1946.

## MENINGITIS

For Meningitis in the Newborn Infant, Tuberculous Meningitis, Lymphocytic Choriomeningitis and Cryptococcosis, see pages 344, 469, 550 and 564.

## PURULENT MENINGITIS

Generalized meningeal disturbances are caused by a variety of pathogenic agents. Nonsuppurative meningeal reactions include meningismus, serous or aseptic, including the meningitides produced by certain viruses, and syphilitic and tuberculous meningitis. Suppurative meningitis is characterized by a purulent exudate and is caused by the Meningococcus, Pneumococcus, Streptococcus, *Hemophilus influenzae*, Staphylococcus, colon bacillus and other pyogenic organisms. In early infancy purulent meningitis is frequently caused by some member of the colon group of organisms. The typhoid bacillus and various types of the Salmonella group may cause meningitis in infancy and childhood, and nonhemolytic strains of streptococci and of staphylococci are occasionally encountered. Less frequently, organisms closely related to *Listerella monocytogenes* have been isolated from meningeal infections in human beings, as have the Friedländer bacillus, *Pseudomonas pyocyanea*, *Aerobacter aerogenes*, *Lactobacillus lactis*, the Gonococcus and others. The clinical patterns of the various purulent meningitides are usually so uniform that the etiology can be established only by bacteriologic methods.



**Treatment.** As a result of studies by Alexander and others, a better understanding of the principles concerned in the selection and use of the antimicrobial agents has been established. Intrathecal therapy, except with penicillin and streptomycin in special but infrequent circumstances, has been abandoned, as has also the use of specific antisera, except for the infrequent use of *H. influenzae* antiserum.

The decrease in mortality from purulent meningitis has been attended with a significant increase in permanent and serious neurologic and mental sequels. The reduction of them is one of the problems of the moment. Best results can be expected when the causative agent is identified at the earliest possible moment so that an appropriate selection can be made of the antibiotic agents to be used. The principal reasons for the use of more than one chemotherapeutic agent are (1) to prevent or delay emergence of resistant variants, (2) to obtain a greater and more rapid bacteriostatic or bactericidal effect, and (3) to minimize the toxic effects of the agents.

Subdural collections of fluid in infants and small children whose clinical response to therapy is not satisfactory are relatively frequent. The exact significance of this complication is not defined, but it is the policy in many clinics to perform a subdural tap when the clinical course is not considered satisfactory. See page 1087 for therapy of subdural effusion.

The adjunct therapeutic role of adrenal cortical extract and of cortisone in the shock syndrome of meningococcal infection has re-emphasized the importance of recognizing the metabolic problems as well as the infectious one (see p. 428).

Whenever meningitis is suspected, a lumbar puncture should be performed immediately. The appearance of the fluid should be noted, a cell count made and a stained smear prepared from the sediment of a centrifuged sample. When examination of the smear suggests the Meningococcus, *H. influenzae* or the Pneumococcus, a portion of the sediment is mixed with the appropriate antiserum for the detection of capsular swelling (quellung test). The results of the gram stain usually suggest the appropriate media for culture, but it is well to inoculate the following: a rabbit blood agar plate, an Endo-agar plate, and a tube of thioglycolate broth, to be incubated at 37° C., normal atmosphere. In addition, an inoculated chocolate agar plate is incubated at 37° in a jar containing 10

per cent carbon dioxide. The remainder of the fluid is incubated at 37° C. One tube of cerebrospinal fluid should be used for chemical analysis for sugar, chlorides and protein. If available, a third tube is saved for viral studies or for future reference.

In the majority of instances proper antibiotic therapy can be instituted after the preliminary examination. When no organism is found in a purulent fluid, a combination of agents, for example penicillin, sulfadiazine and chloramphenicol, is prescribed. Subsequent changes may depend upon isolation of an organism, determination of its susceptibility in vitro and/or the clinical response to therapy.

#### MENINGOCOCCAL MENINGITIS AND MENINGOCOCCEMIA

(CEREBROSPINAL FEVER, EPIDEMIC CEREBROSPINAL MENINGITIS, SPOTTED FEVER)

**Etiology.** The Meningococcus (*Neisseria intracellularis*), first described by Weichselbaum (1887), is a gram-negative, biscuit-shaped diplococcus which in the body may be found extracellularly or intracellularly. It may be responsible for infection of the upper respiratory tract, septicemia, meningitis and other metastatic lesions. Any one or all three types of infection may occur in the same subject. The three immunologic types of the organism are as follows:

*Group I* includes the old types I and III, the strains of which cross-agglutinate one another and have a common polysaccharide (Scherp and Rake). Group I strains were the most prevalent ones in recent epidemics.

*Group II* includes most of the remaining strains, many of which are serologically nonhomogeneous. Group II strains are most often encountered in non-epidemic cases.

*Group IIa* includes a number of strains formerly included in group II (Branham).

Strains belonging to groups I and IIa are encapsulated and are definitely antigenic, exhibiting capsular swelling in the presence of group-specific antisera. Group II strains are less antigenic and do not show capsular swelling with antiserum. A few strains, chiefly nasopharyngeal, do not react serologically with any of the group antisera and are included in a "polyvalent" group. Certain toxic properties of the organism are related to an endotoxin (perhaps a nucleoprotein) which may be obtained from either living or dead organisms. Group-specific exotoxins have been described, but not proved.





FIG. 117. Purpuric eruption in meningococcal meningitis in a boy  $6\frac{1}{2}$  years of age.

**Epidemiology.** The disease is endemic throughout the world; epidemics occur infrequently. Since 1916 four distinct epidemics have occurred in the United States, with their peaks in 1917, 1929, 1936 and 1943.

Both endemic and epidemic infections occur most often in late winter and early spring months. Even in the civilian population, males are infected more often than females. About 45 per cent of all cases occur in children under fifteen years of age, about 25 per cent in those under five years, and about 15 per cent in infants under one year. The case fatality rates are highest in infants and in adults over fifty years of age.

About 3 per cent of the population are carriers during interepidemic periods, and the rate may increase to 70 to 80 per cent during an epidemic. Upper respiratory infections may be caused by the *Meningococcus*, and it may be that recovery from such an infection confers immunity against subsequent, more serious infections such as meningitis.

**Immunity.** One attack of the disease usually confers permanent immunity, but relapses and recurrences do occur. Probably the bactericidal power of the blood determines whether the organisms gain contact with the meninges. This mechanism of immunity, which would support the hematogenous theory of invasion, would also explain the low incidence of the disease during the first few weeks or months of life, when the infant may have protection from placentally transferred humoral antibodies.

**Pathology.** The mechanism of infection appears to be that of a bacteremia originating from a focus in the nasopharynx, the central nervous system being infected as a metastatic focus. In the blood the organisms multiply and elaborate toxin which aids in their dissemination and localization. Petechial and purpuric areas are characteristic of meningo-

coccal septicemia and occur in the skin and in the mucous and serous membranes. Hemorrhagic and purulent metastatic lesions occur in the peritoneum, pericardium, pleura, joints, eyes and epididymis. Vegetative endocarditis may also occur.

The lesion of the central nervous system is a purulent inflammation of the arachnoid and pia mater, usually heaviest over the parietal and occipital lobes and over the cerebellum. The infection may extend to the ventricles and may obstruct the various openings, resulting in obstructive hydrocephalus. The intracranial portions of various cranial nerves, particularly the optic, facial and auditory, may be involved. Throughout the brain perivascular foci of leukocytes, round cells and red blood cells may be found, as well as hemorrhagic and necrotic areas. This aspect of the infection is often overlooked.

When there is an extensive purpuric eruption and death occurs suddenly in the initial stage, there is often a massive hemorrhage into the adrenal glands (the Waterhouse-Friderichsen syndrome, p. 1185).

**Clinical Manifestations.** Several clinical types of meningococcal infection are recognized, the most important being the meningitic and the septicemic forms.

**Meningitic form.** Meningitis is the characteristic form of the disease. The onset is abrupt with general malaise, headache and irritability. Repeated and often projectile vomiting and prostration occur. Chills and convulsions, particularly in infants, are frequent. The temperature is high, the pulse is fast, and the respirations may be irregular. General muscular rigidity develops, especially in the muscles of the spine, producing the positive spine sign and even opisthotonos. Attempts to flex the neck produce pain and cause the patient to bend his knees and hips (Brudzinski's sign). If the leg is flexed at the



hip, the leg cannot be straightened at the knee (Kernig's sign). *The rigidity of the neck and back is frequently absent in very young infants.*

Disturbances of the sensorium are frequent, causing delirium, stupor and even coma. Petechial or purpuric skin lesions are an early characteristic manifestation (Fig. 117). Herpes labialis is common. The *tache cérébrale*, a conspicuous linear mark produced by drawing the fingernail across the skin, indicates a disturbance of the vasomotor mechanism. A tense or bulging fontanel, choking of the optic disks and a positive Macewen sign are evidences of increased intracranial pressure. The last sign is a "cracked-pot sound" elicited by percussion over a distended lateral ventricle. Urinary retention, constipation, anorexia and rapid loss of weight may be clinical features.

The fulminating meningitic form is characterized by an explosive onset and rapid course, terminating in death. The entire course may last only six to forty-eight hours. The attack usually begins with violent headache, chills or convulsions, vomiting and high fever. Delirium or coma appears early, and the skin manifestations are pronounced; massive hemorrhages in the adrenals are associated with profound shock and usually with sudden death (Waterhouse-Friderichsen syndrome, Fig. 118).

Infrequently a meningitic infection may exist for days or weeks before suggestive signs lead to a lumbar puncture. This mild form usually occurs in infants as a sporadic case or near the end of an epidemic. Diarrhea and vomiting are common symptoms. Irritability is usually noted, but meningeal signs may be equivocal. Increased tension of the fontanel or weakness of an external ocular

muscle may be the first clue. Relapses are common in this atypical form.

**Chronic meningitic form.** The clinical course may extend over a long period, usually characterized by emaciation, opisthotonos, hydrocephalus, cranial nerve palsies and by persistence of the Meningococcus in the cerebrospinal fluid. The usual outcome is death, but the illness may last for months. Such clinical patterns are usually the result of delay in starting therapy or of suppressive rather than curative therapy.

**Septicemic form.** The onset is usually sudden, with fever, chills, vomiting and weakness. Skin lesions (Figs. 117, 118) develop rapidly. If meningeal manifestations occur, they usually appear one to three days later. Most often if meningitis does not occur, the course of the septicemic form is rapid, ending either in death or, if therapy is effective, in recovery. In certain instances low grade fever with joint pains and muscular tenderness suggests a grippal infection or acute rheumatic fever, and the proof of meningococcemia by blood culture is unexpected.

**Diagnosis.** In the meningitic form this is by examination of the cerebrospinal fluid, which is usually under increased pressure. The total cell count may range from only a few cells to several thousand per cubic millimeter. The majority of the cells are polymorphonuclear; rarely, at the outset, mononuclear cells may predominate. The protein content is elevated, the sugar content is usually reduced, and the chloride content is diminished. Though purulent cerebrospinal fluid containing intracellular and extracellular gram-negative diplococci is strong evidence in favor of meningococcal meningitis, a definite diagnosis is made only from culture. Samples of the cerebrospinal fluid should be taken in three



FIG. 118. Fulminating type of meningococcemia in a male child 2½ years of age; onset 36 hours before admission, with vomiting and fever; 18 hours before admission extensive purpuric eruption began; death 8 hours after admission. Blood culture positive, Meningococcus type II. Nasal and cerebrospinal fluid cultures negative. One sibling had meningitis; another was found to be a carrier.



sterile tubes: one for cell counting and direct smear, and then placed in the incubator for future reference; the second for determinations of protein, chlorides and sugar; and the third for bacterial culture.

Cultures from the nasopharynx and from the blood are advisable before treatment is instituted. The white blood cell count is usually increased, sometimes as high as 20,000 to 30,000 per cubic millimeter, with a preponderance of polymorphonuclear cells.

**Complications.** *Hydrocephalus* and subdural collections of fluid (see p. 1087) are frequent and important complications. Inability to obtain fluid by lumbar puncture when it is readily obtained by ventricular puncture may be the first indication of basilar obstruction. Unless the obstruction is relieved, either death occurs during the acute period, or hydrocephalus develops.

Other nervous system complications include headache of varying degree which may persist for weeks or months, impairment of the intellectual faculties, chronic pachymeningitis, convulsions and various types of paralyses, spasticity and contractures.

*Otitis media* is common in the acute stage of the infection. Deafness is usually bilateral and usually permanent. It results from infection of the inner ear with or without associated middle ear infection.

*Ophthalmia* occurs in about 5 per cent of cases. There may be an optic neuritis, uveitis or purulent choroiditis which is usually embolic in origin and may lead to destruction of the eye. Fortunately these lesions are usually unilateral. Optic atrophy may result, particularly in association with hydrocephalus. Conjunctivitis is common, and corneal ulcers may develop unless proper precautions are taken.

Arthritis of the large joints may occur, especially during the first week of the disease. *Endocarditis* is most frequently observed in meningococcemia without meningitis. *Pneumonia*, an occasional complication, is usually caused by secondary invading organisms.

**Prognosis.** The death rate from meningococcal meningitis varies considerably in different epidemics. Before the introduction of specific serum therapy the case fatality rate was about 75 per cent; in patients treated with serum, it was about 20 to 30 per cent. The case fatality rate is now less than 10 per cent and is almost entirely limited to the group with adrenal inadequacy (Waterhouse-Friderichsen syndrome). However, recent surveys indicate that the incidence of neurologic

and psychotic sequels may be relatively high.

**Treatment.** Sulfadiazine is the drug of choice, but it is often given in combination with penicillin. Initially, while the cerebrospinal fluid is being examined, an intravenous infusion of equal parts of physiologic saline solution and 5 per cent glucose is started. After hydration has been established an initial dose of sodium sulfadiazine (50 mg. per kilogram) in a 5 per cent solution is introduced through the clamped tube for fifteen to thirty minutes. If the intravenous route is continued, the total daily dose is approximately 150 mg. per kilogram per day in three equal eight-hourly doses. If the oral route is possible, after the initial dose, 200 mg. per kilogram (100 mg. per pound) are given in four to six equally divided doses. In some instances the drug may be given through a gastric tube.

Sulfadiazine should be continued for seven to eight days, during which time blood levels should be determined, the first one twenty-four hours after beginning of therapy. A blood level of 8 to 10 mg. per 100 ml. is ideal and should produce a level of 60 per cent of this amount in the cerebrospinal fluid. Certain reactions to sulfadiazine may be expected, such as fever, rash, renal complications and peripheral neuritis. Determinations of hemoglobin, white blood cell counts and urinalyses should be made every other day. The occurrence of drug eruptions, severe leukopenia, hemolytic anemia or gross hematuria is generally an indication for cessation of sulfonamide therapy and change to penicillin. Adequate hydration and alkalization serve to minimize the likelihood of renal complications.

Procaine penicillin, 300,000 units twice daily for infants and twice this amount for older children, may be injected for the first two or three days.

In circulatory collapse and shock (Waterhouse-Friderichsen syndrome), as indicated by a fall in blood pressure and a decrease in the total eosinophil count, cortisone should be given intravenously (50 mg. for an infant and 100 mg. for a child). If, after one or two doses, there is a favorable response, the drug is continued orally in half the intravenous dose every four to six hours for two days.

Specific antitoxin is no longer used. Two examinations of the cerebrospinal fluid are usually adequate—one for diagnosis and one five to seven days later to check the therapeutic response.



**General supportive treatment.** Symptomatic care is often neglected. Adequate nutrition should be maintained; feeding by gavage is often necessary. Good nursing care serves to prevent the development of bed sores, stomatitis and the excessive drying of the conjunctivas in delirious patients. Distention of the bladder should be avoided, by catheterization if necessary. Excessive headache and restlessness may be relieved by administration of a suitable sedative, such as paraldehyde, or by spinal drainage. Excessive vomiting and fever quickly cause dehydration, which may be prevented or treated by the intravenous administration of 5 per cent glucose and saline. Solutions of amino acids are an efficient means of supplying nitrogen when parenteral feeding is required. Blood transfusions are indicated if the hemoglobin level is less than 9 gm. per 100 ml.

The convalescent period should be adequate to permit the child to regain his previous physical status. Before isolation precautions are discontinued it should be ascertained by culture of the nasopharynx that the child is not a carrier.

#### **STREPTOCOCCAL MENINGITIS**

The hemolytic *Streptococcus* is a relatively frequent cause of purulent meningitis, especially in the first six months of life. In the newborn infant the *Streptococcus* may gain entry to the blood through a superficial infection, such as an umbilical one, or may reach the meninges directly through an infected meningocele. In older children otitis media, mastoiditis, sinus thrombosis, erysipelas or suppurative lesions of the head and scalp may constitute the portal of entry.

Anatomically, there is a considerable amount of purulent exudate over the surface of the brain, resembling that of pneumococcal meningitis except that there is somewhat less fibrin in the exudate.

Streptococcal meningitis cannot be distinguished from other types of purulent meningitis except by bacteriologic examination of the cerebrospinal fluid, which should be made immediately if a meningeal infection is suspected.

**Treatment.** Treatment should be instituted at the earliest possible moment. Penicillin is the drug of choice and may be administered alone or in conjunction with a sulfonamide (see p. 402). Other antibiotics such as chloramphenicol and the tetracyclines are effective, but, except in the ex-

tremely rare instance of penicillin-resistant beta-hemolytic streptococci, penicillin is preferable. It is always desirable to obtain determinations in vitro of the relative sensitivity of the infecting organism to the various antibiotics.

Whenever there is any question of a significant mastoid involvement, the mastoid should be opened and, if indicated at operation, the dura exposed. If there is early and adequate medical and surgical care, the mortality rate should not be more than 10 per cent.

#### **PNEUMOCOCCAL MENINGITIS**

Pneumococcal meningitis is more prevalent among infants than among older children. The seasonal distribution is similar to that of pneumococcal pneumonia, of which it is an important complication. There may frequently be a history of pneumonia, upper respiratory infection or infection of the middle ear. Trauma, particularly fracture of the skull, may be a predisposing factor. Infection of the blood stream is frequent.

**Etiology.** Any of the specific types of *Pneumococcus* may be responsible for pneumococcal meningitis, but types III, V and XIV appear to be the more common ones.

**Pathology.** The lesions of the brain and meninges resemble those produced by the *Meningococcus*. The heavy exudate of pus and fibrin may be more abundant over the anterior lobes and less marked over the basilar areas of the brain. For this reason spinal rigidity and opisthotonos may be slight or absent. The spinal meninges are usually only slightly involved.

**Diagnosis.** The clinical manifestations do not differ from those of purulent meningitis caused by other pathogenic bacteria. The diagnosis depends upon the bacteriologic findings. The cerebrospinal fluid is purulent, containing many polymorphonuclear cells and gram-positive lancet-shaped diplococci which are usually easily recognized on direct smear and easily cultured on blood-agar medium. The sugar and chloride contents of the cerebrospinal fluid are decreased and the protein increased.

**Complications.** As with other purulent meningitides, the decreasing case fatality rate has been associated with a definite increase in serious complications, many of which are permanent and severely handicapping. There may be a variety of pneumococcal lesions outside the nervous system such as empyema,

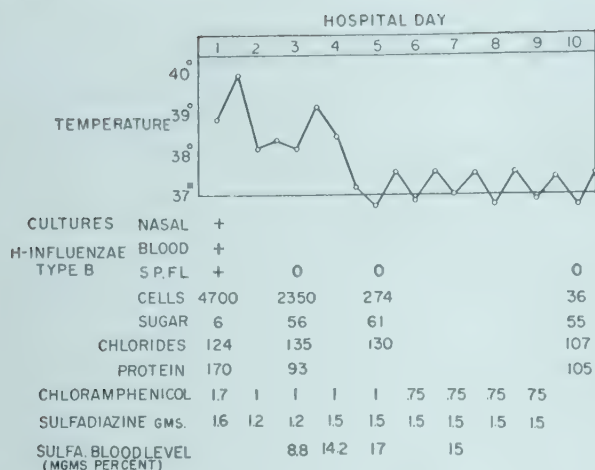


FIG. 119. L. C., female, 6 months of age. *H. influenzae* meningitis. Onset 5 days before admission, with cold and diarrhea (2 siblings with "grippe"). One day before admission, fever, vomiting, irritability, stiff neck, full fontanel. No organisms seen in initial smear of cerebrospinal fluid; hence 3 million units of aqueous penicillin were injected daily for 2 days. Complete recovery.

pericarditis, peritonitis and arthritis, but the more frequent and usually more important ones involve the central nervous system.

**Prognosis.** Most patients can and do survive. Both survival and the extent of residual damage are related to the promptness of instituting therapy and to its adequacy.

**Treatment.** Penicillin is the drug of choice, but many clinicians also use sulfadiazine in conjunction with it.

Because the blood-brain barrier is higher for penicillin than for sulfadiazine or chloramphenicol, total doses of two to twelve million units of the aqueous crystalline form are given daily by continuous intravenous drip for the first three days. After this, procaine aqueous penicillin is continued intramuscularly in doses of one million units twice daily.

Sulfadiazine is given in an amount to maintain a blood level of 10 to 15 mg. per 100 ml. (see Meningococcal Meningitis, p. 428).

Chloramphenicol is sometimes added to the penicillin-sulfadiazine regimen. The total daily dose is 100 mg. per kilogram intramuscularly, or 200 mg. orally.

All therapy is discontinued after eight to ten days, provided the clinical and cerebrospinal fluid findings are satisfactory. There is no indication for specific antiserum therapy.

Adequate fluid intake must be maintained. Sedation should be prescribed as indicated, but depression of the respiratory mechanism

should be avoided. Early surgical drainage of foci, such as those of otitis media and mastoiditis, is indicated.

### INFLUENZAL MENINGITIS

**Etiology.** *Hemophilus influenzae* is a common cause of bacterial meningitis in infants. The strains causing meningitis are serologically related and are included in the group termed type b. In most instances the disease is preceded or accompanied by an infection of the upper respiratory tract which frequently includes involvement of the middle ear. Influenzal meningitis is essentially a disease of infancy, the peak of incidence occurring between six and twelve months of age. It is rare during the first two months of life and infrequent after the fourth year.

**Clinical Manifestations.** The clinical pattern of influenzal meningitis is essentially that of any other type of purulent meningitis. Though bacteremia is usually present, skin manifestations are rare. The cerebrospinal fluid rapidly becomes purulent, and in most instances the organism is readily identified. Infrequently in untreated cases for a short time and frequently when therapy has been suppressive rather than curative, the cerebrospinal fluid changes may be those of a lymphocytic type of response simulating tuberculous meningitis. The presence of gram-negative, pleomorphic, coccobacillary organisms in the direct smear of the sediment should suggest *H. influenzae*. Direct typing of the organisms from the cerebrospinal fluid may be made. The organism is easily cultured on a medium consisting of chocolate agar.

**Complications.** Many complications of influenzal meningitis, but not all, seem to be related to delay in starting therapy, inappropriate selection of therapeutic agents or the use of appropriate agents in too small amounts for too short a time. Complications of the central nervous system include paralysis, mental retardation, nerve deafness and hydrocephalus. Subdural collections of fluid appear to be a factor in the production of some of these (see pp. 428, 1087).

**Prognosis.** Before the advent of effective antibacterial agents the mortality rate approximated 95 per cent; now the recovery rate should be about 95 per cent. However, the incidence of serious and permanent complications has increased markedly.

**Treatment.** A combination of chloramphenicol and sulfadiazine appears to be the therapy of choice. After an initial intravenous administration of 50 mg. of chloram-



phenicol per kilogram of body weight (25 mg. per pound) a dose of 100 mg. per kg. per day is given orally in four equal doses or through a nasal polyethylene catheter if the infant will not swallow. However, if the child is vomiting or if there is any question of gastrointestinal absorption, administration by the intravenous route should be continued at intervals of six hours in individual doses of 25 mg. per kilogram.

Sulfadiazine (0.2 gm. per kilogram per day) orally will usually maintain the desired blood level of 10 to 12 mg. per 100 ml.

Therapy should be continued for at least five to seven days after the temperature has become normal.

Streptomycin and sulfadiazine are also effective, but not more so than chloramphenicol. The recommended dose of streptomycin is 40 mg. per kilogram of body weight (20 mg. per pound) per day in four intramuscular injections. Streptomycin should not be administered for longer than one to two days, owing to danger of vestibular damage. The administration of sulfadiazine should be continued and chloramphenicol added as indicated above.

There now appears to be little indication for the use of specific antiserum. General therapeutic measures are enumerated under Meningococcal Meningitis (see p. 429).

#### STAPHYLOCOCCAL MENINGITIS

Staphylococcal meningitis is usually blood borne from such primary foci as cutaneous lesions (especially in newborn), otitis media, mastoiditis, sinusitis or sinus thrombosis. The infection may also be introduced at the site of a wound or from a surgical operation on the brain or meninges. There is widespread inflammation of the pia with a heavy accumulation of pus and frequently localized abscesses of the brain and meninges.

*Diagnosis* depends upon examination of the cerebrospinal fluid, in the sediment of which the organisms are usually numerous. The culture is confirmatory.

Prior to 1938 only nine recoveries had been reported; now the recovery rate is approximately 40 per cent.

*Treatment.* A combination of penicillin, sulfadiazine and chloramphenicol constitutes good initial therapy and is adequate in most instances. Aqueous penicillin in a daily dose of 12,000,000 units should be given intravenously for three to five days and continued intramuscularly in doses of one million units twice daily for another week. Sulfadiazine

and chloramphenicol are used as prescribed for *H. influenzae* meningitis.

Owing to the high incidence of strains of *Staphylococcus aureus* resistant to all available antibiotics, sensitivity studies should be obtained on the initial culture and repeated if the infection is not controlled or if there is a relapse. Under such circumstances antibiotics shown to be effective against the particular strain by tests in vitro should be selected. These might include erythromycin, novobiocin, and even bacitracin if no other agent is effective.

WILLIAM L. BRADFORD

#### REFERENCES

##### *Purulent Meningitis*

- Alexander, H. E.: Treatment of Pyogenic Meningitis. A. Research Nerv. & Ment. Dis. Proc., 34: 3, 1956.
- Idem: Guides to Optimal Therapy in Bacterial Meningitis. J.A.M.A., 152:662, 1953.
- Bahrenburg, J. H., and Ecker, E. E.: Meningitis Due to Organisms Belonging to the Salmonella Group. J. Infect. Dis., 60:80, 1937.
- Bergstrand, C. G., Fahlen, T., and Thilen, A.: A Follow-up Study of Children Treated for Acute Purulent Meningitis. Acta paediat., 46:10, 1957.
- Bradford, W. L., and Kelley, H. W.: Gonococcal Meningitis in a Newborn Infant, with a Review of the Literature. Am. J. Dis. Child., 46:543, 1933.
- Finegold, S. M., Bradley, J. G., Campbell, M. K., and Greenberg, A. J.: Listeria Monocytogenes Meningitis. Arch. Int. Med., 93:515, 1954.
- Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children, with Special Reference to Age-Incidence and Bacteriologic Diagnosis. J. Pediat., 2:696, 1933.
- Jawetz, E.: Antibiotic Synergism and Antagonism. A.M.A. Arch. Int. Med., 90:301, 1952.
- Kerman, W. Z., Perlstein, M. A., and Levinson, A.: *Bacillus Pyocyaneus* Meningitis Following Pneumoencephalography. Am. J. Dis. Child., 65:912, 1943.
- McKay, R. J., Jr., Ingraham, F. D., and Matson, D. D.: Subdural Fluid Complicating Bacterial Meningitis. J.A.M.A., 152:387, 1953.
- Moll, F. C., and Warrington, W.: Treatment of Purulent Meningitis with Terramycin (Oxytetracycline) and Sulfadiazine. J. Pediat., 44:541, 1954.
- Rog, T. E., and others: Studies on the Absorption of Chloramphenicol in Normal Children in Relation to the Treatment of Meningitis. Antibiotics and Chemotherapy, 2:505, 1952.
- Stimson, P. M., and Hodes, H. L.: Common Contagious Diseases. Philadelphia, Lea & Febiger, 1956.

##### *Influenzal Meningitis*

- Koch, R., and Carson, M. J.: Management of Hemophilus Influenzae Type B. Meningitis; Analysis of 128 Cases. J. Pediat., 46:18, 1955.

*Staphylococcal Meningitis*

Finland, M.: *Antibiotic Therapy* by Henry Welch.  
New York, Blakiston Co., 1954.

**TETANUS**

(LOCKJAW)

The systemic manifestations of tetanus are caused by the powerful exotoxin, liberated during the actively growing phase, of *Clostridium tetani*, a spore-forming organism. Like diphtheria, the infection remains localized. Infection is almost always acquired from a contaminated wound.

**History.** Tetanus was produced experimentally before the organism was isolated in pure culture. In 1884 Carle and Rattone transmitted it to rabbits by inoculation of material from an acne pustule that represented the nidus of a fatal human case, and Nicolaier produced a tetanus-like disease in mice, guinea pigs and rabbits by inoculating them with suspensions of dirt. Nicolaier suggested that the disease was carried by organisms that multiplied locally and produced a strychnine-like poison. Kitasato (1889) isolated the organism in pure culture by heating pus to a temperature of 80° C. for forty-five to sixty minutes. Von Behring and Kitasato (1890) demonstrated that tetanus toxin was antigenic, capable of producing antitoxin.

**Etiology.** *Clostridium tetani* is an anaerobic, spore-bearing organism, widely distributed in soil in many parts of the world. The bacillus is frequently found in the intestinal tracts of herbivores and, at times, of man. Under suitable conditions the tetanus bacillus produces several poisons: a lysin for red blood cells, a substance injurious to leukocytes and a neurotropic toxin (tetanospasmin) which produces muscle rigidity and spasms. Unlike diphtheria toxin, tetanus toxin produces no skin reaction suitable for the assessment of immunity.

**Epidemiology.** Tetanus occurs most frequently in areas where soil contamination is heavy and standards of cleanliness and care of wounds are poor. It is rare in the newborn infant when aseptic obstetrics is practiced, but otherwise it constitutes a serious problem. In 1950, 486 cases were reported in the United States with 336 (69 per cent) deaths. During World War II active immunization of the personnel of the armed services with toxoid almost completely prevented its occurrence (eight cases with three deaths).

**Pathogenesis.** There is no typical wound that gives rise to tetanus. It may result from the most trivial scratch or insect bite, and the portal of entry is often not apparent. Injuries most likely, however, to lead to

tetanus are deep puncture wounds, because they afford ideal anaerobic conditions, and crushing wounds and burns, because they provide necrosis of tissue. The site of infection has been reported in the tonsil, the alimentary tract and in ocular and aural lesions. A number of cases have resulted from the use of contaminated catgut and serologic products. Though tetanus occasionally results from smallpox vaccination, it is practically always due to improper care of the secondarily infected lesion rather than to contaminated virus.

The manner of absorption and the mode of action of the toxin have been the subject of considerable controversy. There are two main hypotheses: (1) that the toxin is absorbed at the motor nerve endings and reaches the anterior horn cells of the central nervous system by means of the axis cylinders; and (2) that the toxin is absorbed by the lymphatics and distributed to the central nervous system by the arterial blood supply. After the toxin has become fixed to nerve tissue, it apparently is not easily neutralized by specific antitoxin, but it is in its free, circulating form.

**Immunity.** Immunity to tetanus may be natural or acquired. Mammals vary in their susceptibility. The blood of naturally resistant animals contains practically no antitoxin; hence their immunity cannot be humoral. Persons of all ages are susceptible. The proportion of cases among adults has gradually increased. In Massachusetts (1954) more than half of those over twenty years of age had antibody levels of less than 0.01 unit; women had lower levels than men. The newborn has placentally transmitted antitoxin, but it is usually inadequate for protection.

The toxin is highly antigenic, and the prophylactic and therapeutic use of its specific antitoxin is of tremendous practical importance. It acts by neutralizing toxin, but does not prevent the germination of spores or multiplication of the bacilli in tissue. Modification of the toxin into toxoid by treatment with formalin affords a potent antigen for the production of active immunity.

**Clinical Manifestations.** The incubation period is usually five to fourteen days, but may be prolonged to several weeks in mild infections or when the course has been modified by antiserum.

The clinical manifestations of tetanus are usually generalized, but occasionally may be localized to the area of injury. Localized manifestations are usually the result of in-



complete neutralization of toxin elaborated in the area of the injury with complete neutralization of that in the blood. The action of the toxin in such instances is on the motor end organs, resulting in localized spasm and rigidity.

The onset of the generalized form is usually insidious, with increasing degrees of muscle stiffness, especially those of the jaw and neck. Within forty-eight hours the disease is well defined, and difficulty in opening the mouth (trismus) is evident. Difficulty in swallowing, restlessness, hyperirritability, headache, chilliness, and pain in the extremities are early symptoms. A clonic convulsion, caused by the effect of toxin on the anterior horn cells, is often the first symptom. Rigidity of the abdominal muscles may suggest the possibility of an acute intra-abdominal lesion.

The spasm is characteristic. The body exhibits boardlike rigidity, while the head is drawn back in pronounced opisthotonos with legs and feet extended. The arms are stiff and the fists clenched. The spasm of the facial muscles results in a fixed expression (the sardonic grin, or *risus sardonius*). The eyebrows are raised, and the mouth is distorted by the downward and outward drawing at the angles. The patient is apprehensive. The spasms at first are intermittent and often separated by apparently complete relaxation. Later the periods of relaxation are less obvious, and the seizures become painful. Intramuscular hemorrhage may result from violent contractions. Cyanosis and asphyxia may result from paroxysms affecting the respiratory or laryngeal muscles. Convulsions may be precipitated by the slightest stimulus, such as handling the patient, attempts to drink or even by visual or auditory stimulation. Profuse sweating is common. Retention of urine may be due to spasm of the urethral muscles. In rare instances spasms may be sufficiently severe to cause compression fractures of the spine; hence roentgenographic examination of the spine of patients who have had unusually long and severe spasms should be obtained before they are permitted out of bed.

Fever is usually of a low grade, except that there is often a marked elevation during the terminal stage. Respirations are variable in rate and depth, and the pulse rate is increased. The cerebrospinal fluid is normal, but under some increase of pressure. There is usually a moderate leukocytosis.

**Diagnosis.** The diagnosis usually offers little difficulty. The history of a wound and the characteristic type of muscular spasticity,

particularly of the jaw, are fairly conclusive. In infants other convulsive disorders may be confusing. Spasms due to strychnine rarely involve the jaw muscles and are interspersed by periods of more complete relaxation. Tetany may be recognized by chemical studies of the blood. Meningitis may be identified by examination of the cerebrospinal fluid. Tetanus is probably the only condition likely to be confused with rabies. The history of a bite, mental excitement, constant pharyngeal and laryngeal spasm, absence of trismus, and pleocytosis of the cerebrospinal fluid are distinguishing features of rabies. Local causes of stiffness of the jaw, such as enlarged cervical lymph nodes and retropharyngeal abscess, should easily be recognized.

**Prognosis.** The general mortality rate is still high (20 to 50 per cent). Fatal cases usually terminate within a week or so and are more frequent after short incubation periods. A period of less than forty-eight hours between the first symptom and the first spasm is prognostically unfavorable. Uncontrolled seizures, respiratory complications and grossly contaminated wounds contribute to an unfavorable outcome. Mortality rates are highest in newborns and in the aged. Most deaths are precipitated by respiratory conditions such as obstruction by secretions, asphyxia from laryngeal spasm, prolonged anoxia, atelectasis and pneumonia. The judicious use of tracheotomy appears to have facilitated the management of these complications.

**Prevention.** The prevention of tetanus consists to a considerable degree in the prevention of injuries; it is, in part, an educational endeavor, which should include children. Most communities have legislation to control the sale of fireworks. Competent surgical care of wounds is essential.

The injection of antitoxin within a few hours of the receipt of a wound produces *passive immunization* and prevents tetanus or lengthens the incubation period and results in a milder type of disease.

The generally recommended prophylactic dose of antitoxin is 1500 to 5000 units injected subcutaneously after a preliminary skin test to determine sensitivity to the serum, but some give as much as 10,000 to 20,000 units. The difficulty of deciding when antitoxin should be used, the fear of anaphylaxis, the induction of serum sensitivity and the occurrence of tetanus even when passive immunization has been carried out are all practical objections to this form of prophylaxis.

Glaser emphasizes the advantage of the use of bovine antitoxin, particularly for the passive immunization of allergic children. The administration of penicillin for two or three days following a severe injury may be an *additional* preventive factor because of its bactericidal effect.

When antitoxin is given to a child who has not had active immunization, it should be considered obligatory to give tetanus toxoid within the next few weeks.

*Active immunization* offers an excellent possibility of reducing the incidence of tetanus. Alum-precipitated, aluminum hydroxide-absorbed, and fluid toxoids are available. Though each is definitely antigenic, alum-precipitated and aluminum hydroxide-absorbed toxoids produce more durable immunity than does fluid toxoid. On the other hand, fluid toxoid produces a more rapid secondary response and therefore is the choice for a booster injection after a wound.

For basic immunization, three primary injections of toxoid at intervals of one to three months are advised, with subsequent booster injections (see p. 141). A severely wounded immunized person, or one in whom the last injection of toxoid was made four or more years previously, is afforded maximal prophylaxis by the simultaneous injection of both antitoxin and fluid toxoid in different extremities.

**Treatment.** Constant attention to the general care and supportive measures are essential. The patient should be kept in a quiet room, and external stimulation should be avoided. Oral and gastric feeding should be deferred until the dangers of vomiting and aspiration no longer exist. Proper and immediate surgical care of the wound is important.

**Sedatives.** The ideal sedative would be one capable of controlling spasms and convulsions without respiratory depression. Unfortunately, this requirement is not easily met. Paraldehyde given rectally is one of the safest and most effective sedatives. Avertin (tribromoethanol amylene hydrate) administered rectally in doses of 10 to 15 mg. per kilogram (5 to 7 mg. per pound) is effective, but, since it is a respiratory repressant, its effect must be carefully watched. Spivey considers phenobarbital in individual doses of 15 to 30 mg. by gavage to be the most satisfactory sedative in tetanus neonatorum.

Curare and related drugs should be used only when the spasms cannot be controlled

by the usual measures, and then only by experienced personnel.

Since death is often related to respiratory obstruction, the performance of tracheotomy may be lifesaving and should be carried out when pulmonary ventilation is impaired. Oxygen and the use of the respirator may be required.

Penicillin should be given every twelve hours for its probable effect on *Cl. tetani* and to control secondary infection. Other antibiotics should be given when indicated to control specific secondary invaders.

**Serum therapy.** Antitoxin is the only specific agent. Fifty thousand units intramuscularly and 50,000 units intravenously should be given immediately. After the intravenous administration of antitoxin 5000 to 10,000 units may be infiltrated around the wound in preparation for wide excision, if indicated. The wound should be left open. Firor advises daily intramuscular injections of 5000 units to assure the maintenance of sufficient humoral antibody.

Active immunization should be started during convalescence.

WILLIAM L. BRADFORD

## REFERENCES

- Brooks, V. B., Curtis, D. R., and Eccles, J. C.: Mode of Action of Tetanus Toxin. *Nature*, 175:120, 1955.
- Forbes, G. B., and Auld, M.: Management of Tetanus. *Am. J. Med.*, 18:947, 1955.
- Shackleton, P.: The Treatment of Tetanus. Role of the Anaesthetist, *Lancet*, 2:155, 1954.
- Symposium on Tetanus: Proc. Staff Meet., Mayo Clin., 32:141, 1957.

## BACILLARY DYSENTERY

### (SHIGELLOSIS)

Bacillary dysentery is caused by a variety of closely related organisms and involves chiefly the large bowel. It is characterized clinically by fever, general toxicity, abdominal pain, tenesmus and frequent loose stools containing mucus, pus and blood.

**History.** Hippocrates is said to have distinguished diarrhea from dysentery by associating the former with the frequent passage of liquid stools and the latter with the passage of bloody stools. In 1898 Shiga isolated a gram-negative bacillus from the feces and intestinal wall of dysenteric patients in Japan. His work is an outstanding example of the use of the agglutination reaction of the patient's serum to discover the causative agent of a disease. In 1900 Flexner isolated several strains of dysentery-producing organisms in the Philippines, and in 1915 Sonne described *Shigella sonnei*, an organism which he isolated in Denmark.



**Etiology.** The *Shigella* group of organisms (*Enterobacteriaceae*) is an important cause of diarrhea. Organisms of this genus are nonmotile, gram-negative, nonencapsulated and nonspore-forming rods. All are easily killed by heat, sunlight and ordinary disinfectants. Although earlier methods of differentiation were based upon biochemical reactions, serologic methods are now more generally used.

Upon the basis of biochemical and antigenic characteristics, Cheever suggests the following classification of the more important *Shigellae*:

Group A. *Shigella dysenteriae* (Shiga) is the most important member. It is prevalent in tropical countries and in East Asia and is occasionally encountered in the United States, where the case fatality rate is approximately 10 per cent.

*Shigella ambigua* (the Schmitz bacillus) has been chiefly associated with institutional outbreaks in the United States. Its distribution is worldwide.

*Shigella large sachsii*, described chiefly by Sachs in India, has been reported from North Africa and the United States.

Group B. *Bacillus dysenteriae* Flexner (Flexner bacillus), also called *Sh. paradyenteriae*, causes a significant proportion of dysentery infections in this country. It contains at least six different type-specific strains; in addition, many strains contain secondary antigens common to others.

Group C. *Bacillus dysenteriae* Boyd was first isolated in India in 1930; at least seven specific types of the organism have now been identified.

Group D. *Shigella sonnei* (Sonne-Duval bacillus), one of the important causes of diarrhea in the United States, is worldwide in distribution. Two antigenic types have been recognized.

*Shigella alkalescens* and *Sh. madampensis*, sometimes considered to be pathogenic, are regarded by some authorities as members of the genus *Escherichia*.

**Epidemiology.** The prevalence of shigellosis varies with such factors as climate, living conditions and age. Studies of the presence of shigellae in the normal population reveal rates varying from 0.04 per cent in New York City to 20 per cent in certain southern areas of the United States. In a series of 2865 routine admissions to a children's hospital (Cincinnati, 1954-56; Cooper) rectal swab cultures were positive for *Shigella* in eighty-eight, for *Salmonella* in eighty-five, and for pathogenic *E. coli* in 188. Practically all patients with any of these organisms had diarrhea.

Explosive epidemics are not common, but small outbreaks are frequent. Crowding in institutions and summer camps under conditions of poor sanitation offer favorable conditions for an outbreak. Poor refrigeration

and food contaminated with soil or by flies that have access to human excrement are important factors. Unlike typhoid, bacillary dysentery is seldom water-borne. There is some evidence that there is a lesser tendency to a peak incidence in summer and fall, that the disease is becoming more urban than rural and that the incidence among older children is increasing.

Shigellosis is almost entirely a disease of human beings. The mode of spread is from man to man in which the carrier is highly important. In untreated cases the carrier state may last for a month. Ordinarily carriers of the Shiga type are more persistent than those of the Flexner type. The organism may be excreted intermittently, a factor which adds to the difficulty of detecting it by culture.

*Shigella* infection varies with age. Its prevalence is low during the first six months of infancy, increases during the next six months to a level which is maintained for several years. The disease is often severe, frequently fatal, in early infancy, but less severe and often mild after three years of age.

**Pathology.** Unlike typhoid fever, dysentery is a local infection which chiefly involves the colon. In about half or less of the cases the lower ileum is affected, where the lesions are usually less severe.

The mucosa of the intestine is thickened, hyperemic, inflamed and edematous; it may be covered by patches of fibrinopurulent exudate. Shallow ulcers are present which vary greatly in size; these seldom penetrate below the submucosa, and perforation is rare. Healing of the ulcers is usually complete. The mesenteric lymph nodes are somewhat enlarged, but the spleen is not involved.

**Clinical Manifestations.** The incubation period may vary from a few hours to eight days, but is most frequently two to four days. The symptoms and signs are readily explained by the pathologic changes. The pain, tenesmus and diarrhea result from acute inflammation of the bowel; the mucus, pus and blood, from inflammation of the bowel epithelium. Since the disease is characteristically localized, septicemia and splenic enlargement are rare. Toxic encephalitis and peripheral neuritis occur occasionally in *Shigella* infections, and somewhat less often in Flexner infections.

The clinical severity of dysentery may vary from extreme mildness to such severity that death occurs on the first day. In the *mild* cases there may be practically no constitutional symptoms. Instances with little or no diarrhea have been recorded.

The onset of the usual case of dysentery is sudden with fever, vomiting and frequently abdominal pain. The temperature is usually high, 102° to 105° F. Meningeal signs are frequent. The passage of frequent, loose, thin stools within six to twenty-four hours of the onset which later contain mucus, pus and streaks of bright red blood suggests the diagnosis. The number of stools varies, but ten to twenty a day is average. Abdominal cramps usually precede a passage, which is often accompanied by tenesmus. In some instances tenderness may be elicited by palpation along the course of the colon. There may be weakness, delirium and rapid loss of weight due to dehydration.

The acute symptoms usually last five to ten days. The temperature tends to return to normal as the stools become formed. In some instances normal stools may not be noted for two to three weeks after the onset.

The onset of the *toxic*, or most severe, form is usually even more abrupt, and all the symptoms are exaggerated. The temperature is high, often septic in type, and diarrhea is severe. Tenesmus and often prolapse of the rectum are present. Sunken eyes, dryness of the mucous membranes, coating of the tongue and sordes of the lips and teeth indicate rapid loss of body fluids. Acidosis develops rapidly. Delirium, weakness and convulsions may occur. Abdominal distention in association with a decrease or cessation of bowel movements is an unfavorable situation.

In some instances the infection becomes *chronic*, persisting for weeks or months. The fever is of the low grade type, or the temperature may even be subnormal. The course is characterized by remissions of the diarrhea, the stools containing large amounts of mucus, but little or no blood. Continued poor nutrition, progressive loss in weight, and feeding difficulties are characteristic, and there may be abdominal distention, secondary anemia, nutritional edema and vitamin deficiencies. In such instances sigmoidoscopic examination may reveal a diffusely injected granular mucosa with follicular ulceration, cultures from which frequently reveal dysentery organisms.

**Diagnosis.** The majority of patients with an acute febrile disease associated with loose stools containing gross or microscopic blood, mucus and leukocytes have dysentery. Atypical cases, such as the chronic type, and acute cases in the prediarrheal stage, pose more difficult diagnostic problems. A mild diarrhea without mucus, blood or pus, due to *Shigella* organisms, is fairly common.

The diagnosis depends upon isolation of the organism from the stool or from material obtained by rectal swab. The culture should be made immediately, since the organism dies rapidly upon drying. A highly selective medium such as SS agar (*Shigella*-*Salmonella* thiosulfate citrate bile) is used. Suspicious colonies are transferred to carbohydrate broths (lactose, glucose, mannitol, xylose, and the like) for detection of characteristic fermentation reactions. The organism is also tested for indole and hydrogen sulfide production and for motility. Finally, it is agglutinated with polyvalent and later monovalent antisera.

**Differential Diagnosis.** *Typhoid fever* and other types of *Salmonella* infection may closely resemble bacillary dysentery. *Amoebic colitis* may be differentiated by identifying *Entamoeba histolytica*.

*Intussusception* in its early stage may be mistaken for dysentery. The onset with spasmodic pain and recurrent vomiting, the appearance of an abdominal mass and the shock-like symptoms of intestinal obstruction should distinguish it.

Occasionally there is localization of abdominal pain over the cecum, with tenderness and a delay in the appearance of diarrhea. When there is a moderate leukocytosis, *acute appendicitis* must be considered, and removal of the appendix often is a justifiable, although not profitable, procedure under the circumstances. Mesenteric adenitis is frequently observed at operation, and diarrhea may appear the next day.

Bleeding from focal lesions such as *Meckel's diverticulum*, *papilloma* or *duodenal ulcer* is usually not associated with the passage of frequent stools. Roentgenographic studies may aid in identification.

In the prediarrheal stage of dysentery meningeal and encephalopathic symptoms are frequently present. *Meningitis* or the pre-paralytic stage of *poliomyelitis* may be suspected, and a lumbar puncture may be necessary for diagnostic purposes.

**Complications.** Pneumonia and otitis media are occasional complications, especially in infants. Invasion of the blood stream by the dysentery organism is rare; pyelonephritis is uncommon. Dural sinus thrombosis and venous thromboses have been observed, principally with severe dehydration; encephalitis and peripheral neuritis are rare and usually not permanent residuals. A late complication, more frequently encountered in adults, is nonsuppurative arthritis, particularly of the



knee joints. Vaginitis may occur, but is not common. Dietary deficiencies are frequently observed in the chronic cases.

**Prognosis.** A certain degree of durable immunity appears to follow an attack of the disease. Whether this protection extends beyond group specificity is not established. Second attacks probably represent relapses occurring in a carrier. The disease usually lasts one to six weeks. The case fatality rate is high among infants. Death from toxemia occurs early in the disease; later in the disease it usually results from fluid imbalance and acidosis. Pre-existing malnutrition and concomitant infections are contributory factors to an unfavorable outcome. Infection caused by the Sonne organism is seldom fatal, but that caused by the Shiga organism is most serious. The case fatality rates vary considerably.

**Prevention.** The proper care of food and thorough washing of food which has been in contact with soil are important measures. The child with dysentery should be isolated and protected from flies. The carrier should be subjected to the same precautions as in typhoid fever, although chemotherapy appears to be more effective among dysentery carriers. There is no effective method of active immunization.

**Treatment.** The important aspects are prevention and control of water and electrolyte imbalance, chemotherapy and diet.

The treatment of dehydration by maintaining the proper fluid and electrolyte balance is of the greatest importance, especially in infants. In the more severe cases an initial period (twenty-four to seventy-two hours) of elimination of oral feeding during which parenteral fluids are administered may be desirable (see p. 186). Only small amounts of glucose and saline solution are given orally during this phase. After this time other fluids can usually be given orally. Skimmed lactic acid milk containing scraped raw apple, apple powder, apple pectin-agar or pectin-kaolin mixtures is usually well taken, and banana powder may be added shortly, or fully ripe bananas may be given separately. High-protein, low-residue diets are as a rule well tolerated. Separate administration of all the vitamins in fairly large amounts is indicated. During the postdysentery period, feeding may be extremely difficult, and occasionally gavage may be necessary.

The sulfonamides are effective in most instances. There now appears to be general agreement that the readily absorbed drugs

such as sulfadiazine and Gantrisin are more effective than the poorly absorbed ones. Doses are in the range of 120 mg. per kilogram (60 mg. per pound) in four equal doses. When there is vomiting, the drug may be given intravenously or subcutaneously as its sodium salt until oral medication is possible. Chloramphenicol and the tetracyclines are also effective. Length of treatment varies and should be dependent on control of symptoms and eradication of the dysentery organism, which can be expected in the acute cases within four to seven days.

Paregoric is often indicated to relieve pain and tenesmus, and it may reduce the number of stools. Repeated colonic irrigations are harmful. In Shiga infections antitoxin is indicated if it can be injected early in the course of the disease.

WILLIAM L. BRADFORD

## REFERENCES

- Cheever, F. S.: Bacillary Dysentery and the Shigella, in Dubos, R. J.: Bacterial and Mycotic Infections of Man. 2d ed. Philadelphia, J. B. Lippincott Company, 1952, p. 437.
- Donald, W. D., Winkler, C. H., and Barger, L. M.: The Occurrence of Convulsions in Children with Shigella Gastroenteritis. *J. Pediat.*, 48:323, 1956.
- Conference: Epidemic and Endemic Diarrheal Diseases of the Infant. *Ann. New York Acad. Sc.*, 66:3, 1956.
- Cooper, M. L., Keller, H. M., and Wallers, E. W.: Comparative Frequency of Detection of Enteropathogenic E. Coli, Salmonella and Shigella in Rectal Swab Cultures from Infants and Children. *Pediatrics*, 19:411, 1957.
- Stewart, W. H., Hardy, A. V., and Watt, J.: Shigellosis (Bacillary Dysentery); in Brennemann, J.: Practice of Pediatrics. Hagerstown, Md., W. F. Prior Co., Inc., 1957, Vol. 2, Chap. 5.

## TYPHOID FEVER

### (ENTERIC FEVER)

Typhoid fever is an acute, generalized febrile disease caused by the typhoid bacillus (*Salmonella typhosa*). Though the portal of entry is the gastrointestinal tract, many of the essential features of the disease depend upon the occurrence of early bacteremia.

**History.** The intestinal lesions were described by Bretonneau in 1820; Louis described the disease and named it *fièvre typhoïde* in 1829. One of his pupils, Gerhard, observed an epidemic of typhoid and one of typhus fever in Philadelphia in 1837 and gave a clear clinical differentiation of the two diseases. Badel (1873), another pupil of Louis, emphasized the importance of feces as a source of the infecting agent and described the danger in the excretions of a convalescing patient, as well as the

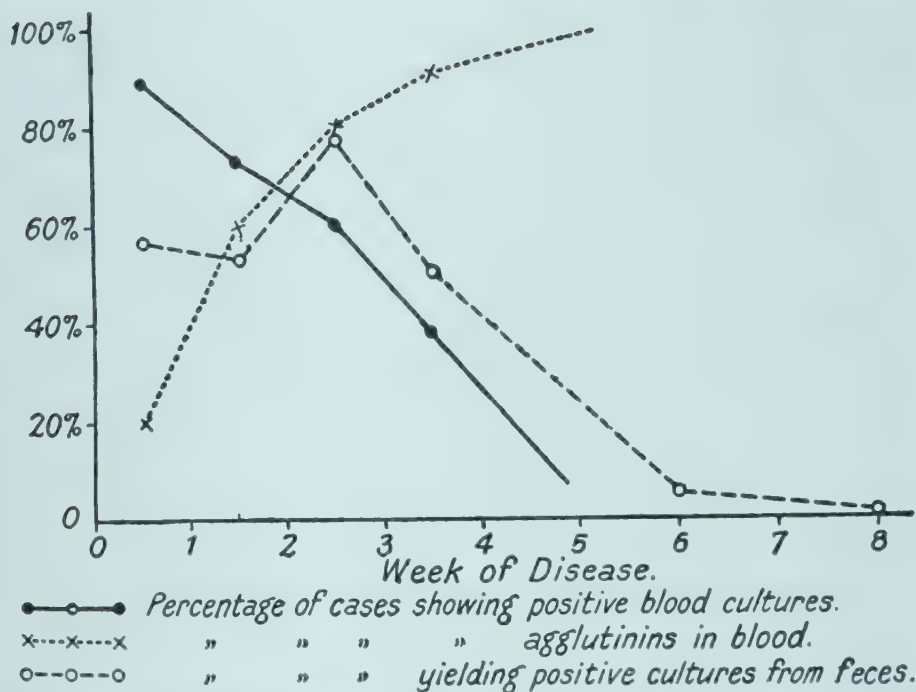


FIG. 120. Illustrating the time relationships in typhoid fever of the occurrence of positive blood and stool cultures and agglutinins in the blood serum. (Topley and Wilson: Principles of Bacteriology and Immunity. Edward Arnold & Co.)

role of water and milk in the spread of the disease.

In 1880 Eberth discovered the causative agent, and in 1896 Widal discovered the agglutination reaction. Russell (1909) used vaccine for the prevention of typhoid fever in the United States Army.

**Etiology.** *Salmonella typhosa* is a gram-negative, motile, nonspore-forming bacillus. It may be easily isolated from the blood during the early stage of the disease, and later from the urine and feces. During the bacteremia it may be found in the spleen, bone marrow, lymphatics and gallbladder. During the second week of the disease specific agglutinins appear in the blood serum.

The bacillus has at least three types of antigens, the "H" (flagellar), the "O" (somatic) and the "Vi." Agglutinins against the "H" antigen result from a previous typhoid infection or vaccination. A high titer of agglutinins against the "O" antigen denotes active infection. The blood of chronic carriers usually contains "Vi" antibodies, but the antigen is not available for practical use. It has been suggested that "H" antibodies may have little protective value, while the "O" and the "Vi" are important from this standpoint. In general, an agglutination titer of 1:160 or higher against a formalinized suspension of typhoid bacilli is significant. A progressively rising titer in subsequent tests is diagnostic. In most cases of typhoid the "O" agglutinins appear

earlier than the "H," and agglutination for them is therefore preferred in performing the Widal test. In the macroscopic method the "O" type produces a small, granular flaky reaction; the "H" type produces a large flaky one.

The rise in the agglutinin titer of the serum is usually associated with a decreasing bacteremia (Fig. 120). The time when the titer reaches its maximum frequently coincides with clinical improvement.

**Epidemiology.** Typhoid fever is a preventable disease and does not exist to a significant degree where rigid rules of sanitation prevail. The most important source of infection is the human typhoid carrier.

Water-borne and milk-borne epidemics are characterized by explosive onsets. One of the most serious epidemics, traceable to a contaminated milk supply, occurred in Montreal in 1927. Between March and July, 4849 cases with 489 deaths occurred. Other food-stuffs, such as ice cream, butter, cheese and shellfish, have been responsible for outbreaks.

The disease is found in practically all parts of the world; in the temperate zones it is more prevalent during the late summer, fall and early winter months. It is typically a disease of childhood and early adult life, occurring most frequently between the ages of fifteen and thirty years. It is fortunately rare



in infancy, when the mortality rate is high.

**Immunity.** Two of the immunologic aspects, the relapse and the so-called permanent immunity, are difficult to explain. The disease may continue or even relapse in the presence of an appreciable concentration of humoral antibodies. Organisms in such instances probably disappear from the blood and remain in the spleen, lymph nodes or other locations where they are protected from the action of antibodies in the serum, but where they liberate toxic factors.

In explanation of permanent immunity to typhoid infection, it is postulated that the tissues of a previously infected person probably remain highly sensitized even though the humoral antibodies have disappeared, and, when reinfected, respond to the antigenic stimulation with the immediate production of humoral antibodies sufficient to prevent another attack.

**Pathogenesis.** The bacillus enters the body tissues through the walls of the alimentary tract. In the blood stream and particularly in the reticuloendothelial cells of the liver and spleen the organisms are destroyed by phagocytosis. In these organs the bacilli also multiply rapidly and secondarily reinfect the blood stream. It has been suggested that the beginning of the second phase represents the clinical onset of the disease. Large numbers of organisms are eliminated from the liver, and heavy secondary infection of the intestinal tract occurs. In this manner the gallbladder is also readily infected and becomes the nidus of the chronic carrier.

The general symptoms of the disease, such as fever, malaise and headache, are caused by the action of toxins. Bacterial emboli in the capillaries of the skin produce the characteristic rose spots. The splenomegaly is caused by congestion of the splenic pulp, by the great accumulation of red blood cells and by endothelial hyperplasia. Ulceration of the bowel accounts to a great degree for the intestinal symptoms. The leukopenia results from the action of toxins on the bone marrow and from its overcrowding by great numbers of phagocytic endothelial cells.

**Pathology.** The lymphoid tissue of the small intestine, particularly of the lower part of the ileum, is one of the initial sites of infection. Peyer's patches become swollen, and necrosis of the mucosa occurs. The necrotic mucosa sloughs, leaving a round or oval ulcer with the long diameter in the long axis of the bowel; hemorrhage and perforation may occur.

The mesenteric lymph nodes become swollen, soft and hemorrhagic. In the intestinal lymphoid tissue, in the lymph nodes and in the bone marrow there is a nonsuppurative cellular reaction composed chiefly of large phagocytic cells from the reticuloendothelial system. These phagocytes contain lymphocytes, red blood cells and other elements. Polymorphonuclear leukocytes and eosinophils are scarce.

The spleen is enlarged, red and soft. The pulp contains great numbers of red blood cells and large phagocytes, and there are areas of focal necrosis. There are also focal necrosis of the liver and cloudy swelling of the liver and kidneys. The bacillus grows readily in bile and invades the wall of the gallbladder, where there are mild inflammatory lesions. Typhoid infection of the gallbladder may lead to establishment of chronic residual infection (carrier state) and to the subsequent formation of gallstones.

Toxic myocarditis is a common finding. Thrombosis of the veins is frequent and occurs particularly in the femoral and saphenous veins. Zenker's degeneration of muscle occurs frequently. Typhoid meningitis, which is purulent and has a high fatality rate, is rare. Chronic inflammatory changes may occur in the bones—the tibia, sternum, ribs and vertebrae being usually involved. The lesions consist of periostitis, abscess or necrosis and contain typhoid bacilli. Bronchopneumonia is usually caused by a secondary infection.

**Clinical Manifestations.** *In children.* The clinical course of typhoid fever from the second year of life through childhood is similar to that in adults, except that it is usually less severe. The incubation period has been reported to vary from three to forty days, but is usually between ten and twenty. It is said to be longest in water-borne, shorter in milk-borne and shortest in food-borne infections. The entire course of the infection is usually not more than two or three weeks; occasionally the febrile period lasts but one week. The temperature curve is more irregular than in adults, and the disproportion between the height of the fever and the pulse rate is not so constant. There is also a less degree of hypotension, and the dicrotic pulse is often not discernible. The onset may be either insidious or abrupt and often resembles an upper respiratory infection. Disturbances of the sensorium and prostration are less frequent and, when present, less pronounced. The intestinal symptoms are usually less severe than in adults. Tympanites tends to be

moderate and is often associated with abdominal tenderness. Diarrhea occurs in about half of the cases. The stools are liquid and contain mucus. About the end of the first week the spleen becomes enlarged and tends to remain so until the temperature becomes normal, or longer in event of a relapse. The embolic skin reactions (rose spots, p. 444) appear upon the trunk and extremities early in the disease. They are small erythematous macules about 2 to 5 mm. in diameter which may appear in successive crops and occur less frequently than in adults. A considerable degree of fatigue and emaciation often develops during the course of infection. The blood reveals evidence of a secondary anemia. There is a definite leukopenia, with disappearance of eosinophils and a relative increase in the number of mononuclear cells. Relapses occur in about 10 per cent of infections, but are usually less severe than those in the adult.

**In infants.** The infection may be present at birth, the organism having been transmitted through the placenta. In such instances the infant may be born prematurely and die soon after birth, though recovery is possible. The symptoms are variable and may include fever, convulsions, jaundice, diarrhea, and enlargement of the spleen. Diagnosis is established by isolating the organism from the blood or feces. A positive Widal reaction indicates infection of the mother and not necessarily active infection of the offspring.

When an infant acquires infection after birth, the clinical pattern may be far from typical. It may resemble that of sepsis or may suggest only a mild intestinal disturbance. Diarrhea, abdominal distention and vomiting are frequent, but there may be constipation. Distention may be related to low levels of potassium in the serum. The temperature is usually high and irregular, and rose spots are present in about half of the cases. The spleen is enlarged. An unexpected diagnosis is occasionally made from blood cultures in otherwise unexplained and atypical infections.

Because opportunity for contact with the typhoid bacillus is relatively limited during infancy, only about 1 per cent of all cases occur during the first year of life. The mortality rate of the disease among infants is about 10 per cent.

**Diagnosis.** Influenza, tuberculosis, malaria, undulant fever, atypical pneumonia, meningitis, rheumatic fever and other *Salmonella* infections are diseases that frequently

must be considered in the differential diagnosis. In the infant the clinical manifestations may resemble those of bacillary dysentery or septicemia. Obviously typhus fever must be considered in localities where both diseases exist.

Bacterial cultures of the blood, feces and urine should be obtained in every suspected case. The organism can almost always be isolated from the blood stream during the first week of the disease; the stool culture is usually positive, and in about one third of the cases the organism can be isolated from the urine. After the tenth day of illness the agglutination test (Widal) becomes positive in the majority of cases (see p. 388).

**Complications.** Complications, including hemorrhage and perforation of the bowel, are less frequent in children than in adults. Symptoms of *shock* accompany perforation of the intestine. The temperature falls abruptly, and the pulse rate increases. Abdominal pain is great, and distention usually develops. The abdominal muscles are rigid. With beginning *peritonitis* the fever reappears and leukocytosis occurs. Peritonitis may occur without evidence of perforation. *Intestinal hemorrhage* seldom occurs in patients under ten years of age. Extensive bleeding from the bowel is characterized by pallor, rapid pulse, fall in blood pressure and absence of abdominal pain. Bleeding from the mucous membranes associated with purpura (hemorrhagic typhoid) is rare. Epistaxis is the most common type of hemorrhage and may be severe. *Thrombosis* and *phlebitis* occur occasionally in children.

*Hepatitis*, of a degree sufficient to produce icterus, occurs occasionally. *Acute cholecystitis* and formation of gallstones are rare complications. *Infections of the respiratory tract*, particularly bronchitis, are frequent during the early stage of typhoid; bronchopneumonia may occur in the late stage. As in other *Salmonella* infections, there may be localized *arthritic*, *periosteal* and *osseous* infections, which are more likely to occur when the bacteremia is prolonged.

*Infection of the urinary tract* occurs in about one fourth of the cases. *Cutaneous* lesions include furuncles and bed sores which may be foci for staphylococcal or streptococcal septicemia. Sudamina, urticarial rashes, herpes, epilation, and grooving of the nails are other occasional epidermal manifestations.

*Nervous complications* are relatively com-



mon, and such symptoms as delirium, stupor and mental depression are frequent. There are rarely residual defects from toxic encephalitis; aphasia, a rare late manifestation, is usually only temporary. Chorea, hemiplegia, optic neuritis and peripheral neuritis have been reported. Purulent meningitis and brain abscess are rare and often fatal.

**The carrier.** During convalescence the patient often continues to harbor the causative agent and excrete it in the stools or urine. About two thirds of the patients are free of organisms by the end of six weeks. Most of the remaining third become free of organisms within a year, but about 3 per cent remain positive after a year and are considered chronic carriers. Adult chronic carriers are about nine times as frequent as child carriers, and females apparently outnumber males.

The nidus of the organism in the permanent carrier is usually in the gallbladder, occasionally in the intestine, kidney or a fistula.

The bacteriophage technique of typing typhoid bacilli is useful for tracing the role of the carrier in the spread of the disease. In addition, the finding of a high titer of serum antibody against the "Vi" antigen is almost entirely confined to the carrier state.

Surgical removal of the gallbladder in selected cases is an effective method of eliminating the chronic carrier state. The practical management of the carrier requires the closest cooperation of the carrier, his family and the health department.

**Prevention.** Sanitary living constitutes the most important preventive measure. In communities where this prevails, routine vaccination may not be necessary. When exposure has occurred or is probable, vaccination should be done. Although vaccine containing only typhoid bacilli is less irritating than the triple vaccine containing paratyphoid A and B organisms, the latter is preferable. For older children (five years and above) three weekly injections of 0.5 cc., 1 cc., and 1 cc., respectively, are sufficient. One half to one third of this dose may be given to children under five years of age. Single "booster" injections may be given every two or three years. There is evidence suggesting that 0.1 cc. of the vaccine injected intradermally is adequate for this purpose.

**Treatment.** Good nursing care and the maintenance of proper nutrition are important. In uncomplicated cases a high caloric,

smooth diet is desirable. A decrease in the fat content and the use of the more readily absorbable sugars are helpful in patients with tympanites or diarrhea. Lactose may be fed in larger amounts than other sugars because it is less sweet and is not fermented by the typhoid bacillus. Minerals and the various vitamins should be given in adequate amounts. The maintenance of fluid and electrolyte balance is especially important in infants and small children. There should be particular attention to the possibility of potassium deficiency when abdominal distention is associated with protracted vomiting or diarrhea.

Excessively high fever (105° F. or higher) may be treated by tepid sponge baths and alcohol rubs. Constipation may be controlled by the administration of mineral oil and by occasional enemas. Purges are contraindicated. In diarrhea a high-protein, low-fat diet should be prescribed. Lactic acid skimmed milk reinforced by the addition of a suitable protein mixture may be helpful. The feeding of scraped raw apple or an apple pectin preparation or the use of one of the hydroscopic agents such as pectin-agar may be beneficial in adding bulk to the stool and decreasing intestinal irritation. Opiates should not be used. Blood transfusions are indicated to correct anemia.

An antiserum, prepared according to the method of Felix, contains antibodies against the "Vi" and the "O" antigens; when injected early in the disease, it is said to be effective against the toxemia.

Chloramphenicol is the drug of choice for the treatment of typhoid fever. An initial dose of 50 mg. per kilogram (25 mg. per pound) is followed by a daily dose of 25 mg. per kilogram (12.5 mg. per pound) given in divided doses every six hours until the temperature is normal (usually about five days). Thereafter the daily dose is 3 mg. per kilogram of body weight for a total of ten to fourteen days. These are relatively small doses; in some clinics 50 to 100 mg. per kilogram of body weight in divided doses are administered for the full period of ten to fourteen days. When oral medication is not feasible, the intravenous preparation of chloramphenicol may be used.

The patient should be carefully isolated and screened against contact with flies. The urine, sputum and feces should be treated with Lysol before being discarded. Three negative urine and stool cultures should be

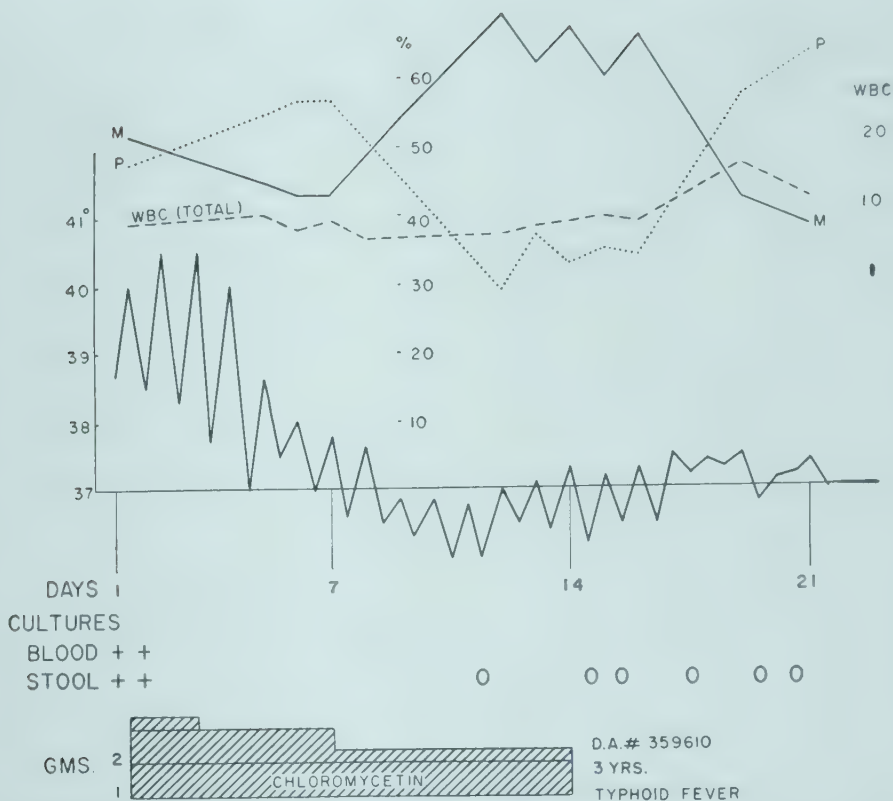


FIG. 121. Showing the curative effect of chloramphenicol in typhoid fever. D.A., 3 years of age, became ill 24 hours before admission with anorexia, lethargy and a temperature of 103° F. A sibling, the mother and 2 neighbors also had the disease, contracted by drinking water from a nearby polluted stream. Note (a) the lag period between onset of treatment and fall of temperature; (b) the characteristic decrease in the percentage of granulocytes (P) as the effect of the drug is manifest, and the increase upon cessation of treatment.

obtained before the patient is released from isolation.

WILLIAM L. BRADFORD

#### REFERENCES

- Boyd, W.: The Pathology of Internal Diseases. 2d ed. Philadelphia, Lea & Febiger, 1935, p. 299.
- Friedman, A.: An Evaluation of Chloramphenicol Therapy in Typhoid Fever in Children. *Pediatrics*, 14:28, 1954.
- Gerhard, W. W.: On the Typhus Fever Which Occurred at Philadelphia in the Spring and Summer of 1836; Illustrated by Clinical Observations at the Philadelphia Hospital; Showing the Distinction between This Form of Disease and Dothineritis or the Typhoid Fever with Alteration of the Follicles of the Small Intestine. *Am. J. M. Sc.*, 19:289, 1837.
- Keefer, C., and Weinstein, L.: in Welch, H.: Principles and Practice of Antibiotic Therapy. New York, Medical Encyclopedia, Inc., Blakiston Co., 1954, p. 471.
- Kitaigorodskaya, O. D.: Typhoid Fever in Childhood. *Pediatrics*, 2:14, 1945.

#### SALMONELLA INFECTIONS

These infections are caused by a number of flagellated organisms which have a common relationship based upon antigenic structure.

They are members of the *Salmonella* genus and have "H" (flagellar) and "O" (somatic) antigens, as does the typhoid bacillus, which some bacteriologists include as a member of the *Salmonella* group. A number of the *Salmonella* bacteria are natural pathogens for animals. The disturbances produced in man are, in general, of two types: a typhoid-like fever (paratyphoid fever) and acute gastroenteritis (food poisoning).

**Etiology.** Based upon antigenic studies, the *Salmonella* organisms are subdivided on the basis of their "O" antigen characteristics. Within each subgroup they are further differentiated on the basis of their "H" components; of the more than 150 identified species, some of the more common ones are:

- Group A: *S. paratyphi* (paratyphoid A bacillus)
- Group B: *S. schottmuelleri* (paratyphoid B bacillus)
- S. typhimurium* (*Bacterium aertrycke*)
- Group C<sub>1</sub>: *S. hirschfeldii* (*S. paratyphi* C.)
- S. choleraesuis* (*Bacterium suispestifer*)
- S. oranienburg*
- S. montevideo*
- Group C<sub>2</sub>: *S. newport*
- Group D: *S. typhosa* (typhoid bacillus)
- S. enteritidis* (*Bacterium enteritidis*)



*S. gallinarum**S. pullorum*Group E: *S. anatis* (*Bacterium anatum*)

Those organisms which are primarily human pathogens and usually cause typhoid-like infections are *S. typhosa*, *S. paratyphi*, *S. schottmuelleri* and *S. hirschfeldii*. Those which are primarily pathogenic for animals or birds, but occasionally cause human infection, chiefly through contaminated foods, are *S. typhimurium*, *S. choleraesuis*, *S. oranienburg*, *S. montevideo*, *S. newport*, *S. enteritidis* and *S. anatis*. *Salmonella gallinarum* and *S. pullorum* are also occasionally responsible for gastroenteritis through contamination of food. Certain species, notably *S. hirschfeldii* and *S. choleraesuis*, frequently invade the blood stream and produce localized purulent lesions such as osteomyelitis.

**Epidemiology.** In general, members of the *Salmonella* group of organisms have two common characteristics: (1) most of them (*S. paratyphi*, *S. schottmuelleri* and *S. hirschfeldii* are exceptions) have a natural habitat in animals, and (2) they remain viable for considerable periods of time and multiply in contaminated food. Rats, mice and hogs and other animals, such as fowls, rabbits, cats, dogs, cows and horses, may act as natural reservoirs. Meat, eggs, vegetables, milk and water are often contaminated, especially at warm temperatures, by food handlers, flies or the droppings of infected rodents. Packaged foods such as powdered egg can be responsible for wide dissemination. Man usually becomes infected by eating contaminated food, but also probably acquires infection by handling animals. Convalescent patients, especially infants, may be infectious for long periods of time. There are permanent carriers for *S. paratyphi* A and B, as well as for some of the other types.

Epidemics of paratyphoid and typhoid fever may coexist, and both infections may even occur simultaneously in the same patient. Standard typhoid vaccines contain paratyphoid A and B bacilli, and it may become practicable to include other organisms of the *Salmonella* group.

**Pathology.** Tissue changes are similar to, though less marked than, those encountered in typhoid fever. Acute enteritis and superficial necrosis of the lymphoid tissue are the principal changes in the intestinal tract. Deep ulceration and frank hemorrhage are rare, and perforation of the bowel in children is practically unknown.

**Clinical Manifestations.** The clinical manifestations may be extremely variable, though the predominating symptoms are usually gastroenteric, pulmonic or septic. Two general clinical types may be recognized: (1) the typhoid-like type (paratyphoid fever) and (2) the food-poisoning type (gastroenteritis). *Salmonella paratyphi* A, *S. paratyphi* B and *S. paratyphi* C usually produce symptoms resembling those of typhoid fever, while *S. typhimurium*, *S. enteritidis* and *S. choleraesuis* more often cause the food-poisoning type. However, either type of illness may be caused by any of the *Salmonella* organisms.

The incubation period may be as brief as a few hours in the food-poisoning type or as long as twelve days in typhoid-like infections. Headache, nausea and vomiting are initial symptoms. Abdominal pain and diarrhea are common in both types and constantly present in the food-poisoning type. The stools may be watery and at times contain mucus and blood, suggestive of dysentery.

There may be considerable drowsiness, and in some instances the sensorium is disturbed. Meningismus is often marked, and in such instances the possibility of meningitis cannot be eliminated without a diagnostic lumbar puncture. In paratyphoid A, B and C infections, rose spots (Fig. 122) may be present. The spleen is not regularly enlarged, but abdominal distention is not uncommon. There may be either leukopenia or leukocytosis, the former occurring more often in paratyphoid B infections, the latter in *S. typhimurium* and *S. enteritidis* infections.

Suppurative lesions of the joints, bones and soft tissues are more common than in typhoid fever, and are particularly characteristic of infection with the members of group C, of which *S. hirschfeldii* and *S. choleraesuis* are the principal ones. Meningitis is an occasional complication and has a high fatality rate.

The duration of the disease, though variable, is shorter than that of typhoid fever. The temperature may remain at a moderately elevated level throughout or may be of the septic type. When death occurs, it usually follows a course of illness in which there have been extreme dehydration, toxemia and circulatory collapse.

**Diagnosis.** Typhoid fever, bacillary dysentery, meningitis, osteomyelitis, acute appendicitis and staphylococcal and streptococcal food poisoning are among the more important conditions likely to be confused with *Salmonella* infections.



FIG. 122. Rose spots in paratyphoid fever in male, 17 months of age. Duration of fever, 15 days. Exanthem appeared on fourth day. Blood culture positive (fourth day) for *S. paratyphi* B. Serum agglutination, seventh day, negative; eleventh day, 1:640 vs. *S. paratyphi* B; stool culture, seventh day, positive, *S. paratyphi* B. (Courtesy of Dr. Kenneth Landauer.)

The bacteriologic diagnosis consists in (1) isolation of the organism from the blood, stools, urine or pus from a suppurative lesion; and (2) demonstration of a significant agglutinating titer of the patient's serum. Identification of an organism as a member of the *Salmonella* group is dependent upon serologic typing. Cross agglutination reactions frequently occur because of the close antigenic relationships among the *Salmonella* organisms. In instances in which contaminated food is suspected, it should be cultured.

**Complications.** The most common complications are those due to septic localization of the organism and include arthritis, osteomyelitis, meningitis and abscess of the soft tissues. Intestinal perforation is extremely rare. Bronchitis is frequently present in the early stage, as in typhoid fever, and is often mistakenly considered to be the cause of the fever. Bronchopneumonia may be a later complication.

**Prognosis.** The case fatality rate, though not accurately known, is less than that of typhoid fever; in certain epidemics, rates of 5 to 10 per cent have occurred, but the general mortality rate is considerably lower. The mortality rate appears to be higher in the paratyphoid group of infections than in cases of acute food poisoning.

**Treatment.** The patient should be isolated, and precautions similar to those recommended for typhoid patients should be practiced. When diarrhea and vomiting are

excessive, it may be necessary temporarily to discontinue feeding by mouth. Adequate fluid administration is necessary. (See p. 187 for treatment of diarrheal states.) Suppurative joints require surgical incision and drainage.

Drug therapy in salmonellosis is difficult to evaluate, since the course of the natural disease is extremely variable. Bacteriologically, some of the antibiotics appear to be effective in the acute phase; but upon cessation of treatment, positive cultures frequently re-occur. By then, however, the general condition of the patient is improved, and a certain degree of immunity established. Chloramphenicol (not so effective against other types as against *S. typhosa*) and Terramycin appear to be the drugs of choice; the latter has been reported to be effective, especially against *S. choleraesuis*. Aureomycin is less effective, the sulfonamides are equivocal, and streptomycin is of little or no value.

In the carrier state the choice of an antibiotic should be based upon sensitivity tests.

WILLIAM L. BRADFORD

#### REFERENCES

- Clyde, W. A., Jr.: Salmonellosis in Infants and Children. A Study of 100 Cases. *Pediatrics*, 19: 175, 1957.
- Edwards, P. R.: *Salmonella and Salmonellosis*. Ann. New York Acad. Sc., 66:3, 1956.
- Welch, H.: *Principles and Practice of Antibiotic*



Therapy. New York, Medical Encyclopedia, Inc., Blakiston Co., 1954, p. 466.

## BRUCELLOSIS

(UNDULANT FEVER, MALTA FEVER, BANG'S DISEASE)

Brucellosis is an infectious disease which primarily affects domestic animals, but is transmissible to man, in whom it produces a variety of clinical patterns. Infection in children is less frequent than in adults.

**Etiology.** There are several strains of *Brucella* organisms, classified as follows: *B. melitensis* (goat), *B. abortus* (cattle) and *B. suis* (swine). These species may be differentiated by the dye-typing method of Huddleson. They may be further identified by their ability to produce hydrogen sulfide.

**Epidemiology.** Human infection occurs where the disease is prevalent among domestic animals. Therefore it is more frequent in rural areas and among farmers, veterinarians and slaughterhouse workers in intimate contact with infected animals. About 10 per cent of the cattle and 3 per cent of swine in the United States are infected.

The disease is worldwide and occurs in all climates. It is four times more frequent in males than in females and is relatively infrequent among infants and children (see Table 69).

Ingestion of raw milk and its products accounts for about one fourth of the cases, the remainder originating from contact with infected animals or their environment (Spink). The skin and conjunctivas are important portals of entry, and inhalation of *Brucella*-contaminated dust is a probable method of infection. The laboratory is an occasional source of infection.

**The disease in children.** Children are considered less susceptible than adults. The apparent relative immunity of the young is not fully understood. McBride states that among forty-eight children who ingested contaminated milk, nine developed agglutinins, and only two exhibited clinical manifestations of the disease. Obviously, children have less opportunity for direct contact with infected animals. In general, the infection in children is less severe than in older subjects. Intra-uterine infection has been reported, and *Brucella* organisms have been demonstrated in the colostrum of an infected mother.

**Pathology.** The pathologic changes are nonspecific and appear to involve principally the reticuloendothelial system. Histologically,

there is hyperplasia of the reticuloendothelial system, and granulomatous foci and focal necroses in the liver, spleen, and lymph nodes.

**Clinical Manifestations.** The incubation period varies between five and thirty days, but is usually about two weeks.

**Acute form.** The onset of the acute form is often gradual, with fatigue, irritability, headache and malaise which may exist for several days or weeks before fever occurs. Pain in the chest with a nonproductive cough may be observed. In other instances the onset is sudden with fever, chills and nocturnal sweating. The onset may resemble that of mild typhoid fever. Frequently the patient feels well in the morning, but quite ill in the afternoon. This alternating daily cycle of well-being and extreme malaise eventually leads to weakness, loss of weight, and secondary anemia. Anorexia, constipation and abdominal pain are frequent complaints, and diarrhea and bloody stools occasional ones. The course may persist for several months. The febrile episodes are often intermittent, with fever, lasting from one to two weeks, followed by afebrile periods.

The wide variety of localized manifestations of brucellosis and the relative infrequency of the infection in infants and children make it impossible to define a characteristic pattern except for the undulating fever, weakness and the possibility of localization in most organs and tissues. The liver and spleen may become enlarged and tender, and occasionally jaundice occurs. Lymph node involvement may be widespread, and there may be abscesses in them as well as in the subcutaneous tissue. Bone and joint involvement is relatively common; the large joints and the spine are more frequent sites of infection. Ocular manifestations include

Table 69. Percentage Distribution\* of 4240 Cases of Brucellosis According to Age

Age	Per Cent	Age	Per Cent
5 years.....	0.8	25-34 years.....	30
5-9 years.....	2.2	35-44 years.....	25
10-14 years.....	3.0	45-54 years.....	11
15-19 years.....	5.0	55 years.....	10
20-24 years.....	10.0	Unknown.....	1

From the Laboratories of the Minnesota State Department of Health.

\*Calculated from data by W. W. Spink, in Brennemann-McQuarrie: Practice of Pediatrics. Hagerstown, Md., W. F. Prior Co., Inc., 1957, Vol. 2, Chap. 33, p. 4.

keratitis, retinitis, uveitis, papilledema and optic neuritis. Purulent meningitis and infections of the urinary tract are occasional manifestations. At times skin lesions resembling rose spots occur.

There is usually a leukopenia with a relative lymphocytosis, although the total leukocyte count is frequently normal and at times increased. An increase in the number of large mononuclear cells and eosinophils may also be observed. The clotting time may be prolonged, with imperfect clot retraction. Secondary anemia is common.

**Chronic form.** Chronic brucellosis presents a variety of symptoms. In older children and adults they may be so vague as to suggest neurasthenia. Generalized weakness, prolonged malaise, low grade fever, insomnia and vague aches and pains are common. The undulating type of fever frequently observed in the acute form is seldom seen in chronic brucellosis. Bursitis, peri-arthritis and spondylitis should suggest the chronic form of infection. Persistent and intermittent lymphadenitis may be observed. In young children there may be no characteristic symptoms.

**Diagnosis.** A history of unexplained fever in a patient who has ingested raw milk products is suggestive of brucellosis. The disorders that may resemble brucellosis include typhoid fever and other *Salmonella* infections, malaria, tuberculosis, Hodgkin's disease, rheumatic fever, influenza, tularemia, arthritis, appendicitis, cholecystitis, subacute bacterial endocarditis and even neurasthenia.

The diagnosis is established by identification of the organism in the blood, urine, bile, joint fluid, aspirates from abscesses or biopsy material. Cultures should be observed for two or three weeks.

Agglutinins may appear in the blood by the tenth day of the disease, or not until late in convalescence; in 5 to 10 per cent of active infections in man they may not be demonstrable at any time. On the other hand, agglutinins may be present in the blood serum of certain persons who have consumed raw milk, but are free from symptoms, and in those who have had intradermal tests with *Brucella* antigens. Though a titer of 1:80 to 1:160 is generally considered significant, dependence cannot be placed on a particular titer because of lack of a standardized antigen. However, the demonstration of a rising titer is of diagnostic significance. Falsely positive agglutinative titers may appear in

tularemia and in persons immunized with cholera vaccine.

The complement fixation is as useful as the agglutination reaction. The complex phagocytic index is of little practical value. Guinea pigs may be injected subcutaneously with suspected infectious material and their serum subsequently tested for agglutinins, and their tissues may be examined for lesions of brucellosis.

A positive intradermal reaction may be obtained in the majority of active human infections by injection of a suspension of heat-killed organisms or the nucleoprotein of the organism (brucellin). The reaction is an allergic one resulting from past or present infection; it is useful for epidemiologic surveys, but has limited value as a diagnostic aid. The combination of nonspecific symptoms and a positive skin reaction is insufficient for a diagnosis of brucellosis.

**Complications.** In a disease whose natural course may be as prolonged as that of brucellosis and whose manifestations are as protean, it becomes somewhat arbitrary to designate particular lesions as chronic manifestations or as complications. In any event, arthritis with or without hydroarthrosis, osteomyelitis (especially spondylitis), pericarditis, peritonitis, pleurisy, meningitis, encephalitis, infection of the urinary tract, abscesses of the lymph nodes and subcutaneous tissues and purpura have all been observed in cases of long standing. Endocarditis of the vegetative type may result from *Brucella* infection superimposed on a previously damaged heart valve.

**Prognosis.** Death occurs in about 1 per cent of recognized cases. The prolonged disability, often lasting for months or years, is the important feature. In children the disease is less severe than in adults. Relapses are more frequent in persons in whom a definite increase of humoral antibodies (agglutinins) fails to develop, and in those with mild symptoms.

**Prevention.** Isolation of the patient is unnecessary, since human transmission seldom, if ever, occurs. Caution, however, should be exercised in handling infected tissues or exudates. The infection may possibly be transmitted by blood transfusions.

The prevention of brucellosis consists in (1) pasteurization of milk and its products; (2) eradication of the infection in domestic animals; (3) vaccination of persons intimately associated with diseased animals or who have laboratory contact with the organ-



ism; and (4) public education concerning the danger of consuming raw milk.

**Treatment.** The first successful therapy was accomplished with streptomycin and sulfadiazine. Later it was found that one of the broad-spectrum antibiotics or a combination of one of them with streptomycin was more effective, especially in reducing the incidence of relapses. Spink recommends Aureomycin (other tetracyclines are also effective) alone for the milder infections caused by *Br. abortus*. For the more severe *Br. abortus* infection and for all infections due to *Br. suis* or *Br. melitensis* he suggests a combination of Aureomycin with dihydrostreptomycin.

The Aureomycin is given orally four times daily for three weeks, and the dihydrostreptomycin intramuscularly twice daily for at least two weeks.

Corticotropin and cortisone appear to be of benefit in controlling the acute manifestations, but should be given only to the acutely ill patient with toxemia.

Desensitization by injection of a *Brucella* antigen has been used, particularly in the chronic type of the disease, but is inferior to antibiotic therapy.

Rest and psychotherapy are important adjuvants in the management of the chronic case.

WILLIAM L. BRADFORD

## REFERENCES

- Braule, A. I.: Studies in the Pathology and Pathogenesis of Experimental Brucellosis. *J. Infect. Dis.*, 89:76, 87, 1951.
- Bruce, D.: Note on Discovery of a *Micrococcus* in Malta Fever. *Practitioner*, 39:161, 1887.
- Knight, V.: Brucellosis, Plaque, and Tularemia; in Welch, H.: Principles and Practice of Antibiotic Therapy. New York, Medical Encyclopedia, Inc., Blakiston Co., 1954, Chap. 20, p. 499.
- Meyer, K. F.: Trends in Brucellosis Control. *Pub. Health Rep.*, 71:511, 1956.
- Spink, W. W.: Brucellosis; in Brennemann's Practice of Pediatrics. Hagerstown, Md., W. F. Prior Co., Inc., Vol. 2, Chap. 33, 1957.
- Wallis, H. R. E.: Brucellosis in Children. *Brit. M. J.*, 1:617, 1957.

## TULAREMIA

(RABBIT FEVER)

Tularemia is an infectious disease of rodents which is transmissible to man.

**History.** Tularemia was identified in Tulare County, California, in 1910 by McCoy, who observed a "plaque-like disease" among ground squirrels. Wherry (1914) described the first case in a human being. Francis (1920) produced the disease

in the guinea pig by inoculating it with the blood of a person who had died after the bite of a deerfly.

**Etiology.** *Pasteurella tularensis* is a small, gram-negative, coccoid bacillus, 0.3 to 0.7 micron in length. It is probably nonmotile, though Ohara described it as slightly motile. It forms capsules and is easily destroyed by the usual disinfectants and by heating at 56° C. for ten minutes.

**Epidemiology.** In the United States important sources of infection are animals, insects and laboratory material. Over 90 per cent of human cases in the United States have occurred after contact with infected wild rabbits. Birds (quails, chickens) and cold-blooded animals may also harbor the organism. Various insects serve as vectors; these include the woodtick, dogtick, horsefly, bedbug, flea, louse; in Utah the deerfly plays an important role. The seasonal incidence is influenced by the period of the year when ticks are prevalent or when rabbits or other game animals are being hunted or trapped.

Tularemia is widely distributed. It has been observed throughout the United States, Alaska and Canada, in Japan, where it is known as "Ohara's disease," and in Norway, Russia and other parts of Europe. The disease is more frequent among adults than among children.

Infection may be acquired by skinning or dressing of rabbits and such other animals as skunks, deer, foxes, rats and tree squirrels; it has followed the bites of such animals as dogs, cats, squirrels and raccoons. Contact with sheep may result in infection, especially among shearers, since the wool may contain infected ticks and contaminated fecal droplets. Infection may also be acquired by ingestion of inadequately cooked contaminated meat or the drinking of contaminated water; the organism has been demonstrated in the water of several streams. Transmission from man to man, though possible, is not probable. Laboratory infection is common; unless extreme care is exercised, practically everyone who handles fluid cultures or infected animals contracts the disease. One attack of the disease usually confers lasting immunity.

**Pathology.** In addition to the local lesion at the portal of entry and the lesions in the regional lymph nodes, there are focal necrotic areas in various stages of evolution throughout the body. Small yellow-white lesions are found in the spleen, liver, kidneys, lungs, lymph nodes and bone marrow. Histologically, the lesions may resemble miliary tuber-

cles with or without central purulent exudate. In the central areas of these lesions polymorphonuclear cells are abundant, often associated with central necrosis and surrounded by an area of small round cell infiltration. In the more diffuse lesions, fibroblasts and mononuclear cells are abundant, particularly during the subacute stage of the infection.

**Clinical Manifestations.** The average incubation period is three to five days. Based somewhat upon the reaction at the portal of entry, six clinical types are generally recognized: (1) ulceroglandular, (2) oculoglandular, (3) glandular, (4) pulmonary, (5) typhoidal and gastrointestinal, and (6) oropharyngeal. Manifestations are both local and generalized.

The onset is abrupt, with fever, chills, headache and vomiting. Generalized pains, prostration and sweating are usually present. Sometimes there is enlargement of the liver and spleen. Various exanthems (macules, papules, pustules and petechiae) may be observed as well as jaundice. Fever lasts one to two weeks.

The local lesion, a papule, usually becomes ulcerated with enlargement and tenderness of the regional lymph nodes, which suppurate in about half of the cases.

When the portal of entry is the conjunctiva, photophobia, itching, lacrimation, hyperemia and swelling of the eyelid, usually the upper, occur. Preauricular and cervical lymph nodes enlarge and frequently suppurate. Though damage to the eye is rare, corneal ulcers may sometimes perforate and permanently impair vision.

The *pulmonary* type occurs from inhalation or by the hematogenous route. The pneumonia is patchy, confluent and often migratory. The mediastinal and peribronchial lymph nodes are enlarged.

The *oropharyngeal* type, resulting from ingestion of contaminated material, is characterized by ulcerated lesions of the oral cavity, throat and tonsils with cervical adenitis. The tonsils may be covered with exudate or a pseudomembrane, not unlike that of diphtheria. Several members of the family may be infected from a common source of food or water. Hughes and Etteldorf observed fifty-five proved cases of tularemia in Memphis (1940-56); thirteen of the patients were under sixteen years of age, and five of the thirteen cases were of the oropharyngeal type. In children this type may be rapidly fatal.

Cryptogenic infection may occur, and the

clinical course may resemble that of typhoid fever.

There is moderate leukocytosis and secondary anemia. Albuminuria is common.

**Diagnosis.** The disease may resemble atypical pneumonia, psittacosis, undulant fever, septicemia, influenza, tuberculosis and the typhoid-paratyphoid group of diseases. The typical case in which the patient becomes ill after dressing or skinning a wild rabbit should offer little difficulty in diagnosis.

Confirmation may be obtained from agglutination and skin tests and from bacterial cultures and inoculation of laboratory animals. By the end of the second week of illness the patient's serum contains specific antibodies, and the agglutinin titer gradually increases, sometimes exceeding 1:1280. The skin test, described by Foshay, consists in the intracutaneous injection of a suspension of detoxified formalin-killed *P. tularensis*. The tuberculin-like reaction is said to occur by the third day of illness.

**Complications.** Chronic bronchitis, bronchopneumonia and pleural effusions are probably more common than clinical symptoms suggest. Peritonitis, sometimes with persistent ascites, may develop. Pericarditis, thrombophlebitis, osteomyelitis, purulent meningitis and encephalitis have been described.

**Prognosis.** The case fatality rate is about 5 per cent. The pulmonary and the gastrointestinal types of the disease are extremely serious, often resulting in mortality rates as high as 60 per cent. The course of the disease is variable. Many patients are only mildly ill; in others there is extreme toxemia. The fever usually lasts three to four weeks, but the glandular enlargement may last three to four months, and convalescence may be prolonged even longer. Because *P. tularensis* is frequently an intracellular organism, it may remain viable in the tissues long after symptoms have disappeared.

**Prevention.** Prevention largely involves avoiding contact with infected rodents or other animals and with ticks and insect vectors. Face masks and rubber gloves should be worn by those handling infectious material in the laboratory. Proper cooking will eliminate rabbit meat as a source of ingestional infection. Prophylactic vaccination of animals or man has not proved practicable.

**Treatment.** *Pasteurella tularensis* is sensitive in vitro to 0.15 to 0.3 microgram per cubic centimeter of streptomycin. Streptomycin in doses of 25 mg. per pound of body weight per day in divided doses every six



hours is usually responsible for rapid recovery; treatment is usually continued for one week. Aureomycin is also effective, but does not excel streptomycin. Experience with other antibiotics has not been extensive.

Symptomatic care is important. The discharges from open lesions should be handled so as to prevent spread of infection. Surgical incision of suppurative lesions is frequently followed by systemic reactions.

WILLIAM L. BRADFORD

## REFERENCES

- Foshay, L.: Tularemia. *Ann. Rev. Microbiol.*, 4: 313, 1950.  
 Francis, E.: Tularemia: A New Disease of Man. *J.A.M.A.*, 78:1015, 1922.  
 Hughes, W. T., Jr., and Etteldorf, J. N.: Oropharyngeal Tularemia. *J. Pediat.*, 51:363, 1957.  
 Larson, C. L.: Tularemia; in Brennemann's Practice of Pediatrics. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 2, Chap. 29.  
 Levy, H. B., Webb, C. H., and Wilkinson, J. D.: Tularemia as a Pediatric Problem. *Pediatrics*, 6: 113, 1950.  
 Meyer, K. F.: Pasteurella Infections. *Pediat. Clin. North America*, 2:3, 1955.

## TUBERCULOSIS

Tuberculosis has a uniquely important place in man's medical history. It has at all times been a major cause of illness and of death in all climates. It was one of the first diseases to elicit widespread organized public health efforts, and the degree of control attained has proved the value of detection and isolation of infected persons. It stands as the prototype of infections which exist in man most often as a parasite without causing significant disease and yet capable of producing both acute and chronic disease patterns of sufficient seriousness to be a major cause of death.

The steady decrease in death rates at all ages (Fig. 123) is evidence of man's gain in his battle with the tubercle bacillus. Only in the last decade can credit for these gains be given to specific antimicrobial agents. It is essential for the young student to know by what means these gains have been made and to recognize that in our improving health situation, tuberculosis remains a major problem—to be solved by the combined means of public health measures and medical therapy.

**Etiology.** Koch demonstrated in 1882 that tuberculosis is caused by the acid-fast bacillus *Mycobacterium tuberculosis*. Subsequently Theobald Smith showed that disease in man could be produced by bovine and human

tubercle bacilli. The bacilli are capable of living and remaining virulent for weeks in a dry state, but in a fluid suspension are killed by a temperature of 60° C. (140° F.) within fifteen or twenty minutes.

The tubercle bacillus does not contain or produce any chemical constituent which has any measurable toxicity for tissues not sensitized to tuberculin; its tissue-necrotizing capacity exists in the protein fraction. The lipids of the tubercle bacillus give it the property of acid-fastness and appear to be a factor in the production of fibrosis as well as in the formation of epithelioid cells and tubercles.

**Epidemiology.** The exact incidence of tuberculosis is not known. Evidence of its frequency is limited to surveys using the tuberculin test and/or roentgenographic films, clinical recognition of the disease, and examination of autopsy material. Available data indicate that the incidence of infection is declining throughout the world and that in general the incidence is lowest in populations with high living standards, and highest in those with low standards. In all areas the incidence of tuberculous infection increases with age and is generally higher in urban than in rural areas. Some idea of the decrease in the rate of infection may be obtained from the decrease in rates of positive tuberculin reactions. Whereas rates of positive reactors were 50 to 90 per cent during high school and college ages twenty to thirty years ago, rates of positive reactions in this same age group at present are only 5 to 20 per cent. Figure 123 illustrates the decrease in mortality during this century, and Figure 124 illustrates the differences in mortality rates by age, sex and race.

Infection rates among children are higher in tuberculous families than in nontuberculous ones. Infection of children below the age of five years is most likely to occur at home from members of the family or domestic servants; infection of older children is more likely to be acquired from contacts outside the home. The relatively high incidence of tuberculosis in persons beyond fifty years of age necessitates the inclusion of *all* contacts irrespective of age (*viz.*, grandparents) as possible sources of infection.

Inspection of death rates (Fig. 123) reveals that there has been a progressive decrease in all age groups since 1900. This drop is especially marked in the groups under fifteen years of age. Although the death rate in infancy and early childhood (Fig. 124) is higher than in the age group of five to fifteen

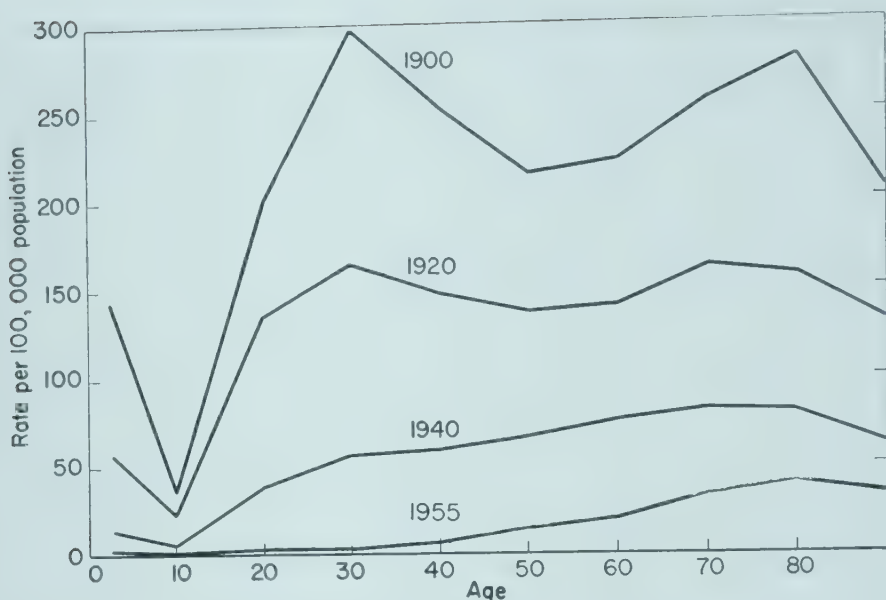


FIG. 123. Tuberculosis death rate by age, United States, 1900-1955 (expanding death registrations). (Tuberculosis Program Charts, 1957, XVII.)

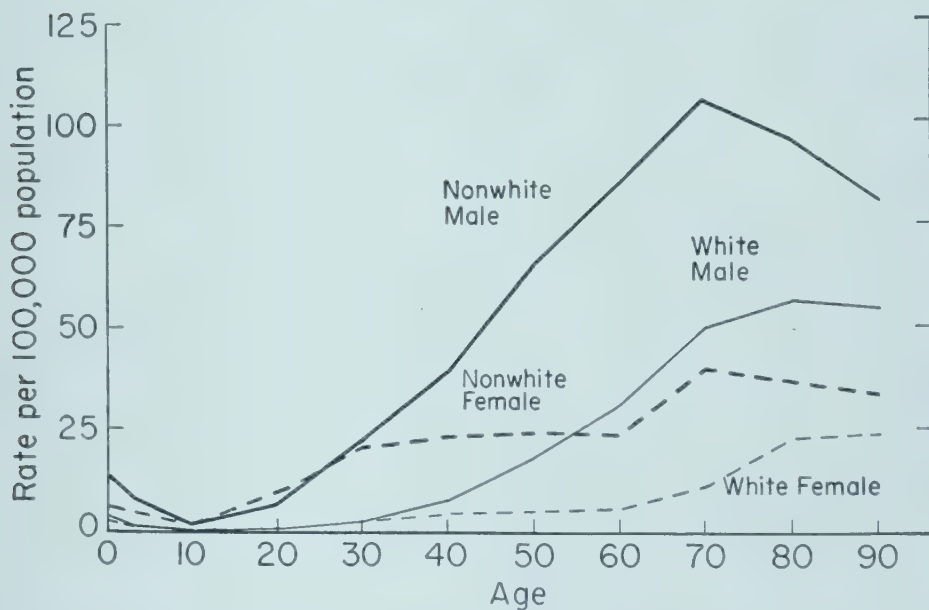


FIG. 124. Age-specific tuberculosis death rates by race and sex, United States, 1955. (Tuberculosis Program Charts, 1957, XVIII.)

years, the difference is much less than was the case in the past. The relatively high mortality rates of infancy and adolescence characteristic of previous years have now been greatly reduced.

**Predisposing Factors.** The introduction of tubercle bacilli into the human body is not invariably followed by the development of significant disease. Pertinent to an understanding of this situation is why certain persons have greater resistance to infection than do others, and why the resistance of a given person may vary from time to time.

Factors related to the tubercle bacillus which may affect the establishment of disease in a given structure of the body (see Pathogenesis) are principally of two orders: the relative virulence of the invading organisms and the number of organisms in the inoculum. Though there are distinct differences in the virulence of various strains of tubercle bacilli, strains of low virulence are rarely encountered in human infections.

**Heredity.** There is no evidence of an inherited tendency to tuberculous infection. Differences in constitutional patterns do



however, appear to influence resistance to disease. Animals of the same species vary in their degree of resistance, and by selective breeding of those with a high degree the increased capacity for resistance can be transferred to the offspring. The question in man is not so simply answered. It has been suggested that persons with a low resistance account for the majority of those who have progressive tuberculosis, and that the decrease in mortality from tuberculosis is at least in part attributable to the law of the survival of the fittest.

**Congenital or intrauterine infections** occur infrequently; infection of the fetus is probably secondary to infection of the placenta.

**Race.** Differences in racial immunity are not well defined. There is a higher mortality rate from tuberculosis in the United States among the nonwhite population than among the white, but it would seem that much of this difference may be attributed to hygienic and environmental factors, such as poor housing conditions and opportunities for frequent reinfection from ambulatory patients.

**Age.** Age is a factor in resistance to tuberculous infection, the fatality rate being higher during infancy and adolescence than in the intervening years of childhood. There are also differences in the nature of the lesion which is initiated at various age levels. These are described under Pathology.

**Sex.** Sex appears to be a factor only in the latter part of childhood and during adolescence, when the incidence of tuberculosis and the fatality rate from it are higher in girls than in boys.

**Temporary factors affecting resistance.** Chronic illness and undernutrition may increase susceptibility to infection, as may a chronic state of fatigue. Acute nontuberculous infections may activate a quiescent tuberculous lesion.

**Allergy and Immunity.** Two to ten weeks after infection of a previously tuberculin-negative person with tubercle bacilli the presence of allergy can be demonstrated by a positive cutaneous reaction to tuberculin. With the development of allergy there is an alteration in the host response to tubercle bacilli, evidenced by exudation and a tendency to localize the infection. At some less well-defined time certain immune reactions also develop which are neither complete nor as adequately measured as in certain other infections. Immunity is not complete; it may be sufficient to protect against moderate infections, but may not be effective against

large numbers of invading bacilli or against those of exceptionally high virulence.

To what extent allergy and immunity are related phenomena is a controversial question. It is variously held (1) that they are related and perhaps identical, (2) that they are entirely separate phenomena, or (3) that they are opposing forces. It may be that the degree of hypersensitivity is the important factor. Thus moderate degrees of hypersensitivity appear to be effective in localizing the lesion and in bringing the phagocytic cells in contact with the bacteria more quickly; whereas greater hypersensitivity is responsible for such extensive destruction of tissue that spread of the infection may be increased by it.

**Pathogenesis.** Infection through the intact skin probably does not occur, but infections may be acquired in open wounds and through inapparent abrasions and have been transmitted by a human bite. Direct blood stream infection is a practical possibility only in placental transmission. Inhalation and, to a lesser extent, ingestion are the principal means by which tubercle bacilli gain entrance to the body and produce infection.

**Pathology.** The response of infants and small children to tuberculous infection differs in certain respects from that of older children and adults. There is, however, a good deal of overlapping between the responses of the two age groups. Thus lesions which have the characteristics of the "childhood type" are seen on occasion in adults, especially of the Negro race, and the "adult type" of infection may occur in children, especially in the latter part of childhood.

In general, the age differences are as follows: (1) The pulmonary lesion in infants and children may be in any part of the lung, but shows some tendency to be localized in the periphery. The site is more likely to be in the lower part of the lungs than in the upper part. By contrast, in adolescents and adults there is a predilection for localization of the lesion in the upper part of the lung, either in the apical region or just below it in the infraclavicular area. (2) The regional lymph nodes are more often involved in infants and children than in adolescents and adults. Initial infections in adults, except in the Negro, show little or no evidence of extensive involvement of the lymph nodes. (3) Both the parenchymal and nodal lesions in children exhibit a strong tendency to heal by calcification, whereas in adults the tendency is to heal by fibrosis. (4) Hematogenous dissemination is much more likely to occur

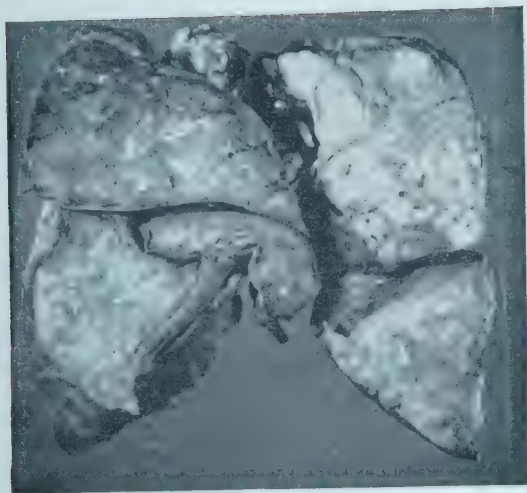


FIG. 125. Tuberculous lesion (primary) in apex of left upper lobe (right upper corner) with associated massive involvement of regional lymph nodes (primary complex). Large wedge-shaped lesion in lower half (lateral portion) of left upper lobe. This last lesion (tuberculosis pneumonitis) is secondary to bronchial erosion from a tuberculous node. (Courtesy of Drs. Charles Dunlap and James B. Arey.)

in infants than in older children. Miliary tuberculosis and tuberculous meningitis occur with much greater frequency in the first few years of life than they do subsequently.

At the site of the initial focus, as, for example, in the parenchyma of the lung, there is at first an accumulation of polymorphonuclear leukocytes. This reaction is temporary and is followed by proliferation of epithelioid cells which surround the tubercle bacilli, creating the typical tubercle formation. The tubercles are usually surrounded by an accumulation of lymphocytes, and giant cells are usually present. The tubercles may remain discrete or may become confluent; central caseous necrosis is commonly present. Individual foci of the primary infection vary considerably in size, but the majority apparently remain small (1 cm. or so in diameter). There is, as a rule, only a single primary focus, but there may be more.

Lymph node involvement is almost a constant accompaniment of the initial parenchymal lesion in children. It has generally been considered that lymph node involvement is a characteristic of the initial lesion of tuberculosis and does not occur in association with the lesion of reinfection. This concept does not appear to be wholly correct. There is evidence suggesting that the extent of involvement of regional lymph nodes is determined in part by age factors, being less with increasing age. The nodes become enlarged, often matted together, and tend to

adhere to adjacent structures. In the mediastinum they may exert pressure on the trachea, bronchi or blood vessels, and at times rupture into them. Softening and liquefaction of the nodes may parallel that in the primary focus or may occur independently. Auerbach believes that hematogenous distribution is more likely to occur from drainage from caseous foci in lymph nodes through lymph vessels into the venous circulation than by direct erosion into a blood vessel.

The tendency of the primary lesions both in the parenchyma and in the lymph nodes is toward healing in the majority of instances. There are, however, three mechanisms by which the primary infection may be responsible for serious damage during its active phase: (1) progressive destruction at its initial site; (2) erosion of a bronchus with intra-bronchial dissemination and the formation of other pulmonary lesions; and (3) hematogenous distribution resulting in one or more isolated foci in such parts of the body as the lungs, bones, kidneys, liver or brain, or in widespread miliary lesions involving some or all of the viscera.

The progressive primary tuberculous focus is a large, irregularly demarcated area of caseation with no definite capsule. The tissue surrounding this area tends to be pneumonic and the overlying pleura to be thickened. Softening and liquefaction may be generalized in the nodular mass or localized in one or more small areas. If the liquefied material is evacuated, there remains an irregular, shaggy excavation with a poorly defined capsule. Hematogenous distribution is more likely to occur during the stage of softening, but before the stage of liquefaction, whereas bronchogenic spread tends to result from the breakdown of an area of liquefaction.

Consolidated lesions in association with primary infections are usually atelectasis or tuberculous pneumonia, or a combination of the two. Bronchi may be occluded by external pressure from a caseous lymph node, or there may be erosion of the bronchus and occlusion of the lumen by the resultant intra-bronchial lesion. When the obstruction is incomplete, there may be greater hindrance to the exit of respired air than to its entrance, so that there is obstructive emphysema distal to the lesion; when the obstruction is complete, resorption atelectasis occurs.

Massive hematogenous dissemination of tubercle bacilli from a tuberculous focus results in widespread formation of tubercles. Though the heaviest distribution is likely to



be in the lungs, any or all of the viscera may be involved, especially the liver, spleen and kidneys. Tuberculous meningitis, as shown by Rich and McCordock, is more likely to result from breakdown of a tuberculoma situated in contiguity with the meninges. Isolated hematogenous lesions may be located in the brain, kidneys and bones and occasionally in other structures.

**Clinical Forms.** Tuberculosis may involve practically any organ or tissue of the body. Exogenous foci are naturally limited to structures which have an epithelial covering or lining, whereas tuberculosis of structures of the body which have no outside contact are of necessity blood-borne or lymph-borne from a pre-existing focus. Symptoms of any tuberculous lesion may be varied and may simulate many other disease entities. In the differential diagnosis of the majority of chronic infections and of many acute ones, the possibility of tuberculosis must be considered.

Intrathoracic tuberculous infection is the most frequent clinical manifestation of tuberculosis observed in this country and accounts for at least 90 per cent of recognized tuberculous disease in children. As noted under Pathology (p. 451), parenchymal and lymph node involvement uniformly occur, although these foci are not always apparent by clinical and/or roentgenographic examina-

tion. The extent of the infection in the pulmonary parenchyma and/or in the lymph nodes is largely responsible for the various clinical patterns. Table 70 provides a classification of intrathoracic lesions based on clinical patterns rather than the more traditional one of primary and reinfection tuberculosis. Extrathoracic tuberculous lesions are tabulated in Table 72 (p. 466).

#### INTRATHORACIC TUBERCULOSIS

**Clinical Manifestations.** The initial lesion in the lung may be, and usually is, a small localized one of 2 or 3 cm. From this lesion tubercle bacilli travel to and colonize in the regional lymph nodes. The two lesions constitute the so-called primary complex. The various possibilities for (1) healing, (2) persistence of indolent lesions, (3) extension at the local site with progressive destruction of tissue, (4) erosion of bronchial walls with partial or complete occlusion of the bronchial lumen (or such occlusions by external pressure of enlarged lymph nodes) with establishment of localized obstructive emphysema or atelectasis and at times with distribution of tubercle bacilli to other parts of the lung and establishment of a number of new lesions, (5) erosion of blood vessels with widespread distribution of tubercle bacilli (miliary tuberculosis) or with establishment of localized lesions at distant sites (cerebral tuberculoma, meningitis, bones, kidney, and the like), (6) subsequent reactivity of the lesion, or (7) reinfection, endogenous or exogenous, are individually and collectively responsible for the great variety of clinical patterns.

*It should be obvious that detection of tuberculin sensitivity in an individual requires careful study (1) to localize, if possible, the site of the lesion or lesions; (2) to determine whether the disease is active, quiescent or healed; and (3) to detect any existing tuberculous contacts.*

When no lesion can be demonstrated in the child by physical examination or on a roentgenogram of the chest, and there is no evidence of active infection manifest by fever, increased sedimentation rate or abnormal blood cell counts, the child may be diagnosed as *hypersensitive to tuberculin without clinically demonstrable disease*. Specific treatment should be considered for such children under three or four years of age and for those of any age who are known to have become tuberculin-positive within recent months (see p. 464).

When there are one or more *calcified foci in the pulmonary parenchyma and/or calcified*

**Table 70. Classification of Intrathoracic Tuberculosis**

Hypersensitivity to tuberculin without clinically demonstrable disease
Calcified pulmonary focus and/or calcified lesions in the tracheobronchial lymph nodes associated with hypersensitivity to tuberculin
Noncalcified pulmonary focus
Extensive pulmonary infiltration
Tuberculosis of the tracheobronchial lymph nodes
Intraluminal and extraluminal bronchial lesions
Localized ulcerative or granulomatous endobronchial lesions
Extraluminal bronchial compression
Lesions distal to bronchial obstruction
Emphysema
Atelectasis
Tuberculous pneumonitis
Or any combination of above 3 lesions
Caseous bronchopneumonia
Bronchogenic or hematogenous
Hematogenous tuberculosis
Single or multiple pulmonary infiltrations (clinically indistinguishable from nonhematogenous lesions)
Miliary tuberculosis
Apical and infraclavicular lesions
Pleurisy
(See page 466 for Classification of Extrathoracic Tuberculosis)

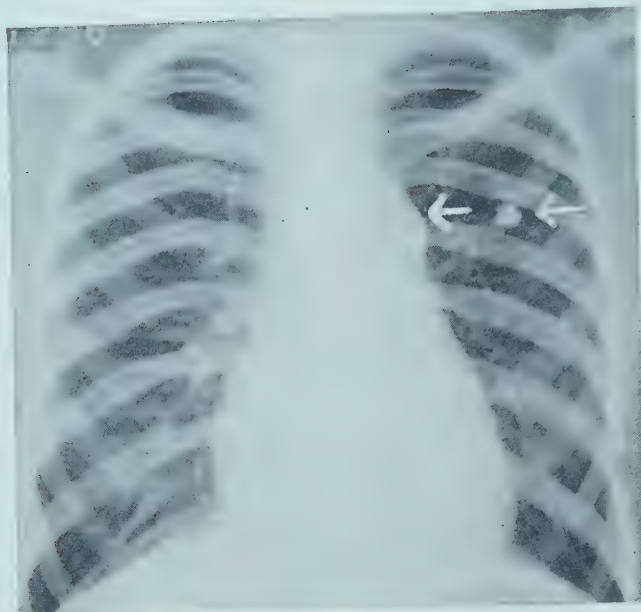


FIG. 126. Calcified tuberculous focus (right arrow) and calcified tracheobronchial lymph node (left arrow) in a Negro girl 10 years of age.

*lesions in the tracheobronchial lymph nodes* (Fig. 126) in a child with a positive reaction to tuberculin and no reaction to histoplasmin or coccidioidin and no evidence of active disease, he may be considered to be in an inactive state of tuberculosis. Calcified foci, especially those located close to the hilum, can usually be distinguished roentgenographically from blood vessels; the latter tend to have a smooth circular or elliptical homogeneous density, whereas the former are usually irregular in outline and density. Such a situation suggests a healed state, but the child must be watched for the possibility of a subsequent "break-down." In all cases a careful search for and elimination of tuberculous contacts are mandatory. Similar calcified intrathoracic lesions may be the residuals of histoplasmosis or coccidioidomycosis.

**Demonstrable noncalcified lesions.** As indicated in the initial paragraph of this section and in Table 70, a variety of lesions exist and require diagnostic differentiation.

The *noncalcified small pulmonary focus* appears on the roentgenogram as a more or less circumscribed area, usually not more than 1 or 2 cm. in diameter. There may or may not be evidence of associated hilar node involvement, but in infants and children there is likely to be. As a rule the child is not ill with this type of lesion. In children in the adolescent years such lesions are often located in the apex of the lung or the infraclavicular area, and in such circumstances initial tuber-

culous lesions may simulate the so-called reinfection lesions of adults.

On occasion the initial lesion in the lung is not confined to a small focal area, but extends into the surrounding lung tissue. Such an *extensive pulmonary infiltration* is often termed "progressive primary tuberculosis" (Fig. 127). Clinically, there are no certain methods for determining whether such a lesion is the initial one or is an exogenous reinfection or one resulting from hematogenous or bronchogenic dissemination. When only one such lesion is demonstrable, it is more likely to be an initial lesion which has been progressive; the distinction is, of course, academic. Such lesions may involve several lobules or most of a lobe.

Though there may be symptoms, not infrequently extensive pulmonary lesions are detected roentgenographically in children who have no complaints and whose parents have not observed any unusual manifestations.

Physical findings vary considerably. There may or may not be impairment to percussion. Rales may or may not be present. Cavitation occasionally occurs but, because it is likely to be farther away from the chest wall than in apical lesions, it may be missed on physical examination and even on roentgenograms. Tubercle bacilli can frequently be found in the sputum or in lavaged gastric contents.

*Infection of the hilar lymph nodes* is an almost constant accompaniment of pulmonary tuberculosis in infants and children. Th



nodes on the side of the parenchymal lesion are the ones usually involved, but the contralateral ones may also be infected. Frequently the only manifestation of the primary infection is the involvement of the tracheobronchial nodes, the parenchymal lesion being so small that it is not demonstrable even on the roentgenogram. The infection in the lymph nodes goes through the same stages as that of the parenchymal lesion and, until calcification is complete, is attended by the same danger of local extension and hematogenous dissemination.

There are frequently no symptoms (see p. 460). Though a brassy, paroxysmal cough is often attributed to enlarged nodes, it occurs so infrequently that it can scarcely be considered characteristic. Enlargement of the nodes is rarely demonstrable by physical signs. Cyanosis, edema of the face and dilatation of the superficial veins have been observed in association with extremely enlarged nodes, owing to compression of the larger blood vessels. Paravertebral dullness is rarely demonstrable. A murmur audible over the upper part of the sternum when the head is thrown

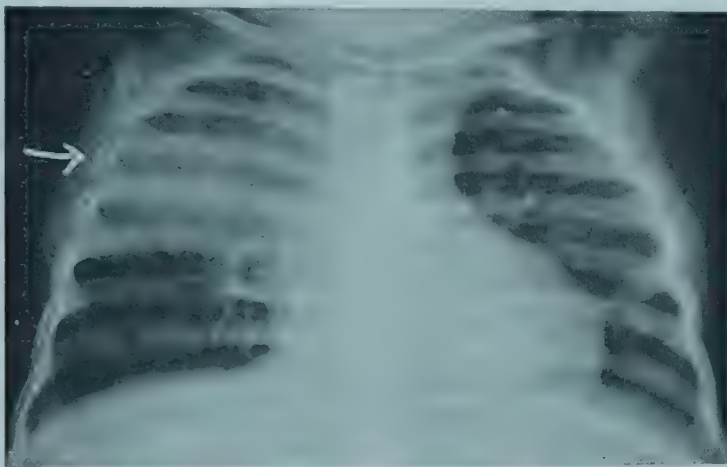


FIG. 127. Extensive infiltrative lesion in the middle portion of the right lung in a white boy 20 months of age.



FIG. 128.

FIG. 129.

FIG. 128. Noncalcified tuberculous lymph node.

FIG. 129. Secondary hematogenous lesions in the third toe (dactylitis) of the same child. The films were taken on the same date.

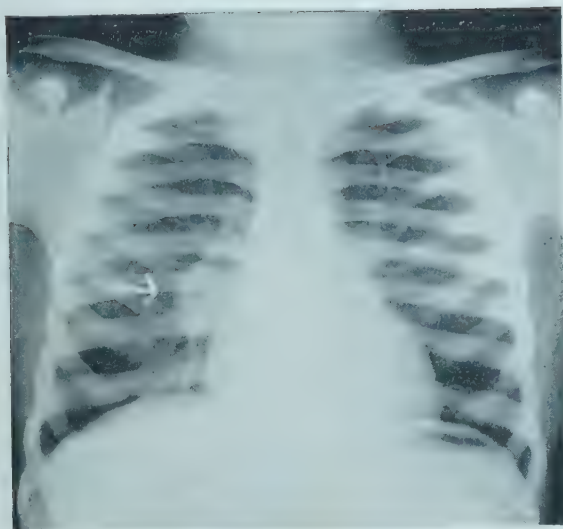


FIG. 130. Tracheobronchial caseocalcareous lymphadenitis in an apparently healthy Negro boy, detected in a routine survey.

back (Eustace Smith's sign) can be heard whether or not there is an enlargement of the lymph nodes, and d'Espine's sign, a spoken or whispered pectoriloquy or an echo from the spoken voice heard below the level of the seventh cervical or first dorsal vertebra, is not discriminating.

Roentgenographic demonstration of enlarged nodes in conjunction with a positive tuberculin reaction constitutes the best evidence for diagnosis. When the lymph nodes are not large and merge into the other hilar structures, they may not be distinguishable. Calcification may be considered evidence in favor of a tuberculous etiology, when the tuberculin test is positive and the histoplasmin and coccidioidin tests are negative.

*Intraluminal and extraluminal bronchial lesions* are of considerable importance in tuberculosis in children. Involvement of the bronchus is almost invariably from a contiguous lesion, rarely by direct infection from an outside source. A small bronchus is occasionally compressed or eroded by extension of an adjacent parenchymal lesion. By contrast, involvement of the larger bronchi is relatively frequent from contiguous tuberculous lymph nodes in the hilar area. It is current practice in our Clinic to examine bronchoscopically all children with enlarged tuberculous lymph nodes.

*Intraluminal lesions* are produced by extension of the tuberculous process from an adjacent lymph node through the bronchial wall with establishment of an ulcerative or granulomatous lesion. The ulceration may permit entrance of infected tuberculous material, dissemination of it to other portions of the tracheobronchial tree, and establishment of one or more new lesions at remote sites (bronchopneumonia). Granulomatous lesions may partially or completely obstruct the lumen of the bronchus.

An *extraluminal lesion* is a partial or complete occlusion of a bronchus by enlarged adjacent and usually adherent tuberculous lymph nodes without erosion through the bronchial wall.

When a bronchus is partially obstructed by compression from without or by an intraluminal granulomatous lesion to a degree sufficient to interfere with the flow of air, the portion of the lung supplied by the bronchus becomes emphysematous (Fig. 131). When the obstruction is complete, absorption atelectasis

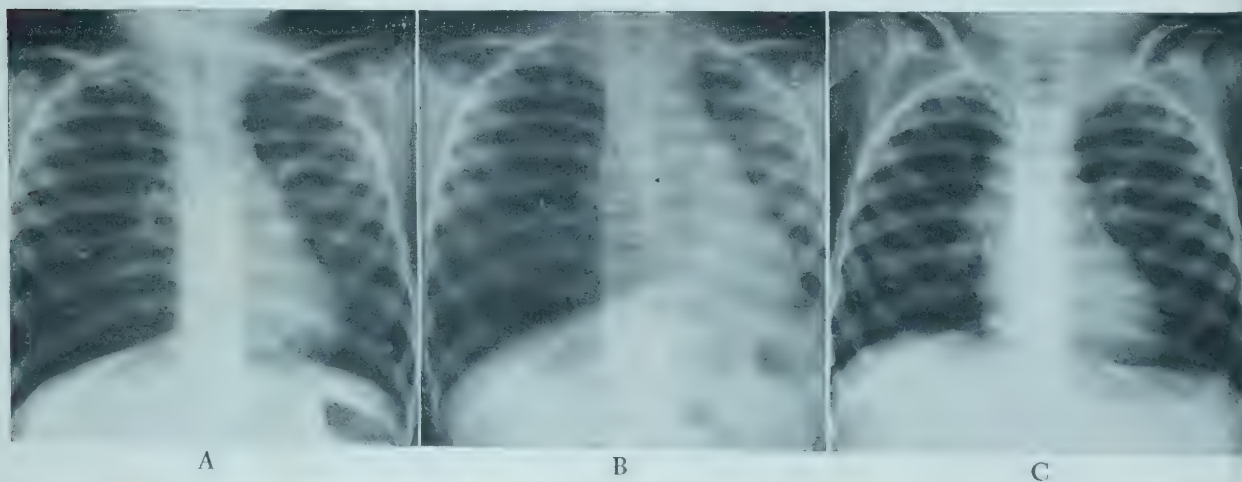


FIG. 131. Obstructive emphysema of the right lung secondary to a granulomatous intrabronchial lesion. A, Inspiratory phase; B, expiratory phase, showing failure of right lung to contract, and shift of heart and mediastinal structures to left; C, film taken 24 hours after bronchoscopic removal of tuberculous tissue from right main stem bronchus, showing normal aeration of right lung.



lectasis occurs (Fig. 132). In each instance there may also be a tuberculous pneumonitis in all or part of the involved pulmonary area (Figs. 133, 134).

Intrabronchial lesions may be responsible for cough, which may be brassy and may also be productive of variable amounts of sputum. When the lesions are in the major bronchi, they may be seen bronchoscopically. Biopsy material can often be obtained for histologic and cultural diagnostic purposes, and on occasion sufficient material can be removed to restore the bronchial airway.

*Caseous bronchopneumonia* may be localized in one area of the lung or widely disseminated. Material from a tuberculous focus in the parenchyma or in a lymph node discharged into a bronchus in a state of liquefaction is likely to be more widely distributed than when it is in a less fluid, caseous state. The lesions are particularly likely to be distal to the portion of the lung supplied by the eroded bronchus where conditions for localization are good, owing to interference with respiratory mechanics (Fig. 133). In some instances all lobes are involved (Fig. 134).

Children with caseous bronchopneumonia tend to be quite sick. There is usually fever, malaise and, not infrequently, a loose, productive cough. The physical findings vary considerably. There may or may not be impairment to percussion, bronchial breathing or rales. If there is cavity formation, there may be pectoriloquy unless the lesion is too deeply situated. The extent of the involvement can be determined only from the roentgenogram. Tubercle bacilli can usually be discovered in the sputum or lavaged gastric contents. Recovery without antimicrobial treatment is possible, but the prognosis in this type of tuberculous involvement is generally grave. Specific antibacterial therapy is indicated (see p. 465).

*Pulmonary lesions of hematogenous origin* may be roentgenographically indistinguishable from lesions described as noncalcified pulmonary foci, extensive pulmonary infiltrations, caseous bronchopneumonia and apical and infraclavicular lesions. The possibility that such lesions may have their origin by hematogenous dissemination is mentioned merely to point out the various means of origin of the different tuberculous lesions. Among the hematogenous pulmonary lesions, only acute miliary tuberculosis is clinically distinctive.

*Acute miliary tuberculosis* is a blood-borne infection characterized by multiple tubercle

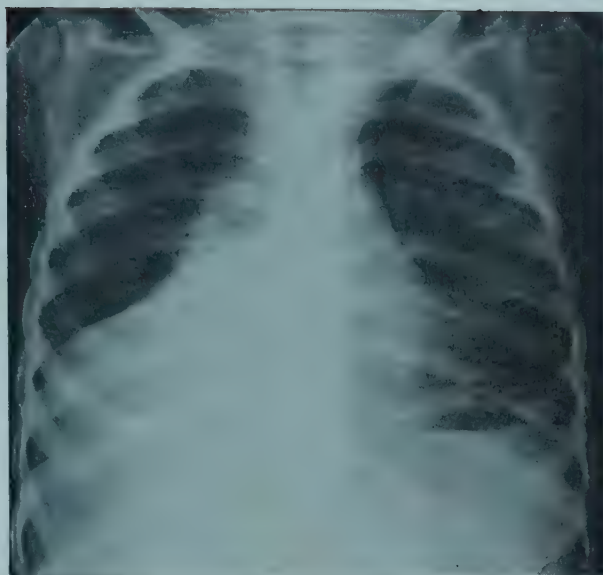


FIG. 132. Atelectasis of right middle and lower lobes secondary to tracheobronchial tuberculous lymphadenitis and an endobronchial granulomatous lesion in a Negro child 4 years of age. Gastric washings were positive for tubercle bacilli. Two months prior to the date of the exposure for the film the child suffered a partial bronchial occlusion which resulted in obstructive emphysema. Subsequently complete bronchial occlusion resulted in absorption atelectasis illustrated here. At this time a portion of the endobronchial granuloma was removed endoscopically. There was no immediate effect, but re-expansion occurred over the next 2 months.

formations. It is more frequent in infants than in older children; beyond infancy, miliary tuberculosis occurs more frequently in the Negro than in members of the white race. Practically all organs of the body may be involved, as may any serous membrane. The latter appear to be less frequently affected by direct hematogenous spread than by rupture of a contiguous tuberculous focus. The distribution of the lesions may be limited to the lungs or may include other viscera—for example, the liver, kidneys, spleen and brain. Tubercle bacilli become lodged in the small capillaries; a lesion develops at each site, and necrosis tends to develop rapidly in each of the small foci. If the life of the child is prolonged for a sufficient time, there is an epithelioid response. It is during this latter stage that the lesions in the lungs become visible on the roentgenogram.

The symptoms are usually those of a general infection. The onset may be abrupt, although at times it is insidious. Fever soon develops and tends to run an irregular course, frequently with peaks as high as 103° or 104° F., and the patient appears extremely ill. Initially there may be no physical signs

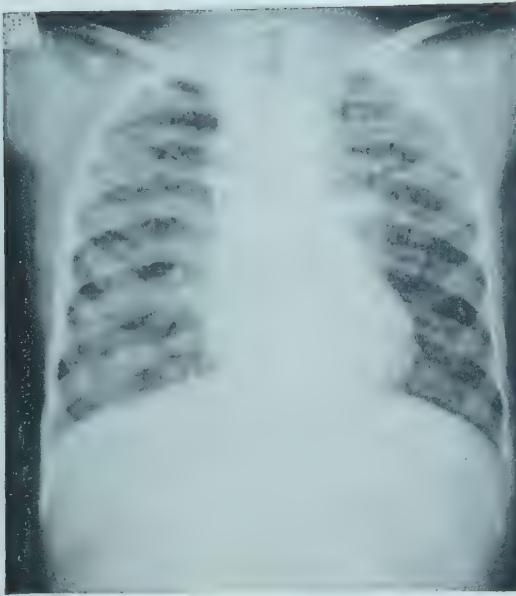


FIG. 133.



FIG. 134.

FIG. 133. Extensive tuberculous bronchopneumonia in a child 5 years of age, more marked on the right side.

FIG. 134. Appearance of lungs at 9 years of age, after recovery (prior to availability of specific antimicrobial therapy).

to indicate the extent of the involvement. The spleen is often enlarged and the abdomen distended, and these findings with the high fever and absence of other physical findings suggest the possibility of typhoid fever. At

times the pulmonary manifestations may be those of generalized obstructive emphysema, and acute bronchiolitis may be suspected. Localized signs which disclose the true identity of the infection frequently do not appear until the last week or so of the illness in the untreated patient. Fine crepitant rales may be heard at this time over all portions of the chest, and the roentgenogram which previously failed to reveal pulmonary changes will show the characteristic, widely distributed miliary lesions, which have a mottled appearance and are frequently described as resembling snowflakes (Fig. 135). The white blood cell count is not distinctive; it may be increased, but leukopenia is perhaps the more frequent response.

Death usually occurs within four to six weeks in untreated cases. Whereas the mortality rate formerly approximated 100 per cent, recovery is now possible in the majority of instances if treatment is instituted sufficiently early (see p. 465).

*Apical and infraclavicular lesions* are most commonly seen in adult life and are often termed "adult tuberculosis," "apical tuberculosis" or "reinfection tuberculosis." They are relatively uncommon before the adolescent period, when they become the most frequent type of tuberculous involvement, being more frequent in females than males. These lesions have generally been considered to be the result of reinfection tuberculosis, their tendency



FIG. 135. Miliary tuberculosis of the lungs in a white boy 3 years of age. His mother had pulmonary tuberculosis. The physical findings were fine, crackling rales throughout both lungs. Death occurred shortly after this roentgenogram was taken. The tuberculin reaction was positive.



to remain localized and the absence of any extensive involvement of the regional lymph nodes being attributed to an altered response of the host because of a previous infection with the tubercle bacillus. It is now known that lesions will develop in the upper portions of the lungs in previously tuberculin-negative as well as tuberculin-positive adolescents and young adults which are clinically indistinguishable. For this reason these lesions are described simply on the basis of their location and roentgenographic appearance.

The clinical course of individual lesions varies, but in general they can be grouped in three categories. In some there is retrogression toward healing almost from the time of recognition; in others the lesion is quite indolent and resists healing. In this latter type, activation of the lesion may be associated with any factor which lowers the host's general resistance. In the third type the lesion is persistently progressive, and there is destruction of lung tissue with cavitation.

The symptoms and physical findings are also variable. In some instances no symptoms whatever can be elicited, and the diagnosis is made only roentgenographically. In others there may be the general symptoms of a chronic infection (p. 460). Physical examination may or may not reveal fine rales; when present, they are likely to be most consistently detected at the beginning of an inspiration which follows a slight cough after forced expiration. Cavity formation of any extent can usually be suspected on the basis of bronchophony and pectoriloquy. The diagnosis is established by roentgenographic examination, the detection of tubercle bacilli in the sputum or lavaged gastric contents, and upon the response to the tuberculin test. It is necessary to recognize that essentially similar lesions can apparently be produced by coccidioidomycosis and histoplasmosis.

*Tuberculous pleuritis* may occur as a dry fibrinous pleurisy, as a serous effusion, and rarely as a necrotic involvement of the pleura stemming from a contiguous caseous focus in the lung. Most often the reaction is a serous one. Though the total number of tuberculous effusions is decreasing, it is still good judgment to regard all serous effusions as tuberculous until proved otherwise. The process is nearly always unilateral.

Children rarely have complaints suggestive of pleural involvement. Occasionally during the dry stage there may be pleural pain with limitation of respirations on the affected side. Rarely an effusion may become so extensive

that there is actual bulging of the intercostal spaces, so that there is respiratory embarrassment. The presence of a pleural effusion is usually suspected from physical findings, and the diagnosis is confirmed roentgenographically and by pleural aspiration.

The prognosis is generally governed by the pulmonary lesion. Treatment is that of tuberculous infection; aspiration, other than for diagnostic purposes, is indicated only when there are severe symptoms of compression. Absorption of fluid is followed by pleural thickening and adhesions. There is no evidence that drainage will lessen such residuals or prevent reaccumulation of fluid.

#### DIAGNOSIS OF PULMONARY TUBERCULOSIS

The diagnosis of pulmonary tuberculosis is established with certainty by the demonstration of tubercle bacilli in the sputum, bronchoscopically aspirated material or gastric contents. In the absence of such information the diagnosis is based on the history of symptoms and of contact with tuberculous infection, on the physical examination, on the reaction to tuberculin, and on roentgenographic examination of the lungs. Of these, the roentgenogram and the tuberculin test are the most informative. Careful search for tubercle bacilli, however, should always be made.

The evaluation of the child suspected or proved to have tuberculosis should include an estimate of whether the tuberculous lesion is in an active, quiescent or healed stage (see p. 462). In the absence of fever and other clinical evidences of disease such an evaluation is rarely clear-cut.

The appraisal is not complete without a careful search for the source of contact. Frequently open tuberculosis is present in some member of the family or other close associate without his being aware of it (Figs. 136, 137). For this reason tuberculin tests should be performed on the siblings; if the reaction is positive, roentgenograms of the chest should be obtained. All adult members should have a careful physical examination, tuberculin test and a roentgenogram of the chest. Grandparents and other older persons with whom there is contact should be included in this examination, since chronic, open tuberculosis is common among older people. It is a good policy to repeat the examination of the members who have no evidence of disease after an interval of about six months. This plan has the dual advantage of detecting other persons with tuberculosis who require treat-

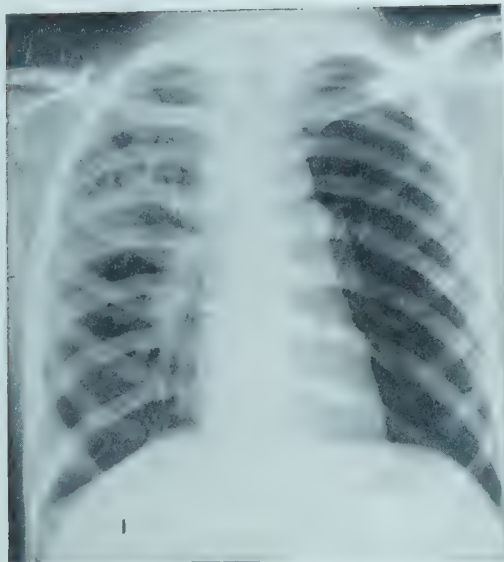


FIG. 136.



FIG. 137.

FIG. 136. Calcified node in left hilar area and tuberculous lesions in upper part of right lung in a Negro child 12 years of age.

FIG. 137. Extensive tuberculous lesion in the chest of the mother, who disclaimed any knowledge of illness or history of tuberculosis in any member of the family. Sputum was positive for tubercle bacilli. Roentgenogram of the mother was taken as part of a survey of the family because of detection of tuberculosis in the child.

ment and of avoiding subsequent contact of the tuberculous child with open tuberculous infection.

**History.** History of possible contact with open tuberculosis should be included in the appraisal of all children with or without symptoms of the disease. Absence of such a history, however, cannot be accepted as evidence against the presence of tuberculosis in the individual child, in members of his family or in other associates, since history of contact is not obtained from the majority of persons found to have tuberculous lesions.

Symptoms of pulmonary tuberculosis vary considerably and to some extent are proportionate to the extent or seriousness of the lesion. However, there are variations in this regard, and it is essential to know that pulmonary infections, even extensive ones, may not be productive of any recognizable symptoms. As a rule, symptoms in children are merely the general ones of chronic infection, such as fatigue, irritability and possibly some degree of undernutrition, and are usually not directly related to the respiratory system. Such symptoms are often overlooked. When all or most symptoms such as cough with expectoration, hemoptysis, fever, fatigue, malaise, loss of weight, and night sweats are present, one may be certain that the lesion is extensive.

**Physical Examination.** The examination should be complete, since tuberculous lesions

may be present in other parts of the body and nontuberculous conditions of the lungs or other parts of the body may be coexistent. Malnutrition may be serious, especially in children of the lower economic groups.

The physical findings of the lungs vary with the nature and extent of the lesion and have been described above. Not infrequently, extensive lesions are found on the roentgenogram when no or only slight abnormal physical signs have been elicited. In general, physical signs of tuberculosis in children tend to be disproportionately few in relation to the extent of the pulmonary damage.

**Roentgenographic Examination.** The common roentgenographic abnormalities have been described and illustrated in the descriptions of the various clinical types of intrathoracic tuberculosis. Those lesions produced by acute bacterial or viral infections can usually be suspected by the clinical course. Chronic intrathoracic disease, such as histoplasmosis or coccidioidomycosis, persistent bronchopneumonia, pulmonary changes following measles or pertussis, lymphoblastomas of the mediastinum, lung abscess, aspiration of foreign material, pulmonary infiltrations due to ascariasis, toxocariasis or *Pneumocystis carinii*, Loeffler's pneumonia, Letterer-Siwe disease and others, are likely to simulate the lesions produced by pulmonary tuberculosis. It should be recognized that inter-



pretation of roentgenograms without adequate knowledge of the history, physical findings and laboratory data will lead to many erroneous diagnoses.

**The Tuberculin Test. Significance of a positive reaction.** A positive tuberculin reaction is evidence that the person has been infected with the tubercle bacillus and is allergic or hypersensitive to its protein. The presence or absence of activity of the lesion cannot be deduced from the extent of the reaction. Properly used, the test constitutes the most reliable method for the selection of children who have had a tuberculous infection and who thus require further examination to determine whether the lesion is active or quiescent.

With certain exceptions, failure to elicit a positive reaction to tuberculin eliminates the possibility of the presence of tuberculous infection. For several weeks after the entrance of tubercle bacilli into the body there is no cutaneous reaction to tuberculin. During advanced or terminal stages of tuberculosis, allergy to tuberculin may disappear; at times it is temporarily inhibited by such nonspecific factors as severe inanition, dehydration and acute febrile diseases. The length of time that allergy to tuberculin will persist after healing of the lesion, and the factors that govern it are not completely understood. In most instances cutaneous allergy persists for years in association with healed lesions.

In the performance of repeated tuberculin tests the question of sensitization to tuberculin is pertinent to the interpretation of all tests subsequent to the initial one. Old tuberculin has been demonstrated to be essentially nonantigenic in the amounts used for ordinary cutaneous testing, as has purified protein derivative (P.P.D.).

**Choice and dose of tuberculin.** Since there is a common allergen for the human and bovine types of tubercle bacilli, the use of tuberculin from human tubercle bacilli is considered adequate. Old tuberculin (O.T.), prepared by concentrating a glycerin broth culture of tubercle bacilli over steam and passing it through a porcelain filter, has long been a standard tuberculin. The principal objection to it is that different batches vary in potency.

Several new tuberculins have been developed which contain no protein other than that of the tubercle bacillus. Of these, only purified protein derivative (P.P.D.) is used at present. Purified protein derivative is the protein of the tubercle bacillus which has

been precipitated from cultures of tubercle bacilli on nonprotein media. Its antigenicity is reduced by heating. It is usually dispensed in the dried state in tablet form, and is dissolved in a measured amount of diluent before use.

The recommendations for dosages of tuberculin by the National Tuberculosis Association (Diagnostic Standards, 1957) are as follows:

For diagnostic and case-finding work and following BCG vaccination, the use of five international units (5 TU) of PPD is recommended as the best single dose, i.e., that amount of any standardized PPD prepared according to acceptable methods which is equal in potency to .0001 mg. of PPD-S, the international standard for human tuberculin. If there is no reaction, or a small one, and suspicion of tuberculous infection still exists, repetition of the test with the same dose is recommended. If there is reason to expect a severe reaction, 1-5 dilution of the above dose may be employed as a preliminary test. This dilution is made with sterile physiological or buffered saline solution.

When OT must be used, it is recommended that the dosage be equivalent to the 5 TU dose of the international OT standard. If the OT used approximates the international standard in potency, the recommended dose would be 0.1 ml. of a 1:2000 dilution (.05 mg.). Unfortunately, there is evidence that some commercial preparations of PPD and OT vary in potency which may lead to variations in results.

There is good evidence that doses greater than 5 TU produce some reactions which are not specific for tuberculous infection. For this reason, the larger doses are of doubtful diagnostic value.

In view of the similarity of certain fungus infections to tuberculosis, it would be wise to perform tests with their antigens simultaneously with the performance of the tuberculin test. This procedure is particularly applicable to histoplasmin in the central part of the United States and to coccidioidin in the far Western states.

**Technique.** There are various methods of performing the tuberculin test, such as the scarification or cutaneous test of Pirquet, the intracutaneous test of Mantoux and the patch test of Vollmer. The percutaneous test of Moro is not used in this country, and the conjunctival test of Calmette is not a safe procedure. In clinical practice or when large numbers of tuberculin tests are to be performed, the intracutaneous method is the one of choice.

For the *intracutaneous test* a 1-cc. tuberculin type syringe graduated to 0.1 cc. and a 27-gauge, short-bevel needle should be used. The injections should be made intracutaneously and not subcutaneously. The tubercu-

lin is so diluted that the testing dose is contained in 0.1 cc. of the diluent.

Tuberculin is heat-stable, and it is practically impossible to remove traces of it from syringes or glassware by ordinary methods of cleaning. For this reason a syringe for tuberculin should be restricted to this testing material and should never be used for any other skin-testing solution. Thus, if a cutaneous reaction was obtained from Schick testing material injected from a syringe previously used for tuberculin, one could not be certain whether the reaction resulted from the Schick material or from the tuberculin.

Recommendations for interpretation of the tuberculin test according to the Diagnostic Standards (1957) of the National Tuberculosis Association are as follows:

The intracutaneous tuberculin test (Mantoux) with either PPD or OT should be read 48 to 72 hours after the injection. Readings should be made in a good light, with the arm slightly flexed. Response to injection is classified on the basis of induration as noted by gentle palpation and stroking with the fingers and not by inspection alone. Reactions should be measured in millimeters at the largest transverse diameter and this measurement recorded.

It has been customary and is recommended that induration over 5 mm. in diameter be regarded as a positive test. There is now some evidence that a better dividing point might be 8 or 10 mm. since almost all patients with active tuberculosis have reactions this size or larger, and smaller reactions may be non-specific. However, the data are inconclusive at this time, and for that reason it is recommended that the exact measurements of reactions be recorded . . . and that [for] persons with reactions over 5 mm., . . . the test should be repeated [and] also if there is redness over 10 mm. in diameter without associated induration. Such redness may be the result of an injection made too deeply.

In extremely severe reactions to the intracutaneous test the inflammation may be decreased and sloughing of the necrotic center at times avoided by prompt application of an ice compress and administration of a corticosteroid.

The *Vollmer patch test* is not as efficient in eliciting positive reactions as the 5 TU dose of PPD and OT. Since, however, it is fairly widely used, a description of the technique and interpretation of the reaction are included here.

The "patch" is applied to the intrascapular area. The skin should be rubbed briskly with some defatting solution such as acetone or ether and permitted to dry. The adhesive is then warmed over a flame or in the palm of the hand and firmly applied. It is removed after forty-eight hours and the test

is read after a second forty-eight-hour period. A positive reaction to the patch test consists of a reddened *indurated* area or several more or less distinct *papules*.

**Bacteriologic Examination.** Tubercle bacilli can usually be isolated in children with active lesions if a diligent search is made. It is the only means for establishing an absolute diagnosis of tuberculosis. There are three principal means for detection of the tubercle bacillus: (1) by direct smear and staining of sputum, cerebrospinal fluid or discharges from such lesions as draining lymph nodes and sinuses of osseous lesions; (2) by guinea pig inoculation of any of these materials; and (3) by cultural methods on artificial media. The last is the most effective. In infants and children who are liable to swallow sputum the lavaged contents of the fasting stomach provide the best source of material for examination. The lavage should be performed early in the morning before the usual breakfast time.

Appropriate studies should always be performed to determine that the acid-fast bacilli isolated are *M. tuberculosis* and not other (atypical) acid-fast bacilli, so-called photochromogens and nonphotochromogens. These bacilli occasionally cause infections in lymph nodes and are also found in the bronchial secretions of patients with chronic bronchopulmonary disease. The significance of these organisms in the production of infection in human beings is not clearly defined. At times they appear to be saprophytes, and on rare occasions appear to be responsible for tuberculosis-like infections. It also appears that some of them are antigenically related to the tubercle bacillus and may induce hypersensitivity which can be elicited by the usual tuberculin test.

**Evaluation of Clinical Activity.** The diagnosis of tuberculous infection is not complete without determining whether the lesion is active or quiescent. When there are such obvious signs of clinical activity as fever and malaise, no further evidence is required. When there are no apparent manifestations of active infection, however, other measures must be used. These include sedimentation rates, blood cell counts, serial roentgenograms, response to exercise and particularly continued observation of the child's apparent well-being and his growth pattern. Rectal temperature should not be taken for at least a half hour after active exercise, since it is normally elevated for a short time after



physical activity. Failure to recognize this fact has often been responsible for unnecessarily confining a child to bed or to reduced activity.

### PROGNOSIS

Most children recover from the primary tuberculous infection, and the majority are unaware of its presence even during its active phase. The realization that recovery is frequent has resulted in the conclusion by some clinicians that the primary infection is a benign lesion. There is an apparent failure to recognize the relatively high fatality rate during the first two years of life, as well as the fact that hematogenous and bronchogenic lesions originate from the primary focus and, in such instances, are in reality a part of the primary infection.

The mortality has been relatively high in the first few years of life and during adolescence (Figs. 123, 124, p. 450). However, the prognosis of pulmonary as well as of other forms of tuberculosis has been tremendously improved by the use of antimicrobial agents. Death, except in tuberculous meningitis, almost never occurs except in patients who are not treated or in whom the diagnosis is made in the terminal phase of the disease. Antimicrobial treatment of pulmonary tuberculosis has resulted in a striking decrease in hematogenous lesions. This observation has led to an extensive clinical trial (p. 464) with the prophylactic administration of isoniazid to young children with possible tuberculin reactions with or without roentgenographically demonstrable lesions and to older children who are known to have become tuberculin-positive within recent months on the possibility that the progression of the localized lesion could be averted and that hematogenous dissemination would be lessened (see Treatment).

### PREVENTION

The only certain means for the prevention of tuberculosis is avoidance of contact with infected persons. Maintenance of an adequate nutritional status and avoidance of fatigue and of debilitating infections are factors in the preservation of the body's natural resistance, but none of them is sufficient to prevent infection.

As yet no certain method has been developed for production of a solid, artificially induced specific immunity.

**Identification of Tuberculous Contacts.** Perhaps the most important measure for the

prevention of tuberculosis in children would be frequent examination of all adults for the presence of tuberculosis. The photofluorographic film is especially serviceable as a survey medium. However, roentgenographic diagnosis is not infallible, and abnormal roentgenographic shadows must be further evaluated by skin tests with tuberculin and fungous antigens and by bacteriologic examinations. Another method of approach is the selection of candidates for roentgenographic examination by means of the tuberculin test. In pediatric practice all children should have a tuberculin test at intervals of two to three years.

In view of the high morbidity and mortality rates for tuberculosis in the crowded sections of the larger cities where poor housing conditions prevail, it is obvious that correction of these factors is an important public health measure.

**Milk.** If at all possible, only pasteurized milk from tuberculosis-free cattle should be used for the feeding of infants and children. Unpasteurized milk, except certified, should not be used without boiling.

**Artificial Immunity.** There have been numerous attempts to develop a satisfactory method for the stimulation of artificial immunity against tuberculosis. Of these, only BCG (*Bacillus of Calmette and Guérin*) vaccination merits continued use. The vaccine is composed of bovine tubercle bacilli whose virulence has been reduced by special cultural procedures. Administration of the vaccine to animals or man produces a limited immunity to reinfection with virulent tubercle bacilli. Intradermal injections seem to be somewhat more effective than subcutaneous ones and less likely to result in indolent ulcers. An occasional infant vaccinated during the first few months of life may acquire suppurative adenopathy, but such a complication almost never occurs in older infants or children. The usual intradermal dose is in the range of 0.1 or 0.15 mg. of freshly prepared vaccine. Positive tuberculin reactions can be expected to develop in most instances after inoculation.

Controlled studies, chiefly in the Scandinavian countries and in the United States, have shown that BCG vaccination produces definite though incomplete protection against tuberculosis. There is general agreement among public health authorities that BCG vaccination is indicated for children who live in areas with high tuberculosis mortality rates and for children who have intimate contact

with persons with inactive or "arrested" tuberculosis.

At present BCG vaccine is prepared in only a few laboratories. Its distribution from these laboratories is usually controlled by local or state health departments.

**Chemoprophylaxis.** In some areas where exposure to tuberculosis is highly probable, trials are under way to determine whether the daily administration of isoniazid to tuberculin-negative persons is an effective and safe prophylactic measure.

#### TREATMENT

The basis for selection of patients for antimicrobial therapy has changed materially in the past few years. Now it is generally agreed that all children with demonstrable active lesions of whatever order and in whatever location of the body should receive such therapy. In addition, it is recommended that all tuberculin-positive children up to three or four years of age and all older children who are known to have become tuberculin-positive within recent months should receive isoniazid in doses of 10 to 20 mg. per kilogram per day for about one year whether or not they have demonstrable lesions. The reasons for this changed policy are largely the effectiveness of isoniazid in the control of progressive lesions, the low degree of its toxicity and, in particular, its apparent effectiveness in the prevention of hematogenous dissemination.

The most useful drugs in the treatment of tuberculosis are isoniazid, streptomycin and aminosalicylic acid. Agents which have occasional usefulness despite their greater limitations include kanamycin, Promizole, Promin, neomycin and viomycin.

*Isoniazid* is the most active and useful of the available agents. It can be administered orally or parenterally. Its toxicity is low, being well tolerated over long periods of time, provided the daily dose does not exceed 10 to 20 mg. per kilogram per day. The emergence of drug-resistant organisms is not rapid, and it can be used as a single agent in many patients with the less serious forms of tuberculosis. The patients with progressive, localized lesions, miliary tuberculosis and meningitis should receive another agent during the early part of their treatment (Table 71). Some adults who received isoniazid for a long time have had convulsive disorders. So far as known, such complications have not been observed in infants and small children. Such reactions have been minimized or averted by the continuous administration of pyridoxine.

*Streptomycin* is an active agent against *M. tuberculosis*, and its use is probably indicated in addition to isoniazid in all serious tuberculous infections. The drug must be administered by intramuscular injection. Long-term treatment is occasionally complicated by labyrinth disorders and less often by deafness, but these are uncommon if the drug is administered only once a day or less frequently. Streptomycin should not be used as the only antituberculous agent, owing to the rapid emergence of streptomycin-resistant organisms. This process can be retarded if another agent is administered concurrently. Dihydrostreptomycin is not recommended, since deafness is a common sequel.

*Aminosalicylic acid* (para-aminosalicylic acid) is tuberculostatic, but is not as effective as either streptomycin or isoniazid. It rarely produces toxic reactions other than gastric irritation, which is occasionally sufficiently severe to prevent its administration. Drug-resistant tubercle bacilli have been infrequently observed after prolonged use of aminosalicylic acid as the sole therapeutic agent. Its value as an antibacterial agent is increased because it inhibits the development of resistance by tubercle bacilli to both streptomycin and isoniazid, and possibly because it results in increased serum levels of isoniazid by competing with it for acetylation.

*Promin* and *Promizole* are not as effective as aminosalicylic acid or isoniazid. Furthermore, both Promin and Promizole can cause serious toxic reactions. Their use, therefore, is rarely indicated.

*Kanamycin* is almost as effective as streptomycin in the treatment of tuberculosis. It does, however, have a slightly greater tendency to produce deafness when used for a prolonged time. Kanamycin does not exhibit cross-resistance to streptomycin, and it can be used in the occasional instance when streptomycin-resistant organisms emerge. Kanamycin is less toxic than neomycin and viomycin. The latter two drugs can cause temporary or permanent renal damage. These agents have been used mainly in the treatment of adults in whom streptomycin-resistant tubercle bacilli have developed. There would seem to be little place for them in the treatment of tuberculosis in children.

Preliminary observations suggest that *corticosteroid therapy* in conjunction with antimicrobial drugs is beneficial in patients with endobronchial granulomas, other severe obstructive lesions of the bronchi and in those with pleural effusions. Corticosteroid therapy



is reported to cause improvement, often within one week, but should be continued for approximately two months even when symptomatic improvement is prompt.

Suggested plans for antimicrobial treatment of the various clinical forms of tuberculosis are detailed in Table 71.

When patients with progressive pulmonary tuberculosis are treated by the suggested plan, symptomatic improvement is usually noted in two to four weeks. Cough decreases, fever declines, and there is increased appetite and sometimes gain in weight. Improvement, as measured by changes in the roentgenograms of the chest, is slow, but extension of the lesion rarely occurs.

Patients with miliary tuberculosis tend to show somewhat more rapid improvement in response to treatment. There is apt to be regression or even disappearance of the miliary densities observed in the roentgenograms within six to ten weeks from the start of treatment. Coexisting extensive pulmonary lesions follow the same pattern of slow improve-

ment noted with other progressive pulmonary lesions. Although meningitis is now an infrequent complication during the treatment of pulmonary tuberculosis when isoniazid is being administered, it is recommended that the cerebrospinal fluid be examined if there is any manifestation to suggest its presence. If meningitis develops, the patient should be treated as outlined on page 470.

*The use of antibacterial agents in the treatment of pulmonary tuberculosis does not eliminate the need for symptomatic and other general therapy.*

Children with nonprogressive primary tuberculous lesions, whether or not they are receiving isoniazid, require no special care beyond that of assurance of adequate nutrition, avoidance of fatigue, prevention of exposure to open tuberculous infection and regular physical examinations, including roentgenograms of the chest. Active immunization against pertussis and passive immunization for measles, whenever exposed, are desirable for children with tuberculous lesions, as is the

Table 71. Suggested Schedules for Antimicrobial Therapy of Pulmonary Tuberculosis in Infants and Children

<i>Type of Disease</i>	<i>Drug<sup>1</sup></i>	<i>Total Daily Dose per Kilogram of Body Weight</i>	<i>Duration</i>
Positive tuberculin reaction in a child under 3 or 4 years of age or a positive tuberculin reaction recently acquired	Isoniazid	10 to 20 mg. (total daily dose should rarely exceed 500 mg.) <sup>2</sup>	One year
Asymptomatic pulmonary tuberculosis	Isoniazid	10 to 20 mg. <sup>2</sup>	One year
Progressive pulmonary lesions; progressive apical and infraclavicular lesions; pleurisy; miliary tuberculosis	Isoniazid	10 to 20 mg. (total daily dose should rarely exceed 500 mg.) <sup>2</sup>	12 to 18 months or for a minimum of 6 months after lesion appears to be inactive
	Streptomycin	20 to 40 mg. in one dose per day (dose not to exceed 1.0 gm./day)	Daily for 1 to 2 months, then 2 to 4 times weekly for 3 to 6 months (concurrently with isoniazid)
	or Aminosalicylic acid (PASA)	300 to 500 mg.	For duration of isoniazid therapy. If streptomycin is given initially, then substitute PASA for it after its discontinuance. Some prescribe it only for an arbitrarily determined shorter time

1. See text for use of corticosteroids.

2. The smaller doses are used for large and overweight children. Pyridoxine is prescribed with isoniazid for adolescent children by some clinicians to lessen the likelihood of convulsive disorders.

early treatment of all intercurrent infections in order to lessen the possibilities of activation of the tuberculous process.

Children who are sick with tuberculosis as evidenced by fever, malaise, loss of weight, anemia, abnormal white blood cell count, increased erythrocyte sedimentation rate and/or roentgenographic evidence of progression of the tuberculous lesion require general medical care.

*Bed rest* is indicated until there are substantial evidences of improvement. Other than maintenance of the necessary isolation procedures (p. 397), the management is that of any child with a chronic illness, whether in an institution or at home.

The *psychologic attitudes* of the child and his family are important. An atmosphere of cheerful optimism should prevail in which the child is provided some regularity of schedule and even some purposeful duties which can be accomplished in bed. Except in severe illness, there is no reason why the child should not be permitted to continue with his schoolwork.

*Fresh air and sunshine* are not important in treatment except as they add to the child's sense of well-being. Heliotherapy is not contraindicated except in excessive amounts in patients with pulmonary lesions. Burning of the skin should be scrupulously avoided. Tanning is permissible if it is acquired gradually.

The *nutritional intake* should be adequate, but forced feeding should be avoided. Special attention should be given to the protein, mineral and vitamin content of the diet. There is need for additional amounts of vitamin C; 100 to 200 mg. of ascorbic acid will meet the daily requirement in the average case. There is no reason why this cannot be supplied by natural foodstuffs. Vitamins of the B complex should be supplied in amounts somewhat in excess of average requirements. There is no need for excessively large doses of vitamin D, nor is there need for more than a quart of milk a day. Fresh fruits and vegetables should be given freely. Feeding of tuberculous infants is, with the exception of those with gastrointestinal disturbances, not different from that of other infants. Low residue diets should be prescribed when there is chronic intestinal involvement.

*Surgical procedures*, other than bronchoscopy, are rarely indicated in the treatment of pulmonary tuberculosis in infants and children. Collapse treatment is occasionally indicated in older children and adolescents. Lobectomy is occasionally required for those

with persistent atelectasis or bronchiectasis following endobronchial lesions.

## EXTRATHORACIC TUBERCULOSIS

### TUBERCULOUS INFECTION OF TONSILS AND CERVICAL LYMPH NODES

Infection of the cervical lymph nodes is, in most instances, secondary to tuberculous infection of the tonsils, which may constitute the primary lesion or may be secondary to a pulmonary lesion. When the tonsillar infection is primary, it constitutes, in conjunction with the cervical lymph node involvement, a primary tuberculous complex. Such infections have become much less frequent with the decrease in incidence of bovine tuberculosis.

**Clinical Manifestations.** The local manifestations of tuberculosis of the cervical lymph nodes vary from slight enlargement of a single node to involvement of a number of them. The nodes of both sides are frequently affected, although usually more on one side than on the other. The initial inflammatory changes are responsible for the enlargement, and at this stage the node or nodes are discrete, firm and usually freely movable. When the lesions of the individual nodes become caseous, however, there is a tendency to erosion of the capsule, and the nodes in the immediate vicinity become matted together in a single, irregular nodular mass, often with variable degrees of firmness in different portions. The mass becomes attached to other

Table 72. Classification of Extrathoracic Tuberculosis

Tuberculosis of tonsils and cervical lymph nodes
Intra-abdominal tuberculosis
Enteritis
Mesenteric and retroperitoneal lymphadenopathy
Peritonitis
Liver
Fistula in ano
Tuberculosis of central nervous system
Tuberculoma
Tuberculous meningitis
Tuberculosis of skin
Tuberculosis of bones and joints
Tuberculous pericarditis
Tuberculosis of genitourinary tract
Kidney
Bladder
Female genital organs
Male genital organs
Tuberculosis of eye
Phlyctenular keratitis
Chorioretinitis
Tuberculosis of middle ear



adjacent structures and to the overlying skin and is no longer freely movable. The skin is often discolored and may be retracted in areas by the underlying adhesions, thus having an uneven contour.

If liquefaction of the caseous mass occurs, rupture into the adjacent tissues is likely. If the overlying skin is perforated, as it often is, a draining sinus results which persists a long time. There may be only a single sinus, or, as new areas break down, other sinuses may be formed. When the nodes of the retropharyngeal area are involved or when the discharge from other nodes or from an osseous lesion in the cervical vertebrae finds its way into the retropharyngeal area, a chronic, burrowing retropharyngeal and retroesophageal abscess results. The draining sinuses on the surface of the neck persist until the involved lymphatic tissue is broken down and evacuated, the course without antimicrobial therapy being measured in months and, at times, in years. Indolent skin lesions frequently result, and healing leaves permanent scarring, discoloration and contractural deformities.

Not all tuberculous lymph nodes undergo such a course, and resolution may take place before extensive caseation occurs, or the caseous mass may become calcified and a number of nodes remain matted together and indurated without suppurating. When calcification is present, it may be visualized roentgenographically. During the period of active inflammation there may be a low grade fever and other evidences of chronic infection.

**Diagnosis.** The tonsillar lesion can be identified only by microscopic examination of the enucleated tonsil.

The differential diagnosis is from other conditions which may cause chronic lymphadenitis, and should include the lymphoblastomas, Hodgkin's disease, actinomycosis and cat-scratch disease. Particular difficulty is experienced in residual or low grade cervical lymphadenitis associated with chronic upper respiratory tract infections. The likelihood of a tuberculous etiology is increased in the presence of a positive tuberculin reaction, but the diagnosis is established only by isolation of tubercle bacilli from the excretions of a draining sinus or by microscopic examination of an excised lymph node.

**Prognosis.** This depends upon the stage at which diagnosis is established and treatment instituted. Most lesions eventually heal even when untreated. In such instances contractural deformities may be expected.

**Treatment.** Treatment varies with the stage of the lesions at the time of diagnosis. If the lymph nodes are still discrete, excision of the involved ones by careful surgical dissection is recommended. Streptomycin, 10 to 20 mg. per kilogram per dose, should be administered two or three times at intervals of twelve hours prior to operation. After excision streptomycin is continued for approximately two weeks, or longer if the operative site shows any drainage. Isoniazid is also administered postoperatively for twelve months in doses of 10 to 20 mg. per kilogram per day.

If the lymph nodes have ruptured spontaneously prior to establishment of the diagnosis, antibacterial therapy as recommended for progressive pulmonary tuberculosis in Table 71 should be instituted. If drainage persists after two weeks of treatment, secondary bacterial infection is probably present, and other antibiotic therapy should be given in addition to the antituberculosis therapy. In most instances the sinus tracts will close within several weeks. Surgical excision can then be performed; antimicrobial therapy should be carried out postoperatively as recommended above.

If the mass of lymph nodes is so extensive that surgical excision is not feasible, a trial of antimicrobial therapy as recommended for progressive pulmonary lesions in Table 71 is suggested.

Whether tonsillectomy should be performed several weeks after excision of the lymph nodes is not established.

#### INFECTION OF OTHER SUPERFICIAL LYMPH NODES

Tuberculosis of other superficial lymph nodes, such as those of the axilla, groin or occipital region, may occur, but is less frequent than infection of the cervical lymph nodes. The course of the infection is that described for cervical lymphadenitis.

#### INTRA-ABDOMINAL TUBERCULOSIS

Tuberculous enteritis may occur as a primary infection or may be secondary to a pulmonary lesion, the bacilli being transported in swallowed sputum. The stomach is rarely infected. Progressive ulcerative enteritis is more likely to be a secondary than a primary infection and is usually associated with a well advanced pulmonary process. In both primary and secondary lesions the mesenteric and, at times, the retroperitoneal lymph nodes are involved. In primary infections the intestinal

lesion is usually relatively unimportant and is overshadowed by the lymph node involvement, whereas the situation is essentially reversed in secondary infections. Tuberculous peritonitis may be part of a generalized hematogenous infection, but more frequently results from rupture of a caseous mesenteric lymph node or by extension from an ulcerative intestinal lesion. Tuberculosis of the liver and spleen is usually a part of generalized miliary tuberculosis. The incidence of primary intestinal tuberculosis in this country has decreased tremendously in recent years, owing to the almost complete eradication of bovine tuberculosis. Secondary intra-abdominal lesions are relatively uncommon during childhood.

#### TUBERCULOUS ENTERITIS

Small tuberculous ulcers frequently produce no symptoms and are discovered only at autopsy. With more extensive lesions the symptoms are those of ileocolitis with tenesmus and chronic diarrhea. There may be gross hemorrhage, but more often there is only slight bleeding. That the lesions are tuberculous may be suspected from the chronicity and also from the presence of tuberculous infection elsewhere in the body, especially in the lungs. Abdominal distention and tenderness may be present; there is irregular fever, wasting is often great, and anemia and debility are marked. In advanced cases the symptoms of tuberculous peritonitis may also be present.

**Treatment.** The diet should be low in residue, but should have adequate caloric value and be high in vitamin content. In the more severe cases parenteral administration of vitamins may be indicated, as at times may be the administration of amino acids, blood and plasma. Antispasmodics such as paregoric and belladonna preparations may be given for the relief of tenesmus. Antimicrobial therapy as outlined in Table 71 for progressive pulmonary tuberculosis should be employed.

#### TUBERCULOUS PERITONITIS

The incidence of tuberculous peritonitis has decreased in the past decade and is now rare in the United States. Scattered miliary tubercles may be found upon the peritoneum in acute, generalized miliary tuberculosis. Tuberculous peritonitis usually originates from erosion of a caseous or liquefied lesion in a mesenteric lymph node; less often from an intestinal lesion which has penetrated through

the outer coat, usually without causing perforation.

**Clinical Manifestations.** The onset is as a rule insidious and is characterized by gradually increasing debilitation, vague or slight abdominal pain or tenderness and low grade fever. The onset may, however, be more abrupt and severe and may be suggestive of appendicitis when the pain and tenderness are located in the right lower quadrant. Vomiting may occur, but usually is not marked, and there are no characteristic changes in the stools except in the presence of an associated enteritis. Often there is nothing on which to base the diagnosis until attention is directed to the gradually increasing distention of the abdomen.

Clinically, tuberculosis peritonitis has been divided into three general types: (1) the ascitic form, (2) the fibrinous or plastic form, and (3) the caseous or ulcerative form. All these processes are frequently present in a single case, and there may be no sharp distinction into a particular clinical pattern.

**Prognosis.** The natural course of tuberculous peritonitis is essentially a chronic one. Only in the rare acute ulcerative type does it proceed rapidly. The outcome is determined not only by the type and extent of the local involvement, but also by the nature of the tuberculous lesions of other parts of the body. In general, the ascitic form has the most favorable prognosis, the caseous form the worst.

**Treatment.** The management of tuberculous peritonitis is essentially that of tuberculosis in general. If there is an associated enteritis, the diet should be low in residue; otherwise it may be adjusted to the patient's appetite. There should be adequate calories as well as a high vitamin and mineral content in the diet. Heliotherapy appears to be of some benefit. Antimicrobial therapy as recommended for progressive pulmonary tuberculosis is indicated.

#### TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

##### TUBERCULOMA

Tuberculomas of the brain or spinal cord may be single or multiple, and may or may not be productive of neurologic symptoms. Though they are often recognized only at autopsy, they may be responsible for symptoms of increased intracranial pressure and/or localized peripheral manifestations and in



such instances are indistinguishable clinically from intracranial neoplasms. Intracerebral calcification, which may be demonstrable on the roentgenogram, may be tuberculous in origin, but more often is the result of such lesions as toxoplasmosis, astrocytomas, Sturge-Weber syndrome or an organized hemorrhage. Tuberculomas at the surface of the brain constitute the principal means for infection of meninges.

#### TUBERCULOUS MENINGITIS

Tuberculous meningitis is the principal cause of death from tuberculosis and is most frequent in the first few years of life. It is usually associated with primary tuberculous infections and is most likely to occur within a few months after the initial manifestation of the primary lesion. The incidence is especially high in the Negro race. Frequently it is the initial and only clinical manifestation of tuberculous infection, although it is always a secondary lesion. The primary focus, usually in the lung, need not be extensive, and caseous foci of not more than 1 cm. or so may be responsible for hematogenous spread of tubercle bacilli. Generalized miliary tuberculosis is observed in about 25 per cent of cases.

**Pathogenesis and Pathology.** The observations of Rich and McCordock indicate that the meninges are rarely directly infected by the hematogenous route, but rather are secondarily involved by the discharge of tubercle bacilli into the cerebrospinal fluid from contiguous older caseous foci such as a tuberculoma in the brain or spinal cord or osseous lesions of the vertebrae.

Tubercles are scattered over the pia and the surface of the brain. The dura is tense, the convolutions are flattened, and the arachnoid space and the ventricles contain serofibrinous exudate.

**Clinical Manifestations.** The clinical manifestations may vary, and at times meningeal symptoms are not present until the terminal stage. In general, however, there is a more or less typical pattern which in the untreated child may be divided into three stages: (1) a prodromal stage of irritation, (2) a transitional stage of increased intracranial pressure and meningeal symptoms, and (3) a terminal stage of paralysis and coma. These stages are not sharply demarcated, and not all may be present in a given case.

**Prodromal stage.** The onset is usually slow, with little or no fever, rarely acute with high fever. The initial manifestations are indefinite and often vague. Changes in disposition are

frequent; a good-natured child becomes irritable. Periods of drowsiness are common, but sleep is frequently restless and interrupted. Older children complain of headache. Anorexia, vomiting and constipation are common.

**Transitional stage.** Convulsions may occur during this stage, and the drowsiness becomes much deeper. Most frequent, however, are the evidences of meningeal irritation. There is nuchal rigidity and stiffness of the back and extremities, at times sufficient to produce opisthotonos. The deep reflexes tend to be exaggerated. There may be bulging of the fontanel. Ocular paralyses are common, or there may be nystagmus or strabismus; the pupils are normal or contracted, and hippus may be present. Occasionally there is choking of the disk, and tubercles may be present along the vessels of the choroid. During this stage there is usually a well marked *tache cérébrale* and at times, because of vasomotor disturbances, irregular flushing of the trunk and face. The temperature is usually elevated, but is rarely high. The course is progressive, and the drowsiness tends to be replaced by stupor.

**Terminal stage.** After a time the evidences of meningeal irritation are replaced by those of paralysis of the final phase of the disease. The child now lapses into a comatose state with cessation of voluntary movement, dilated and unresponsive pupils, insensitivity of the cornea, widespread paralyses, irregular pulse which may be slow or accelerated, and irregular respirations which are at times of the Cheyne-Stokes type. The temperature rises abruptly at the terminal stage, at times to as high as 106° or 107° F., and there may be hyperglycemia and glycosuria. These are terminal manifestations, and death occurs without recovery of consciousness.

**Variations.** The duration of untreated tuberculous meningitis is generally not more than two or three weeks after definite symptoms appear. In general, each of the three stages described averages about a week, although the initial one may be somewhat longer and the last stage shorter. In unusual instances, however, the terminal stage may be prolonged for several weeks. The course is also subject to other variations. The prodromal stage may be absent, with the onset sudden and the total course brief. Temporary improvement and even remission for weeks or months have been recorded. As a rule, the disease in infancy is more abrupt in onset than in childhood; generalized convulsions

are more frequent, the symptoms are less characteristic, and the course is shorter. A clinical course unmodified by treatment is now rarely seen.

**Diagnosis.** A positive tuberculin reaction is supportive but not confirmatory evidence. In the terminal stage cutaneous sensitivity to tuberculin may be lost. The white blood cell count is not characteristic; in the early stages, if there is a change in the total count, it is likely to be decreased. In the late stage there is often a moderate leukocytosis.

The cerebrospinal fluid provides the most important data, but an absolute diagnosis can be made from it only by isolation of tubercle bacilli. The fluid may be clear or only slightly turbid, the so-called ground-glass appearance. It is practically always increased in pressure and amount. The cell count ranges from 20 to about 500 per cubic millimeter. Though there is occasionally a predominance of polymorphonuclear cells in the early course of the disease, this is rarely observed, since, by the time there are sufficient symptoms to suggest the necessity for spinal puncture, the cells present are mainly lymphocytes. The protein content of the cerebrospinal fluid is increased and is often more than 100 mg. per 100 ml.; the sugar content is usually decreased, and the total chlorides are usually significantly reduced in the latter phase of the disease.

On standing, the cerebrospinal fluid usually forms a fibrinous web or pellicle in which the tubercle bacilli are enmeshed and in which they can be demonstrated on staining. The fluid should also be centrifuged and the sediment examined. When the organisms cannot be demonstrated by direct examination, they usually can be by culture or guinea pig inoculation.

The differential diagnosis is chiefly from other conditions responsible for an increase in lymphocytic cells in the cerebrospinal fluid (see Aseptic Meningitis Syndrome, p. 544). There is rarely any difficulty in the differential diagnosis of the various purulent meningitides, except as their course has been modified by suppressive but inadequate antimicrobial therapy. The demonstration of a tuberculous lesion in some other region of the body is strong supportive evidence in favor of a tuberculous etiology for the meningitis.

**Prognosis.** Complete recovery from tuberculous meningitis is now a possibility. The mortality rate is still high, ranging from 10 to 50 per cent in different series of treated cases, and the incidence of permanent physical and mental residuals among the survivors

is also high. The promptness with which specific therapy is instituted would seem to be a determining factor, although recovery has occurred in patients considered to be hopeless.

**Treatment.** The treatment of choice at this time is a combination of streptomycin and isoniazid and adequate supportive measures.

The plan currently used in our clinic is as follows: streptomycin, 50 mg. per kilogram intramuscularly every twelve hours (but not over 2 gm. per day) until there are signs of improvement, then 20 to 40 mg. per kilogram every other day (but not over 1 gm. per dose) for a total of three to six months; and isoniazid in total daily oral doses of 10 to 20 mg. per kilogram for at least eighteen months. Intrathecal therapy with antimicrobial drugs is not used. In some clinics aminosalicylic acid is administered in conjunction with isoniazid after the streptomycin has been discontinued (see Table 71).

One of the major obstacles in the treatment of tuberculous meningitis is the development of obstruction to the flow of cerebrospinal fluid. In the past various surgical procedures were performed in an attempt to relieve the obstructive lesions, but none was uniformly successful. Attempts have been made to remove the obstructions by lysis of the fibrinous exudate by the action of P.P.D. tuberculin or proteolytic enzymes injected intrathecally. Such efforts are usually ineffective. Reports, chiefly from European clinics, suggest that obstruction to the flow of cerebrospinal fluid can be prevented or at times relieved by administration of a corticosteroid during the first two months of therapy.

Supportive measures include adequate nutrition, which often necessitates gavage feeding, vitamin supplements, attention to fluid and electrolyte balance (see p. 191 for salt-losing syndrome), sedation, prophylaxis against bedsores and early detection and treatment of intercurrent infections.

ROBERT H. HIGH  
WALDO E. NELSON

## REFERENCES

### *Epidemiology*

Tuberculosis Chart Series, 1957. U.S. Public Health Service Publication No. 534.

### *Pathology*

Auerbach, O.: Tuberculosis in Children. *Am. J. Dis. Child.*, 75:555, 1948.

Bentley, F. J., Grzybowski, S., and Benjamin, B.: Tuberculosis in Childhood and Adolescence. The National Association for the Prevention of Tuberculosis, Tavistock House, North London, 1954.



Terplan, K.: Morphologic Analysis of Fatal Tuberculosis in Children: *Am. Rev. Tuberc.*, 74:7, 1956.

Terplan, K.: Anatomical Studies on Human Tuberculosis. *Am. Rev. Tuberc. (supp.)*, 42:1, 1940.

#### *Factors Influencing Development of Infection*

Israel, H. L., and Payne, H. M.: Tuberculosis in Negro: Clinical and Roentgenological Characteristics. *Am. Rev. Tuberc.*, 41:188, 1940.

Johnston, J. A.: Nutritional Studies in Adolescent Girls, and Their Relation to Tuberculosis. Springfield, Ill., Charles C Thomas, 1953.

Levine, M. I.: Tissue Response of White and of Negro Children to Induced Tuberculosis. *Am. J. Dis. Child.*, 51:1052, 1936.

Lurie, M. B.: Heredity, Constitution and Tuberculosis; Experimental Study. *Am. Rev. Tuberc.*, (supp.), 44:1, 1941.

Pinner, M.: Pathogenesis of Tuberculosis. *J.A.M.A.*, 107:475, 1936.

Rich, A. R.: The Pathogenesis of Tuberculosis. Springfield, Ill., Charles C Thomas, 1944.

#### *Age Factors in Tuberculous Infection*

High, R. H., and Zwerling, H. B.: Variation with Age in the Frequency of Tuberculous Pulmonary Calcification. *Pub. Health Rep.*, 61:1769, 1946.

Israel, H. L., and Long, E. R.: Primary Tuberculosis in Adolescents and Young Adults. *Am. Rev. Tuberc.*, 43:42, 1941.

Rich, A. R.: Influence of Age-Determined Factors on Development of Tuberculosis. (John W. Bell lecture). *Minnesota Med.*, 21:745, 1938.

#### *Lesions Simulating Tuberculosis*

Christie, A., and Peterson, J. C.: Histoplasmin Sensitivity. *J. Pediat.*, 29:417, 1946.

Furcolow, M. L., High, R. H., and Allen, M. F.: Some Epidemiological Aspects of Sensitivity to Histoplasmin and Tuberculin. *Pub. Health Rep.*, 61:1132, 1946.

Palmer, C. E.: Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin. *Pub. Health Rep.*, 60:513, 1945.

Smith, C. E.: Coccidioidomycosis. *M. Clin. North America*, 27:790, 1943.

#### *Tuberculin*

Diagnostic Standards and Classification of Tuberculosis. New York, National Tuberculosis Association, 1957.

Edwards, L. B., and Krohn, E. F.: Skin Sensitivity to Antigens Made from Various Acid-Fast Bacteria. *Am. J. Hyg.*, 66:253, 1957.

Furcolow, M. L., Hewell, B., Nelson, W. E., and Palmer, C. E.: Quantitative Studies of Tuberculin Reaction. I. Titration of Tuberculin Sensitivity and Its Relation to Tuberculous Infection. *Pub. Health Rep.*, 56:1082, 1941.

Nelson, W. E., Mitchell, A. G., and Brown, E. W.: Possibility of Sensitization to Tuberculin. *Am. Rev. Tuberc.*, 37:286, 1938.

Nelson, W. E., Seibert, F. B., and Long, E. R.: Technical Factors Affecting Tuberculin Test. *J.A.M.A.*, 108:2179, 1937.

Seibert, F. B., and Dufour, E.: A Study of Certain Problems in the Use of Standard Tuberculin. *Am. Rev. Tuberc.*, 58:363, 1948.

#### *Prognosis*

Lincoln, E. M.: Course and Prognosis of Tuberculosis in Children. *Am. J. Med.*, 9:623, 1950.

#### *Prophylaxis*

Aronson, J. D., Aronson, C. F., and Taylor, H. C.: A Twenty-Year Appraisal of BCG Vaccination in the Control of Tuberculosis. *Arch. Int. Med.*, 101:881, 1958.

A United States Public Health Service Tuberculosis Prophylaxis Trial: Prophylactic Effects of Isoniazid on Primary Tuberculosis in Children. *Am. Rev. Tuberc.*, 76:6, 1957.

Palmer, C. E., Shaw, L. W., and Comstock, G. W.: Community Trials of BCG Vaccination. *Am. Rev. Tuberc.*, 77:6, 1958.

Report of AD HOC Advisory Committee on BCG to the Surgeon General of the United States Public Health Service. *Am. Rev. Tuberc.*, 76:5, 1957.

#### *Treatment*

A Public Health Service Cooperative Investigation: Chemotherapy of Miliary Tuberculosis and Tuberculous Meningitis. *Pediatrics*, 12:1, 1953.

Cocchi, C.: Cortisone and Corticotropin in the Treatment of Tuberculosis in Infancy and Childhood. *Am. Rev. Tuberc.*, Supplement, 74:209, 1956.

High, R. H., and Nelson, W. E.: Experiences with Intra- and Extraluminal Bronchial Tuberculous Lesions. *Am. Rev. Tuberc.*, Supplement, 74:256, 1956.

Kendig, E. L. Jr., and Rodgers, W. L.: Tuberculosis in the Neonatal Period. *Am. Rev. Tuberc.*, 77:3, 1958.

Lincoln, E. M.: Symposium on Tuberculosis. *Pediatrics*, 20:723, 1957.

Lincoln, E. M., Sewell, E. M., and Anastasiades, A. A.: The Treatment of Primary Tuberculosis in Children. *Postgrad. Med.*, 16:5, 1954.

Lincoln, E. M., Harris, L. C., Bovornkitti, S., and Carretero, R.: The Course and Prognosis of Endobronchial Tuberculosis in Children. *Am. Rev. Tuberc.*, Supplement, 74:246, 1956.

Robinson, A.: Pulmonary Tuberculosis: The Primary Lesion. *Pediat. Clin. North America*, 4:255, 1957.

Smith, M. H. D.: Practical Management of Tuberculosis. *Pediat. Clin. North America*, 3:427, 1956.

## SPIROCHETAL INFECTIONS

## SYPHILIS

Syphilis is a chronic infectious disease in which periods of activity with demonstrable signs and symptoms alternate with long periods of latency, when the infection seems to lie dormant, only to appear later in a somewhat modified form. In infancy and childhood, congenital syphilis is much more common than acquired syphilis.

**Etiology.** The causative agent of syphilis, the *Treponema pallidum*, is a slender spiral organism which can be demonstrated by darkfield examination of scrapings from acute exudative lesions. It does not survive long outside the body.

The disease can be transmitted only when the organism enters an abrasion of the skin or mucous membrane or is introduced directly into the blood stream. Infection of the fetus occurs from the mother through the placenta, seldom before the fourth month of intrauterine life.

Syphilis is not a common cause of early abortion. When the infection of the mother is recent and untreated, the fetus is almost certain to be infected. Infants born at term from mothers who have had the infection for some time usually appear normal at birth; they may escape the disease or show manifestations of it later. Fetal syphilis may occur during pregnancies subsequent to one which resulted in the birth of a normal uninfected child from a syphilitic mother; syphilitic infants have been born fifteen to twenty years after the mother became infected. Syphilis is rarely transmitted to the third generation. The father plays no part in transmission of the disease except as he infects the mother.

**Pathology.** *Treponema pallidum* may be found in enormous numbers in fetuses dying of congenital syphilis. In the syphilitic infant there is widespread extramedullary hematopoiesis, similar to that in infants with erythroblastosis fetalis. An extensive inflammatory reaction may also be present, with resultant destruction of tissue and ultimate scarring.

Splenomegaly, osteochondritis and extramedullary hematopoiesis are among the most constant findings in newborn infants dying with congenital syphilis. Pancreatitis, moderate hepatomegaly and syphilitic inflammation of the lungs (pneumonia alba) are also com-

mon. Less frequent findings include involvement of the leptomeninges, bowel, adrenals and hypophysis.

## CONGENITAL SYPHILIS

**Incidence.** The incidence of congenital syphilis depends on the frequency of syphilis in pregnant women, the treatment these women receive and the proportion of live births among those who are inadequately treated. Of pregnancies in untreated syphilitic women, stillbirth will occur in about 30 per cent, and approximately 70 per cent of the infants born alive will have the disease.

**Symptoms.** Since congenital syphilis is acquired through infection of the placenta, the child has no lesion comparable to that of primary syphilis. The two stages in the child are usually termed "early congenital syphilis," which is roughly similar to secondary syphilis of the adult, and "late congenital syphilis," which corresponds somewhat to tertiary syphilis. Certain defects caused by early congenital syphilis last throughout life and are easily recognizable as stigmas in older children and adults.

Syphilitic infants occasionally have manifestations at birth, a feature which usually indicates a severe infection. Most often, however, the infant appears healthy at birth and exhibits symptoms between the second and sixth weeks of life. In some instances there may be no symptoms until the infant is a year or two of age, or even none except in later childhood. Rarely the infection may remain permanently latent.

## EARLY CONGENITAL SYPHILIS

**Clinical Manifestations.** Early congenital syphilis is a much more serious disease than secondary syphilis of the adult. It may resemble septicemia in which all organs of the body are involved. Untreated, it frequently results in death of the infant. General symptoms such as anemia, wasting, restlessness and fever may develop before the local symptoms, or the infant may appear quite well even though the local evidences of disease are marked. The most common localized symptoms are rhinitis, usually known as "snuffles," skin eruptions, pseudoparalysis, and moist lesions around the mouth, anus and genitals. The spleen, lymph nodes and





FIG. 138. Saddle nose in early syphilis.



FIG. 139. Maculopapular eruption of congenital syphilis.

liver are usually enlarged. Septicemia may be caused by bacteria which gain access through the external syphilitic lesions.

**Rhinitis or "snuffles."** This manifestation is generally the first to appear and is rarely absent in the infant with clinically manifest syphilis. Beginning as a swelling of the nasal mucosa, a profuse mucopurulent discharge soon develops which excoriates the upper lip. With ulceration of the mucosa and sometimes of the submucosa, bleeding occurs. Nasal obstruction may interfere with breathing and nursing. Subsequent flattening of the bridge of the nose gives delayed evidence that the cartilages and the base of the nose are involved (Fig. 138).

**Eruption.** Eruptions of the skin are common in the early stage of congenital syphilis. The rash is usually maculopapular, circular and slightly elevated and does not itch (Fig. 139). At first it is bright red, but gradually fades to a brownish color, leaving staining for some time. In Negro children especially the eruption is likely to be circinate. It may involve the entire body or be present only on the face, back and extremities. It usually involves the palms and soles, where the skin is infiltrated, swollen, red and moist with desquamation, or dry, shrunken and scaly with bright or dark spots of eruption (Fig. 140). The region of the eyebrows and sometimes of the eyelashes is often involved in a scaly eruption, with partial or complete loss of hair. The nails may have a pinched appearance with transverse ridges, and there is often a syphilitic paronychia. Sometimes the eruption does not appear until late in the first year, or the early eruption may fade only to recur weeks or months later.

**Mucocutaneous lesions.** Lesions often occur around the nose, mouth, anus and vulva. They are moist and produce fissuring and bleeding. If those around the mouth are deep, they lead to radiating scars or rhagades, one of the stigmas of syphilis. Condylomas, flat raised plaques with moist surfaces, occur around the anus and female genitals (Fig. 141). They may appear early, but more commonly are associated with a recurrence of symptoms. In a child of two or three years of age condylomas may be the only mani-



FIG. 140. Syphilitic scaling of feet in an infant 6 weeks of age. Snuffles and cutaneous eruption developed at the age of 2 weeks.

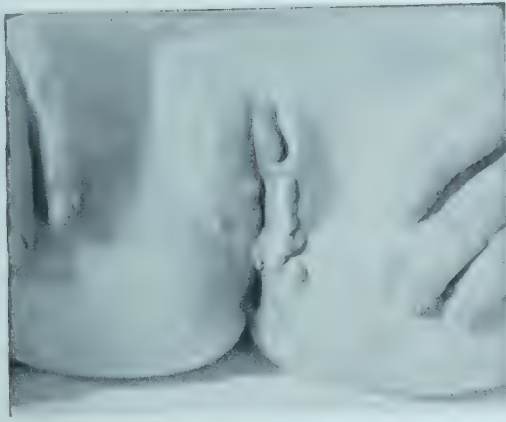


FIG. 141. Condylomas (condylomata lata) of vulva in a girl 8 years of age. Spirochetes were obtained from the lesions.

festation of syphilis; in older children they may be a manifestation of acquired syphilis.

**Anemia.** Anemia is almost always present and is likely to be marked in severe infections. The anemia may result from the effect of the disease on the bone marrow or from hemorrhage, as, for example, from the nose or periumbilical area. Nucleated red blood cells may be abundant.

**Edema.** Edema is often present. In severe infections the serum proteins reach extremely low levels, and the "swelling" of the child may be one of the initial symptoms recognized by the parent.

**Osteochondritis and pseudoparalysis.** Osteochondritis is one of the most characteristic and frequent lesions of early congenital syphilis. It may be sufficiently marked at birth to enable a diagnosis of syphilis to be made roentgenographically. When severe, it causes, after the first few weeks of life, fractures at the ends of the long bones proximal to the epiphysal lines and separation of the epiphyses. A pseudoparalysis (Parrot's) of the extremity with pain on passive motion then results which is more common in the arms than the legs and usually occurs between one and four months of age. There may be true osteomyelitis of the bones with local periostitis (Fig. 142) and even fractures farther back in the shaft. Mistaken diagnoses of birth injury to the brachial plexus, poliomyelitis or scurvy are sometimes made, though the age of the child and other evidences of syphilis should enable one to avoid this error.

In the fetus, syphilis of the bone manifests itself chiefly as osteochondritis. The line of ossification becomes wider, irregular and indefinite, owing to incomplete ossification and dense cellular infiltration. Granulation tissue is abundant; if this becomes necrotic, there

is disintegration of the bone with separation of the epiphysis, and bone formation ceases at this site. Spirochetes are found in great numbers in such areas and in the periosteum when it is involved. After birth, periostitis is usually also present.

**Hepatosplenomegaly.** The liver is almost always enlarged, and there is usually some jaundice when manifest infection is present. The jaundice, with the anemia, edema and the staining left after a mild eruption, produces the peculiar dirty, whitish brown (*café-au-lait*) appearance of the child. The spleen is usually enlarged to a relatively greater extent than are the lymph nodes.

**Neurosyphilis.** Jeans found changes in the cerebrospinal fluid, with or without clinical evidence of meningitis, in more than a third of cases which showed other early manifestations. Clinical evidence of meningitis, with bulging of the fontanel, opisthotonos and, at times, convulsions is a serious prognostic sign, especially in a child who is poorly nourished and has severe lesions elsewhere. A low grade syphilitic meningitis may cause a mild hydrocephalus, which can be a contributing factor to the peculiar, high square forehead in older syphilitic children. Meningovascular involvement occasionally occurs in infancy and continues into childhood. Children with this type of involvement are mentally retarded and prone to convulsions and transient hemiplegias. Simple meningeal involvement or asymptomatic neurosyphilis usually disappears with treatment. Even when symptoms are present, the cerebrospinal fluid cell count in syphilitic meningitis is seldom over 100 cells per cubic millimeter. The protein level is increased, and that of the sugar is normal; the serologic tests and the colloidal gold curve are positive.

**Roentgenographic Examination.** The roentgenographic changes are always multiple, the findings usually being most evident in the wrists, ankles and knees. There is increased density and widening of the epiphysal line with an area of decreased density behind it. The epiphysal line is sometimes finely serrated. Irregular destructive lesions near the ends of the bones in severe cases are often best seen on the medial surface of the tibia at the knee, where they constitute an almost pathognomonic finding. Periostitis usually involves several bones simultaneously and can be recognized easily in the roentgenogram. The evidences of osteochondritis have usually disappeared by about the sixth month, but periostitis may remain much





FIG. 142. Roentgenogram of forearm (A) and lower leg (B) of infant 6 weeks of age with congenital syphilis. O, Osteochondritis; P, periostitis.

longer, and the bones show great thickening of the cortex.

Periostitis also involves the bones of the skull; when severe, it is at least partially responsible for the peculiarly flat, overhanging forehead which remains as a stigma in children who have been severely infected in infancy. Dactylitis with involvement of both phalanges and metacarpal or metatarsal bones occurs in some instances. Suppuration of the bones and overlying soft tissues is always due to secondary invasion by pyogenic organisms.

**Stigmas.** The child who has had severe syphilis in infancy is usually left with stigmas of the disease. He tends to have a flat face, usually with a high forehead, a small nose with little bridge, and a small mouth which appears slightly drawn together. He often has rhagades or scars around the nose and mouth. Changes in the bones of the skull and face and maldevelopment of the teeth may become evident only as the child grows.

**Teeth.** The deciduous teeth of children with early congenital syphilis are prone to decay, but show no specific deformities. The most common stigma is maldevelopment of the permanent teeth, most often of the incisors and the sixth-year molars. The buds of

these teeth are being formed during the first few weeks of life, when congenital syphilis is most likely to be active. The outstanding defect involves the incisal edge of the middle lobe of the upper central incisors, though all the lobes are undersized at the biting edge. The tooth appears as if it had been pinched together at the incisal margin. The result is a peg-shaped tooth, which at times has a notch in the middle (Hutchinson's teeth, Fig. 143). The cusps of the sixth-year molars may be badly formed and look as if they had

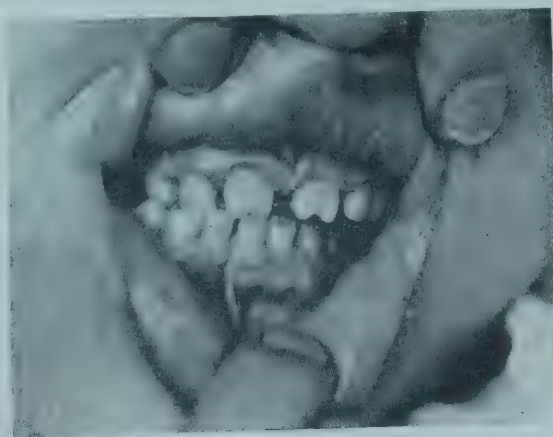


FIG. 143. Hutchinson's teeth in congenital syphilis in a boy 10 years of age.

been squeezed together, thus producing the lobulated mulberry appearance (Moon).

### LATE CONGENITAL SYPHILIS

**Interstitial Keratitis.** This severe and exceptionally uncomfortable lesion of the cornea is the most frequent active manifestation of late congenital syphilis. It does not occur with acquired syphilis, except perhaps that acquired at birth or in early childhood. It may occur as early as four years of age or as late as twenty years, but is most common from the sixth to the twelfth year of life. Photophobia and lacrimation are marked, and the child suffers great discomfort. The inflammation usually begins in one eye, but eventually involves both eyes in most instances. There is vascular infiltration of the deep layers of the cornea, with exudation. Gradually the cornea becomes opaque and appears reddish-gray. The infiltration lasts for weeks or months; though it may be somewhat arrested by treatment, it is not readily healed. Sometimes the second eye becomes involved after treatment has started. Scarring of the cornea and deep corneal vascularization usually remain after the process has healed.

**Neurosyphilis.** This manifestation is unfortunately the second most common lesion of late congenital syphilis and may become manifest from one to ten years of age. The clinical picture is usually that of meningo-vascular syphilis. At times there may be signs of involvement from early infancy with hemiplegia, spastic paralysis or convulsions. More often the child is somewhat mentally retarded, slow in speech, irritable and restless. Even with an acute hemiplegia the child usually has no fever and does not appear very ill. The paralysis often improves, only to recur on the same or on the opposite side. The vascular disease may proceed slowly with no acute episodes and lead to progressively greater mental deterioration, often with decided spasticity and increase in deep reflexes. The pupils may be unequal and fail to react to light. The cerebrospinal fluid shows an increase in cells and protein, a strongly positive serologic reaction and a paretic colloidal gold or mastic curve.

True juvenile paresis with memory defects, delinquencies, delusions and hallucinations occurring after a period of apparently normal development is rare. It is usually late in appearance, not becoming manifest until at least the second decade of life. Juvenile tabes is exceedingly rare. Several of the symptoms



FIG. 144. Saber tibia in a boy 10 years of age.



FIG. 145. Syphilitic perforation of the palate in a girl 10 years of age.

seen in adults are usually lacking, though incontinence of urine is frequent.

**Other Manifestations.** Osseous changes are found in about 15 per cent of children with clinical evidence of syphilis after infancy. The skull and the tibiae are most commonly affected. Although there may be destructive osseous lesions, periostitis is the most common finding. In the tibia, thickening of the anterior surface gives rise to the characteristic outward curving known as *saber shin* (Fig. 144). Pain in the legs may be present at night or after exercise. Gummas may occur in the bones of the skull or in the long bones, where they erode the bone and later involve the skin and produce ulceration and a foul-smelling discharge. They are most common in the nasal septum and palate. Although the gumma may respond to treatment, repair is never complete, and the child is left with a saddle nose or a perforation of the palate (Fig. 145).

Subcutaneous gummas occur most com



monly about the face and on the legs. In the early stages they produce an indurated gray swelling with red edges. As they become necrotic, ulcers with thick, indurated borders are formed.

Arthritis may affect any of the large joints, but is common only in the knees. An effusion into bilateral joints is known as *Clutton's joints*. The lesion is usually painless, is unaccompanied by fever and yields readily to treatment, or may disappear without treatment, leaving no residuals.

Choroiditis, retinitis and optic atrophy are encountered as late syphilitic manifestations. Optic atrophy usually occurs in conjunction with neurosyphilis.

Deafness was apparently more frequent in the past than it is now. Though the pathol-

ogy of syphilitic deafness is not clear, it has been attributed to involvement of the eighth nerve either as a primary lesion or secondary to compression changes in the temporal bone or to involvement of the cochlea. The combination of nerve deafness, deformity of the central incisors, and interstitial keratitis is known as *Hutchinson's triad*.

Visceral lesions are rare in late congenital syphilis; the heart and blood vessels, which are often affected in adults, are almost never involved in children. Paroxysmal hemoglobinuria, a rare disorder which follows exposure to cold or, rarely, exertion, is a manifestation of late congenital or acquired syphilis.

**Differential Diagnosis.** Syphilis seldom produces a single manifestation. "Snuffles" may be mistaken for ordinary coryza. Pseudo-

Table 73. Clinical Manifestations of Congenital Syphilis

	Early Manifestations	Stigmas	Late Manifestations
Skin.....	Maculopapular rash Diffuse inflammation of palms and soles Mucocutaneous lesions about nose, mouth and anus Condylomas <i>Café-au-lait</i> appearance Pemphigus Paronychia Deformities of nails Alopecia	Rhagades	Condylomas Syphilides Gummas
Mucous membrane...	Rhinitis Mucous patches	Saddle nose	
Bones.....	Periostitis Osteochondritis (epiphysitis)  Pseudoparalysis (Parrot's) Dactylitis	Bossing of head Hutchinson's teeth  Mulberry molars	Osteoperiostitis Saber shin Gummas Hydrarthrosis Arthritis
Eye.....	Chorioretinitis Iritis	Keratotic scar Chorioretinitis Pupillary change Optic atrophy	Interstitial keratitis Chorioretinitis Optic atrophy
Nervous system.....	Meningitis Hydrocephalus	Deafness	Deafness Neurosyphilis
Other.....	Pneumonia alba Hepatitis Jaundice Splenomegaly Nephritis Lymphatic hyperplasia Orchitis Malnutrition Anemia Gastrointestinal disturbances Fever Hemorrhage	Syphilitic facies	Paroxysmal hemoglobinuria

paralysis may suggest birth injury, poliomyelitis or scurvy. Scabies, which in infancy usually involves the palms and soles, may be confused with a syphilitic eruption. Enlargement of the liver and spleen is common in many diseases other than syphilis. Transverse ridging of the teeth with poor enamel at the biting edge may be caused by poor nutrition in early infancy, but the characteristic deformity of Hutchinson's teeth is present only in syphilis. Interstitial keratitis and phlyctenular keratoconjunctivitis are often confused; the latter involves both conjunctiva and cornea and has a great tendency to relapses and remissions. The changes of the long bones in early syphilis may be confused with those of pyogenic osteomyelitis, sickle cell anemia or even with infantile cortical hyperostosis, hypervitaminosis A and scurvy.

**Diagnosis.** *Treponema* can often be found in scrapings from moist lesions by means of the darkfield microscope.

The Wassermann test or any one of the flocculation or precipitation tests is extremely reliable in congenital syphilis except during the first six months of life. At birth a positive serologic test does not necessarily mean that the baby has syphilis, since antibodies are transferred to the fetal circulation from the mother. A negative test likewise is unreliable, for the infant may not have developed antibodies of his own. By the time he is three months of age the positive serologic reaction due to passive transfer from the mother has usually been lost, and he has nearly always established his own antibodies if he is going to do so. At six months serologic tests can be relied on with almost complete certainty. A single positive serologic test, however, is never adequate evidence for treatment at any age unless symptoms or roentgenographic signs are present, since the reaction may be due to an error in the laboratory or to one of the conditions which produce falsely positive reactions. A second test should be obtained promptly and decision concerning treatment delayed until it has been ascertained that no error has been made.

When there is evidence of disease, treatment should be instituted immediately, since irreparable damage may otherwise occur even within a week. If the infant has a positive serologic test and no clinical evidence of disease, the decision concerning treatment may be deferred, pending determination of titrated serologic tests at monthly intervals. If there is no decrease in titer at three months or disappearance of the reaction by six

months, he should be treated. Many physicians now prefer to treat an infant with penicillin immediately after birth if there is any doubt as to whether he is infected with syphilis, and especially if there is any doubt about the opportunity for subsequent observation of the infant.

**Prognosis.** Many syphilitic infants are born dead. If syphilis is recognized early and treated adequately, the infant will usually grow and develop normally. The lesions disappear rapidly, and few, if any, stigmas remain. When treatment is begun after manifestations have developed, the child is usually left with stigmas. Death may, however, occur in spite of treatment; rarely treatment, perhaps by rapidly destroying many spirochetes, seems to hasten the fatal outcome. Secondary sepsis with pyogenic organisms may also cause death. That infected infants may survive without treatment is evidenced by positive serologic reactions in children who are otherwise apparently normal. Interstitial keratitis often results in impaired vision. Meningovascular syphilis leaves the child in a pathetic, useless state.

**Prevention.** If preventive medicine were practiced ideally, congenital syphilis would rarely occur. Tests for syphilis should be obtained on every pregnant woman as early in pregnancy as possible and should be repeated about the sixth or seventh month. Adequate treatment of the mother before or during pregnancy will prevent the development of syphilis in all but 1 or 2 per cent of instances. Even inadequate treatment of the mother will greatly reduce the incidence of the disease in the offspring.

Penicillin passes through the placental barrier and can provide a sufficient bacteriostatic level in the fetal circulation to prevent and treat prenatal syphilis successfully.

#### TREATMENT OF CONGENITAL SYPHILIS

See Diagnosis for selection of patients for treatment.

Penicillin is the treatment of choice for all forms of congenital as well as acquired syphilis. It causes disappearance of the *Treponema pallidum* from early lesions, initiates healing more rapidly than the therapeutic agents formerly used, and greatly shortens the course of therapy. Secondary infections, common in syphilitic infants, may also be favorably influenced. Therapy of early syphilis is usually given over a period of fifteen days with a total dose of not less than 50,000 units of penicillin per pound of body weight.



It should always be given by injection. If crystalline penicillin is used, one one-hundred twentieth of the total dose is given every three hours, and, if procaine G penicillin in an absorption-delaying vehicle is used, 75,000 to 150,000 units are given once daily. Older children with late congenital syphilis are given up to four and one-half million or more units of penicillin over a period of fifteen days. Although about half of the children will suffer a febrile Herxheimer reaction, most pediatricians agree that there should be no reduction in the initial dose. Such treatment has produced complete healing in almost 100 per cent of infants under four months of age. Serologic reversal may be expected by one year and occurs in almost all instances by two years of age. As treatment is instituted at increasingly later ages, the serologic response is less complete and in late congenital syphilis is hardly noticeable.

### NEUROSYPHILIS

Abnormalities of the cerebrospinal fluid in early congenital syphilis disappear as the other lesions heal. Meningovascular syphilis, paresis and tabes apparently respond better to penicillin therapy than they did to formerly used chemotherapy. Cerebrospinal fluid findings revert slowly to normal, but irreparable damage to nerve tissue often prevents restoration to normal function.

### INTERSTITIAL KERATITIS

The response to penicillin is no better than to older forms of therapy. Penicillin should, however, be given to untreated patients for its general systemic effect. Topical cortisone or hydrocortisone acetate, 5 mg. per milliliter in isotonic saline solution applied every hour or two to the affected eye, relieves symptoms promptly in early cases. It also resolves dense infiltration and vascularization of the cornea, but must often be continued for a long time. Drops or ointment should be applied several times a day when improvement is assured. Cortisone cannot be expected to have any effect on established scars or necrotic tissue. Systemic steroid therapy or fever therapy is used only when there is failure with topical therapy. The pupil should be kept dilated until all signs of active disease are gone.

### ACQUIRED SYPHILIS

With the decrease in congenital syphilis, acquired syphilis in children has come to as-



FIG. 146. Chancre of the lip in a child of 1½ years. Spirochetes were easily demonstrated in scrapings from the lesion.

sume a relatively more important role. Ten per cent of the children with syphilis in the Vanderbilt Clinic had acquired syphilis. Smith was able to collect 125 undoubted instances of acquired syphilis in children up to eleven years of age. He found that, in children over ten years of age, syphilis acquired in the usual way by sexual contact was common.

The mouth, face, neck, genitals and anus are the most common sites of primary chancre (Fig. 146). The infection is most often acquired from intimate contact with some infected adult, through sexual play with a playmate or by attempts at sexual intercourse, usually by an adult. Several cases of syphilis acquired by transfusion of blood are reported. The disease, unless acquired in early infancy, resembles that in the adult. "Snuffles" and extensive involvement of the bones are uncommon. Often the chancre remains unnoticed, and a skin rash or condylomas, particularly around the anus, are the first symptoms observed.

More cases of acquired syphilis in childhood undoubtedly exist than are recognized, since, unless there is proof that syphilis is acquired, one is likely to conclude that the disease in a young child is congenital in origin. If the infection is discovered early, the response to treatment with penicillin is usually excellent, with prompt disappearance of lesions and reversal of the serologic reaction.

KATHARINE DODD

## REFERENCES

- Hanchett, L. J., and Perry, M. E.: Results of Penicillin Treatment in Congenital Syphilis. *J. Ven. Dis. Inform.*, 31:277, 1950.
- Horne, G. O.: Topical Cortisone in Interstitial Keratitis. *Brit. J. Ven. Dis.*, 31:9, 1955.
- Jean, P. C., and Cooke, J. V.: Prepubescent Syphilis, in *Clinical Pediatrics*. New York, D. Appleton-Century, Inc., 1930, Vol. 17.
- McLean, S.: The Osseous Lesions of Congenital Syphilis; Comparison of Clinical, Roentgenographic and Pathological Findings. *Am. J. Dis. Child.*, 41:130, 363, 607, 877, 1128, 1411, 1931.
- Nelson, N. A., and Struve, V. R.: Prevention of Congenital Syphilis by Treatment of Syphilis in Pregnancy. *J.A.M.A.*, 161:869, 1956.
- Platou, R. V.: Treatment of Congenital Syphilis with Penicillin, in *Advances in Pediatrics*. New York, Interscience Publishers, Inc., 1949, Vol. IV, p. 39.
- Smith, F. R., Jr.: Acquired Syphilis in Children; Epidemiologic and Clinical Study. *Am. J. Syph., Gonorr. & Ven. Dis.*, 23:165, 1939.
- Whipple, D. V., and Dunham, E. C.: Congenital Syphilis: Incidence, Transmission, and Diagnosis. *J. Pediat.*, 12:386, 1938; *Prevention and Treatment*, 13:101, 1938.

## LEPTOSPIROSIS

(WEIL'S DISEASE AND CANICOLA FEVER)

Of the many varieties of *Leptospira* which cause infectious disease in man and animals, two have been demonstrated to be important in the United States. *Leptospira icterohæmorrhagiae*, transmitted by the rat, causes spirochetel jaundice, or Weil's disease, and *Leptospira canicola*, carried by the dog, initiates canicola fever. Human infection may result from ingestion of food or water contaminated by the urine of infected rats or dogs, or by direct contact through the abraded skin. In the earliest clinical phase of the infections the organisms are present in the blood, and are thus responsible for inflammatory changes in striated muscle, liver, kidney, eyes and meninges. The incubation periods are from one to two weeks.

Infection by either organism may result in several different clinical pictures. The severe form of either disease is characterized by sudden onset, often with a chill, followed by a remittent fever ranging between 102° and 104° F. Muscular pains, headache, vomiting and suffusion of the conjunctiva follow. Jaundice and hemorrhage into the skin usually appear on the third to fifth day. Confusion, disorientation and coma may ensue. There is reduction of urinary output; the urine contains albumin, casts, bile and, at times, red blood cells. There is retention of nitrog-

enous waste products in the blood, and in fatal cases the kidney involvement is an important factor. Leukocytosis with shift to the left is usually present, and the cerebrospinal fluid frequently shows the changes of serous meningitis. The duration of the disease may be as long as two months, and relapses sometimes occur. On the other hand, the clinical course may be so mild that fever and conjunctival suffusion are the only symptoms.

A pure meningeal form may occur without icterus or renal involvement. The onset is sudden with headache and photophobia and at times is accompanied by suffusion of the eyes. There may be muscular pain severe enough to prevent movement of one or more extremities. Nuchal rigidity is slight, and other meningeal signs are often absent. The cerebrospinal fluid is clear and colorless and under slightly increased pressure, and contains from 50 to 500 cells, which are predominantly polymorphonuclears at the onset, but change to lymphocytes as the disease progresses. The sugar, chloride and protein content is not significantly affected. This form of the disease is of short duration. Leukocytosis is absent.

Spirochetes may be isolated from the blood early in either disease by culture or animal inoculation, from the urine during the second to fourth week and from the cerebrospinal fluid. Specific antibodies which appear in the blood during the second week are often present in high titers and persist for two to three years. There is some cross agglutination between the two leptospira. The case fatality rate varies from 4 to 48 per cent; it is lower in children than in adults; death is rare in nonicteric cases.

There is no specific therapy for either disease. Good therapeutic effects have been claimed for both penicillin and Aureomycin, particularly when administered early, but these claims have not been adequately established.

KATHARINE DODD

## REFERENCES

- Ashe, W. F., Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease; Complete Review of American Literature and Abstract of World Literature, 7 Case Reports. *Medicine*, 20:145, 1941.
- Beeson, P. B., and Hanky, D. D.: Leptospiral Meningitis. *Arch. Int. Med.*, 89:575, 1952.
- Rosenbaum, H. D.: Canicola Fever: Case Report and Review of the Literature. *Arch. Int. Med.*, 78: 531, 1946.



## INFECTIONS TRANSMITTED BY RAT BITES

### RAT-BITE FEVER (SODOKU)

**Etiology.** Rat bites are common in children, particularly among those living in poorly constructed houses and congested areas. Though such bites may be the cause of any of the more common forms of septicemia or of tetanus, two distinct diseases are directly attributable to the bite of a rat. One, the classic type of rat-bite fever, or sodoku, is caused by the *Spirillum minus*, a spiral organism 2 to 10 microns in length, with spirals at intervals of about 1 micron. Man is infected by the bite of an infected rodent.

The other disease, known as Haverhill fever, or erythema arthriticum epidemicum, is caused by the *Streptobacillus moniliformis*. It is possible that some of the confusion in the differentiation of the two diseases is due not only to the similarity of many of the symptoms, but also to the fact that they may occasionally exist together.

**Clinical Manifestations.** Clinically, rat-bite fever is characterized by primary healing of the bite wound, followed in one to four weeks by painful induration at this site, with development of a chancre-like ulcer and of regional lymphadenopathy. The temperature rises suddenly to 102° to 105° F. (38.8° to 40.5° C.), and a peculiar rash appears, consisting of slightly raised bluish-red macules 1 to 10 cm. in diameter. The rash is usually prominent over the trunk and face and may be so around the area of the bite (Fig. 147). The symptoms are those of a severe, generalized febrile disease with nausea, vomiting, generalized aching and occasionally delirium or convulsions.

After three to four days the temperature subsides, the local lesion and regional nodes become less painful, and the eruption tends to disappear. An afebrile period of three to five days ensues, followed by a repetition of all the signs and symptoms, with the onset of another bout of fever. Intermittent fever with remissions, in which the patient usually appears well, may continue for months. The site of the rat bite does not always become inflamed, and at times the characteristic rash appears only with the second or third rise in temperature. Except in these instances the diagnosis of rat-bite fever is not difficult.

**Diagnosis.** *Spirillum minus* may be seen in darkfield examination of serum obtained from



FIG. 147. The typical rash of the spirochetal form of rat-bite fever and the local lesion.

scrapings of the original lesion. Identification of the organism is usually obtained by intraperitoneal inoculation of animals with serum from the primary lesion or material from an infected lymph node or blood. White mice or guinea pigs free of the disease are the most suitable subjects. The organism can be demonstrated in the blood of the animal, four to eight days after inoculation, by the darkfield microscope or by suitable staining methods.

The leukocyte count is increased to about 10,000 to 20,000 cells per cubic millimeter with each febrile period. The flocculation tests for syphilis as well as the Wassermann test often becomes positive.

**Prognosis and Treatment.** The disease may be fatal during the first paroxysm of fever or may lead to profound anemia and cachexia and, if untreated, to a long, protracted course. Treatment with penicillin will almost always bring about a prompt cure.

### HAVERHILL FEVER\*

(ERYTHEMA ARTHRITICUM EPIDEMICUM)

**Etiology.** *Streptobacillus moniliformis*, the causative agent of Haverhill fever, is a microorganism which exhibits extreme pleomorphism. The disease is transmitted to man by the bite of an infected rat and by contaminated food and liquids.

\* From an etiologic standpoint, Haverhill fever is not a spirochetal disease, but is included here in association with rat-bite fever because its usual vector is the rat.

**Symptoms.** The clinical symptoms of the disease are intermittent fever, rash and arthritis. The incubation period is usually three to five days. Leukocytosis is slight or absent, and the skin eruption finer and often less marked than in rat-bite fever. The febrile paroxysms are less regular in duration and severity and may be inapparent in small infants. The region of the bite may suppurate. The most characteristic feature of the disease is the arthritis. Both large and small joints are involved. The swelling, redness and tenderness of the joints are at first remittent with the fever. Later, if suppuration occurs, large amounts of fluid accumulate in the joint cavity.

**Diagnosis.** *Streptobacillus moniliformis* can be isolated from the patient's blood or from fluid obtained from infected joints. The addition of sterile ascitic fluid to the medium

(30 per cent by volume) is recommended. After two or three days of incubation characteristic "fluff balls" appear. The organism is best shown by preparing air-dried smears stained by either Wayson's method or alkaline methylene blue. The microorganisms appear in preparations as chains of bacilli which have beadlike swellings. Specific agglutinins may be found in the serum after the disease has been present for two weeks or more.

**Prognosis and Treatment.** The disease may last for weeks or months, but is apparently never fatal. Treatment with penicillin produces rapid cure.

KATHARINE DODD

#### REFERENCE

Watkins, C. G.: Ratbite Fever. J. Pediat., 28:429, 1946.



# VIRAL INFECTIONS AND THOSE PRESUMED TO BE CAUSED BY VIRUSES

## MEASLES

(RUBEOLA)

**Definition.** Measles is an acute communicable disease commonly occurring in childhood. It is characterized by three stages: (1) an incubation stage of approximately ten to twelve days with few, if any, signs or symptoms; (2) a prodromal stage with enanthem on the buccal (Koplik's spots) and pharyngeal mucosa, rising temperature, slight conjunctivitis, coryza and an increasingly severe cough; and (3) a final stage with morbilliform or maculopapular rash erupting successively over the neck and face, body, arms and legs and accompanied by high fever.

**History.** Sydenham described the disease as a separate entity in the seventeenth century.

In 1759 a Scotsman, Home, transmitted the disease by scarifying the arms of susceptibles and applying bandages soaked in blood from subjects during the early stages of measles. Hektoen in 1905 confirmed this observation by injecting blood from subjects in the early stage of measles into susceptible persons.

Anderson and Goldberger in 1911 first produced measles in *Macaca mulatta* (rhesus monkey) by injection of filtered material from acute cases and suggested a virus as the causative agent. The virus was later grown on the chorio-allantois of the chick embryo by Rake and Shaffer from filtered nasopharyngeal washings and blood of patients in an early phase of measles. With Stokes and O'Neil they demonstrated the presence of the virus by inoculation of monkeys and susceptible children with material from numerous chorio-allantoic passages. Plotz had apparently produced measles previously in one monkey after ten passages of the virus in chick embryo tissue cultures. Enders and his co-workers established the virus in successive tissue culture passages.

**Etiology.** The virus is present in the nasopharyngeal secretions and in the blood, at least during the prodromal period and for a short time after the appearance of the rash. It will pass through a Seitz EK or Berkefeld N filter. It can remain active for at least thirty-four hours at room temperature, for at least fifteen weeks after desiccation from the frozen state, for at least four weeks in storage at  $-72^{\circ}\text{C}$ . to  $-35^{\circ}\text{C}$ ., and for several days at  $0^{\circ}\text{C}$ . It is readily inactivated at a low pH.

The production of typical giant cells in

successive passages in tissue cultures of human renal cells and in human amnion cells by Enders et al. has made possible the development of neutralization and complement fixation tests. Virus cultivated in the chorio-allantois has produced modified measles in the *Macaca mulatta* and in man. After such modified disease the monkeys usually have shown immunity when challenged with active virus. In man, after such modified disease, the resistance to challenge inoculation has been variable.

**Epidemiology.** Epidemics of measles occur irregularly, but in large urban centers they appear at two- to four-year intervals, probably resulting from the accumulation of large new groups of susceptible children. Epidemics commonly appear in the late winter or early spring. The virus spread is not dependent on subclinical cases, since approximately 98 per cent of the population exhibit frank measles. There is no evidence that a carrier state exists, nor has any other mode of interepidemic transmission been established. During an epidemic the air-borne route appears to be the commonest mode of spread, although contact or direct "droplet hits" from speaking, sneezing or coughing are also important means of cross infection. Rarely third persons may carry the virus on clothing if the time interval from source to susceptible is not great. Since the virus is more readily transmitted during the prodromal stage, it is difficult to detect a case in time to prevent spread to susceptibles. The differences in severity are probably associated with secondarily invading bacteria, which are also often responsible for the complications.

In large urban centers epidemics are more frequent than in less thickly populated areas, and a larger percentage of children are infected during the preschool years. Epidemics in army posts have been attributed to the collection of adult susceptibles from rural communities. Approximately 90 per cent of susceptible children under six years of age with family exposure during an epidemic will contract the disease. Most of the remaining 10 per cent will contract measles subsequently.

Rarely a person does not acquire immunity from an attack and has measles repeatedly,

perhaps as the result of hypogammaglobulinemia or agammaglobulinemia. In most instances so-called second or third attacks in children are actually German measles or exanthem subitum, which has been improperly diagnosed. Although immunity starts soon after subsidence of the fever and rash, rarely a patient will suffer two attacks of measles in rapid succession.

Infants acquire immunity transplacentally from mothers who have had measles. This immunity is usually complete for the first four to six months of life and disappears rapidly in the next month or two. Infants of susceptible mothers have no such immunity and may contract the disease with the mother at any time before or after delivery.

Most evidence suggests that solid immunity is produced in children whose measles is attenuated by human immune serum.

**Pathology.** The essential lesion of measles is found in the skin, in the mucous membranes of the nasopharynx and bronchi, and in the conjunctivas. It is a reaction of the capillary bed to the invading virus. Serous exudate and proliferation of mononuclear cells and a few polymorphonuclear cells occur around the capillaries. There is usually hyperplasia of the lymphoid tissue, where multinucleated giant cells, often 100 microns in diameter with as many as 100 nuclei, may be found. In the skin the reaction is particularly marked about the sebaceous glands and hair follicles. Koplik's spots\* consist of serous exudate and proliferation of endothelial cells similar to those noted in the skin rash. Rarely, ulceration occurs in the center of the lesions. There is a general inflammatory reaction of the buccal and pharyngeal mucosa which extends into the lymphoid tissue and the tracheobronchial mucous membrane. Bronchopneumonia frequently occurs in severe measles as the result of bacterial invasion.

**Clinical Manifestations.** The incubation period is approximately ten to twelve days if the first symptoms are selected as the time of onset, or approximately fourteen days if the appearance of the rash is selected; rarely it may be as short as six to ten days. A slight rise of temperature may occur nine or ten days from the date of infection and then subside for twenty-four to forty-eight hours.

The prodromal phase is characterized by fever, a slight hacking cough, coryza and

\* So-called Koplik's spots were apparently first described by Dr. John Quier in his Fifth Letter written from the West Indies to London in 1774.

conjunctivitis, which practically always precede the Koplik's spots, the pathognomonic sign of measles—one of the few in the field of medicine. As a rule the maculopapular or morbilliform rash of measles then appears within a day or two. Rarely the interval may be four or five days, or occasionally the rash precedes the spots or appears at the same time. This prodromal phase of the disease lasts approximately four to five days. There may be a considerable variation in the time of appearance of one sign or symptom in relation to others. An enanthem or red mottling may occur with or without Koplik's spots over the hard and soft palates. Koplik's spots are grayish-white dots, usually as small as grains of sand, with a slight reddish areola; occasionally they are hemorrhagic. They tend to occur opposite the lower molars, but may spread irregularly over the rest of the buccal mucosa. Rarely they are found within the midportion of the lower lip, on the palate and on the lacrimal caruncle. They appear and disappear rapidly, usually within twelve to eighteen hours. As they fade there may remain red, spotty discolorations of the mucosa. Examination for Koplik's spots should be carried out, if possible, in bright daylight. Trauma from biting the cheeks may result in tiny ulcers with an areola which may simulate them.

The prodromal phase lasts approximately four to five days. Occasionally it may be unusually severe, being ushered in by sudden high fever, at times with convulsions and even bronchopneumonia. Such a prodromal phase accounts for the mistaken idea that hot baths are effective in "bringing out" the rash, since laymen recognize that, when the rash is full-blown, improvement generally follows. Usually the coryza, fever and cough are increasingly severe up to the time the rash has covered the body. The conjunctival inflammation, with redness, swelling and photophobia, leads one to suspect measles before the Koplik's spots appear. In addition a transverse line of conjunctival inflammation, as described by Stimson, sharply demarcated along the eyelid margin, may be of diagnostic assistance in the prodroma stage. As the entire conjunctiva is involved the line disappears.

The temperature tends to rise abruptly as the rash appears and usually reaches 104° or 105° F. When the rash reaches the leg and feet, within about two days, the symptoms subside rapidly in uncomplicated cases. The patient up to this point may appear





FIG. 148. Morbilliform rash of measles.

desperately ill, and yet within twenty-four hours after the drop in temperature, which is usually abrupt, he will appear to be essentially well.

The rash usually starts as faint macules on the upper lateral parts of the neck, along the hairline and on the posterior parts of the cheeks. The individual lesions become increasingly maculopapular or morbilliform in appearance as the rash spreads rapidly over the entire face, neck, upper arms and upper part of the chest within approximately the first twenty-four hours (Figs. 148, 149). During the succeeding twenty-four hours it spreads over the back, abdomen, entire arms and thighs. As it finally reaches the feet on the second or third day it is beginning to fade on the face. The fading of the rash proceeds downward in the same sequence as that of its appearance. The severity of the disease is directly related to the extent and confluence of the rash. In mild measles the rash tends not to be confluent, and in very mild cases there are few, if any, lesions on the legs. In severe measles the rash is confluent, the skin being completely covered, including the palms of the hands and soles of the feet, and the face is swollen and disfigured.

The rash is often slightly hemorrhagic; in severe cases with a confluent rash, petechiae may be present in large numbers, and there may be extensive ecchymoses. Itching is generally slight, although on occasion it may be annoying. As the rash fades, the coppery appearance changes to a brownish discoloration, which disappears within approximately seven to ten days. There is a fine, branny type of desquamation, which may be extensive in severe measles.

Variations in types of rash may occur. In-

frequently a slight urticarial, a faint macular or a scarlatiniform rash may appear during the early prodromal stage and disappear well in advance of the typical rash. Complete absence of rash is rare except in patients who have received human antibodies during the incubation period. When cardiac failure supervenes in severe cases, the rash usually recedes; occasionally death may occur before the rash has appeared. In the hemorrhagic type of measles ("black measles") bleeding may occur from the mouth, nose or bowel. In mild cases the rash may be less macular and more nearly pinpoint, closely resembling that of scarlet fever.

Lymph nodes at the angle of the jaw and in the posterior cervical region are usually enlarged, and mild splenomegaly occurs at times. In infants and small children gastrointestinal symptoms, such as diarrhea and vomiting, and otitis media and bronchopneumonia are more common than in older children.

The white blood cell count is lower than usual with a relative lymphocytosis.

**Differential Diagnosis.** The most important diseases from which measles must be differentiated are German measles, scarlet fever and exanthem subitum.

In *German measles* there are no Koplik's spots and rarely cough, conjunctivitis or photophobia. The enlarged suboccipital, posterior cervical and postauricular lymph nodes in German measles also help to distinguish it. The rashes are somewhat similar



FIG. 149. Purpuric rash of measles.

only when measles is not severe; on the second day the rash of German measles is frequently fading or pinpoint in appearance, closely resembling that of scarlet fever. Fever is minimal in contrast to the typically high temperatures during the height of the rash in measles.

*Scarlet fever* (see p. 404): Mild cases of either disease may lack a number of their distinguishing features.

The rash of *exanthem subitum* appears as the fever subsides, and the disease is thus readily distinguished from measles.

Rashes from drugs or serum sickness are usually not difficult to differentiate from that of severe measles, but those caused by phenobarbital, Dilantin and the sulfonamides may closely resemble that of mild measles. Koplik's spots, cough and conjunctivitis in measles are differentiating factors.

**Complications.** The chief complications of measles are otitis media, bronchopneumonia, and encephalitis. Noma of the cheeks and gangrene elsewhere are rare complications in severe cases.

*Bronchopneumonia* may be caused by the measles virus, but is more commonly due to secondarily invading bacteria, particularly the *Pneumococcus*, *Streptococcus*, *Staphylococcus* and *Hemophilus influenzae*. Laryngitis with hoarseness, tracheitis and bronchitis, commonly present, may be due to the virus alone. The greatest danger from bronchopneumonia is in the youngest age groups and in very old persons. It usually occurs late in the course of measles. One of the potential dangers of measles is the exacerbation of a tuberculous focus.

Whether *encephalitis* as a complication is due to a variety of agents or to a single one is not established, but available evidence suggests that the measles virus itself may be responsible. The symptoms and course do not differ from those of other postinfectious encephalitides (p. 546).

**Prognosis.** Case fatality rates in the United States have decreased in recent years to low levels for all age groups, in part perhaps because of improved living conditions, but also because of effective antibacterial therapy for the treatment of secondary infections.

When measles is planted upon a highly susceptible population, the results may be disastrous. Such an occurrence in the Faroe Islands in 1846 resulted in the deaths of about one-quarter, nearly 2000, of the total population regardless of age. On the other hand, in a recent epidemic in Greenland with

100 per cent involvement of 4257 inhabitants the mortality rate was only 1.8 per cent, although 45 per cent of them had complications. At Ungava Bay, Canada, where 99 per cent of 900 persons had measles, the mortality rate was 7 per cent.

**Prophylaxis.** Quarantine is of little value, owing to the high communicability of the disease during its prodromal stage, when its presence is usually not suspected. Susceptibles known to have been exposed to the first case or group of cases may be permitted freedom for one week and then kept under strict isolation for eight days. Under ordinary school or home conditions such attempts at isolation are ineffectual. The isolation of children with measles will decrease the opportunities for them to acquire secondary bacterial infections. Quarantine of the patient may be lifted one to two days after return of the temperature to normal.

The value of *active immunization* procedures must await further studies with the measles virus grown in chick embryo tissue cultures.

*Passive immunization* with pooled adult serum, pooled convalescent serum, placental globulin and gamma globulin of pooled plasma is effective for prevention and attenuation of measles.

For attenuation intramuscular injections are best made in the first seven days after exposure; the amount of gamma globulin required is considered to be 0.02 to 0.025 cc. per pound (0.045 to 0.05 cc. per kilogram) of body weight. Gamma globulin, including that now prepared in the United States from placental blood, is approximately twenty-five times as potent in antibody titer as pooled adult serum.

For prevention the amount required of these agents is approximately three to four times as large as for attenuation, and they must be administered within seven days after exposure. There is great advantage in the use of gamma globulin because of the small volume required, the almost complete absence of local or general reactions, and the absence of the virus of hepatitis.

The modified clinical patterns resulting from such attenuation vary from instances in which there are few or no symptoms with only mild fever to, rarely, little or no modification. The rash and Koplik's spots, as well as the coryza and cough, may be slight or absent.

After the seventh or eighth day of incubation the amounts of immune bodies must be



increased greatly for any degree of protection. If the injection is delayed until the ninth, tenth or eleventh day, slight fever may already have started, and only slight modification of the disease may be expected.

**Treatment.** It is possible that ten to twenty times the usual amounts of gamma globulin will modify the disease to some extent even when injected in the prodromal stage, or at least the danger of complications may be lessened. Greenberg et al. found that among 165 cases of measles encephalitis only one patient had had gamma globulin prophylactically. There is suggestive evidence that large doses of gamma globulin, 0.40 to 1.0 ml. per pound of body weight, may prevent death and lessen residual complications in measles encephalitis; there are also some favorable reports from the use of corticoids and corticotropin. The real value of each method of treatment awaits confirmation.

The ordinary treatment for children with high fever and an irritating cough suffices for measles, except that care must be taken to protect the eyes from strong light; ordinary daylight is not irritating. Sedatives, antipyretics for high fever, proper skin lotions for itching or irritation, complete bed rest and an adequate fluid intake are the usual requirements. Humidification of the room may be necessary for laryngitis or an excessively irritating cough, and it is best to keep the room comfortably warm rather than cool. The complications of otitis media and pneumonia require appropriate antibacterial therapy.

JOSEPH STOKES, JR.

## REFERENCES

- Anderson, J. F., and Goldberger, J.: Experimental Measles in the Monkey. A Preliminary Note. *Pub. Health Rep.*, 26:847, 1911.
- Goldberger, J., and Anderson, J. F.: An Experimental Demonstration of the Virus of Measles in Buccal and Nasal Secretions. *J.A.M.A.*, 57:476, 1911.
- Hektoen, L.: Experimental Measles. *J. Infect. Dis.*, 2:238, 1905.
- Home, F.: *Medical Facts and Experiments*. London, A. Millar, 1759, p. 253.
- Karelitz, S.: Does Modified Measles Result in Lasting Immunity? *J. Pediat.*, 36:697, 1950.
- Koplik, H.: The Diagnosis of the Invasion of Measles from a Study of the Exanthema as It Appears on the Buccal Mucous Membrane. *Arch. Pediat.*, 13:918, 1896.
- Maris, E. P., and others: Studies on Measles. V. The Results of Chance and Planned Exposure to Unmodified Measles Virus in Children Previously Inoculated with Egg-Passage Virus. *J. Pediat.*, 22:1, 1943.

Ordman, C. W., Jennings, C. G., and Janeway, C. A.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation. XII. The Use of Concentrated Normal Human Serum Gamma Globulin (Human Immune Serum Globulin) in the Prevention and Attenuation of Measles. *J. Clin. Investigation*, 23:541, 1944.

Panum, P. L.: *Observations Made during the Epidemic of Measles on the Faroe Islands in the Year 1846*. New York, Delta Omega Society, 1940.

Plotz, H.: Culture "in vitro" du virus de la rougeole. *Bull. Acad. de méd. Paris*, 119:598, 1938.

Shaffer, M. F., Rake, G., and Hodes, H. L.: Isolation of Virus from a Patient with Fatal Encephalitis Complicating Measles. *Am. J. Dis. Child.*, 64:815, 1942.

Shaffer, M. F., Rake, G., Stokes, J., Jr., and O'Neil, G. C.: Studies on Measles. II. Experimental Disease in Man and Monkey. *J. Immunol.*, 41:241, 1941.

Stokes, J., Jr., and others: Studies on Measles. IV. Results Following Inoculation of Children with Egg-Passage Measles Virus. *J. Pediat.*, 22:1, 1943.

Stokes, J., Jr., Maris, E. P., and Gellis, S. S.: Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation. XI. The Use of Concentrated Normal Human Serum Gamma Globulin (Human Immune Serum Globulin) in the Prophylaxis and Treatment of Measles. *J. Clin. Investigation*, 23:531, 1944.

## GERMAN MEASLES

(RUBELLA)

**Definition.** German measles is a common communicable disease of childhood characterized by mild constitutional symptoms, a rash similar to that of mild measles or mild scarlet fever, or a combination of them, and enlargement and tenderness of the postoccipital, retroauricular and posterior cervical lymph nodes.

**History.** Wagner in 1829 distinguished German measles from measles and scarlet fever. The need for recognition has been re-emphasized by the work of Gregg in 1941, who observed severe congenital anomalies in newborn infants whose mothers had German measles during early pregnancy.

**Etiology.** German measles is caused by a viral agent, which Hiro and Tasaka in 1938 transferred successfully to children with nasopharyngeal secretions filtered through Seitz EK and Berkefeld W filters. It has also been grown on the chorio-allantois of the developing chick embryo by Habel. Anderson in 1949 demonstrated the presence of rubella virus in throat washings at the time of onset of the rash and the occurrence of German measles without rash (inapparent infection). Krugman and co-workers (1953) showed

that rubella virus could be obtained from the blood two days before and on the first day of the rash.

**Epidemiology.** Transplacental immunity is well recognized and is lost by about six months of age. Epidemics occur approximately every three to four years, but are not as extensive as those of measles. A single attack apparently produces permanent immunity, and second attacks almost never occur. The higher incidence of German measles among adults, in contrast to that of chickenpox and measles, suggests that German measles is less contagious than either of these diseases.

**Clinical Manifestations.** The incubation period for German measles is generally fourteen to twenty-one days, but may be slightly shorter or longer. The prodromal phase of mild catarrhal symptoms is shorter than that of measles and may be so mild as to go entirely unnoticed. The most characteristic sign, of which the patient frequently complains, is the presence of retroauricular, posterior cervical and postoccipital adenitis. No other disease causes the tender enlargement of all these nodes to the same extent that German measles does. An enanthem often appears just prior to the onset of the skin rash. It consists of discrete rose spots on the soft palate which may coalesce into a red bluish and may extend over the fauces.

The rash does not appear until the nodes have been enlarged for approximately twenty-four hours. The rash is much more variable than that of measles. It starts on the face, but its evolution is so rapid that it may be fading on the face by the time it appears on the trunk. Maculopapules are usually present in large numbers and are discrete, but in addition to the eruption there are large areas of flushing which spread rapidly over the entire body within twenty-four hours. The rash may be confluent, particularly on the face. In many instances, during the second day, the rash will change to a more pinpoint appearance, especially over the trunk, resembling that of scarlet fever. By the third day of the disease the rash usually disappears; owing to the lack of hemorrhages into the lesions, any residual brown pigmentation lasts only a few days, and there is only slight desquamation.

The pharyngeal mucosa is reddened, and the conjunctivas are slightly inflamed. Photophobia is not present as in measles. There is slight or no fever accompanying the rash, but, when present, it is always when

the rash is full blown and persists for one, two or occasionally three days. The temperature rarely exceeds 101° F. Anorexia, headache and malaise are not frequent. The spleen is often slightly enlarged. Mild itching is sometimes present. There are no characteristic changes in the white blood cells; the total cell count remains normal or is slightly reduced.

**Differential Diagnosis.** Particularly in its more severe forms, German measles may be readily confused with the mild types of scarlet fever (p. 408) and measles (p. 485). *Exanthem subitum* is readily distinguished from German measles by the appearance of the rash at the end of the febrile episode rather than at the height of the signs and symptoms. *Drug rashes* are at times extremely difficult to differentiate from German measles. The characteristic enlargement of the lymph nodes would, of course, point to German measles. *Infectious mononucleosis* at times has a rash similar to that of German measles and is easily confused with it because of the enlargement of the lymph nodes. The alteration in the blood picture, however, should be sufficient to differentiate the two diseases.

**Prognosis and Complications.** Under ordinary circumstances there are few complications, and the signs and symptoms subside as rapidly as they appear. Neuritis and arthritis occasionally occur. Resistance to secondary bacterial invaders does not seem to be lowered. Encephalitis similar to that in measles is a relatively important complication, and a number of deaths have been recorded.

Microcephaly, deafness with secondary mutism, cardiac anomalies and congenital cataracts are found relatively frequently in infants whose mothers had German measles during the first three months of pregnancy.

**Prevention.** Prophylactic measures are rarely indicated. It is important for girls to be exposed and to contract the disease before the age of child-bearing. Pregnant women should be guarded from exposure to German measles. Apparently immunity in the pregnant mother resulting from a previous attack may not protect her fetus from the serious anomalies secondary to her exposure in the first trimester. Thus, even though the mother has had German measles, she should avoid exposure during the first three or four months of pregnancy.

When isolation is desirable, the exposed susceptible should be kept strictly isolated



from approximately the tenth to the twenty-first day after exposure. Intramuscular injection of gamma globulin or small amounts of pooled adult serum or plasma within the first seven or eight days after exposure may or may not afford protection from, or attenuation of, the disease, apparently depending upon the batch used, upon possible strain differences in the virus or upon other factors as yet unknown. Such prophylaxis is rarely indicated except in early pregnancy. Owing to the lack of danger of viral hepatitis, gamma globulin is the preferable prophylactic agent.

**Treatment.** Unless bacterial complications occur, treatment is symptomatic. The patient should be kept in bed until the temperature is normal. When quarantine appears necessary, it need be continued only two days from the onset of the rash.

JOSEPH STOKES, JR.

## REFERENCES

- Anderson, S. G.: Rubella in Volunteers. *J. Immunol.*, 62:29, 1949.
- Gregg, N. M., and others: The Occurrence of Congenital Defects in Children Following Maternal Rubella during Pregnancy. *M. J. Australia*, 2:122, 1945.
- Habel, K.: Transmission of Rubella to *Macacus Mulatta* Monkeys. *Pub. Health Rep.*, 57:1126, 1942.
- Hess, A. F.: German Measles: An Experimental Study. *Arch. Int. Med.*, 13:913, 1914.
- Hiro, Y., and Tasaka, S.: Die Röteln sind eine Virus-Krankheit. *Monat. f. Kinderh.*, 76:328, 1938.
- Krugman, S., Ward, R., Jacobs, K. G., and Iazar, M.: Studies on Rubella Immunization. I. Demonstration of Rubella without Rash. *J.A.M.A.*, 151:285, 1953.
- McIoriman, H.: Diagnosis and Prophylaxis of Rubella. *M. J. Australia*, 37:390, 1950.
- Miller, H. C., and others: Study of the Relation of Congenital Malformations to Maternal Rubella and Other Infections: Preliminary Report. *Pediatrics*, 3:259, 1949.
- Schick, B.: Die Röteln. *Ergebn. d. inn. Med. u. Kinderh.*, 5:280, 1910.

## EXANTHEMA SUBITUM

(ROSEOLA INFANTUM)

**Definition.** Exanthema subitum is an acute disease of infants and young children, usually occurring sporadically, but occasionally in epidemics. It is unique in that the diagnostic rash and the end of the disease occur almost simultaneously. The disease is characterized by a period of high fever lasting three to four days, during which time there are insufficient clinical findings to explain the hyperpyrexia, and by an abrupt termination

with a precipitous drop of the temperature to normal and the appearance of a generalized eruption, which fades quickly.

**History.** Zahorsky first described the disease in the United States in 1910 as roseola infantum; later Veeder and Hempelmann applied to it the more suitable term of "exanthema subitum."

**Etiology.** The typical disease has apparently been produced in susceptible infants by injection of blood serum (Kempe and co-workers) and of heparinized blood (Hellström and Vahlquist) from patients with exanthema subitum. A febrile disturbance was similarly produced in monkeys by Kempe.

Nothing is known of the pathologic changes of the disease.

**Epidemiology.** The degree of contagiousness is not known, although it appears to be low. There is a tendency for the disease to occur chiefly in the spring and fall. It attacks both sexes equally. In the rare epidemics described the incubation period was estimated to be from seven to seventeen days. The epidemiologic pattern is not clear. The occurrence of exanthema subitum sporadically in early life with rare epidemics in older age groups suggests the possibility of an endemic spread through most of the population in early infancy and childhood, with production of permanent immunity. Most of the cases occur between the ages of six months and three years, although the disease does occur infrequently in older children and even in adults. The peak of the incidence appears to be during the second year of life.

**Clinical Manifestations.** The onset is sudden, with fever which rises abruptly as high as 103° to 105° F.; convulsions occur on occasion at this time. Although the pharyngeal mucosa is slightly inflamed at times and there may be slight coryza, there are no typical signs. The outstanding feature is the absence of physical findings sufficient to explain the height of the fever. The diagnosis is suspected chiefly by exclusion of other possible infections, particularly those which at this age are the most common causes of high fever and in which the diagnosis may not be evident, such as otitis media, acute pyelonephritis and pneumonia. There is usually a leukopenia, the total cell count being in the range of 3000 to 5000 per cubic millimeter, and a relative lymphocytosis which may be as high as 90 per cent. Occasionally a large number of monocytes are present.

As the fever falls by crisis on the third or fourth day or just before or shortly after its

return to normal, a macular or maculopapular eruption appears which is disseminated over the body, starting on the trunk and spreading to the upper extremities and neck, with slight involvement of the face and legs. The rash quickly fades, rarely remaining as long as twenty-four hours. Desquamation is rare, and no pigmentation remains. In the rare instances of epidemic outbreaks, cases without a rash may be suspected, but a definite diagnosis cannot be made. Clemens described an enanthem on the soft palate consisting of small erythematous spots and streaks. Occasionally the lymph nodes, especially in the cervical area, may be enlarged, but not to the extent that they are in German measles.

**Differential Diagnosis.** The principal difficulty in differential diagnosis is with *German measles*, from which exanthema subitum is distinguished chiefly by the prodromal period of high fever. *Measles* and *dengue* can be distinguished primarily by the time of appearance of their rash in relation to the other clinical findings. In measles, though there is usually a fever of variable degree for three or four days just before the rash, the temperature becomes abruptly elevated to 103° to 104° F. at the time of appearance of the rash and remains elevated for the next two days or so. The lack of Koplik's spots, severe coryza, conjunctivitis and cough also helps to distinguish exanthema subitum from measles. Certain allergic rashes—for example, those resulting from sensitivity to drugs—may be difficult to distinguish from exanthema subitum, but the characteristic clinical pattern of the latter is usually sufficiently definite to establish the diagnosis.

**Prophylaxis and Treatment.** There are no known methods for shortening the course of the disease or for prophylaxis. In infants and young children, who are prone to convulsions, the administration of relatively large doses of a sedative at the appearance of the sharp febrile onset of exanthema subitum may be effective as prophylaxis against such seizures. Aspirin may be of some help in partially reducing the fever and in allaying restlessness.

JOSEPH STOKES, JR.

#### REFERENCES

- Berenberg, W., Wright, S., and Janeway, C. A.: Roseola Infantum (Exanthema Subitum). *New England J. Med.*, 241:253, 1949.  
 Clemens, H. H.: Exanthema Subitum (Roseola Infantum). *J. Pediat.*, 26:66, 1945.  
 Hellström, B., and Vahlquist, B.: Experimental In-

oculation of Roseola Infantum. *Acta pædiat.*, 40: 189, 1951.

Kempe, C. H., Shaw, E. B., Jackson, J. R., and Silver, H. K.: Studies on the Etiology of Exanthema Subitum (Roseola Infantum). *J. Pediat.*, 37:561, 1950.

Veeder, B. S., and Hempelmann, T. C.: A Febrile Exanthema Occurring in Childhood (Exanthema Subitum). *J.A.M.A.*, 77:1787, 1921.

Zahorsky, J.: Roseola Infantum. *J.A.M.A.*, 61:1446, 1913.

#### HERPES SIMPLEX

(DISEASES DUE TO HERPESVIRUS HOMINIS)

*Herpesvirus hominis* is a widespread and ancient parasite of man that can produce a number of clinical manifestations. These can be classified under diseases of the skin, the mucous membranes, the eye and the central nervous system and generalized systemic involvement. The lesions at the various sites have the following points in common: (1) Visible manifestations are characterized by vesicle formation; (2) histologic examination reveals an intranuclear inclusion body; and (3) the virus can be isolated with relative ease from infected tissues.

It is now clear that infection may be manifested in two forms: (1) *primary* herpes, in which first exposure of a susceptible host to the virus results in either subclinical infection without symptoms (approximately 85 per cent) or in a general systemic reaction. The latter may be severe and even fatal, associated with a transient viremia and with local lesions in the majority of instances. Circulating antibodies, absent at the onset of the illness, develop during the recovery phase. (2) *Recurrent* herpes, in which the lesion is localized and there is little or no systemic reaction. The recurrent lesions are thought to be the result of activation of latent virus by such nonspecific stimuli as changes in environment, febrile reactions, menstruation and emotional upsets. Such reactions occur only in persons who have had a primary infection and consequently have circulating antibodies at the time of the recurrence.

#### CLINICAL PATTERNS

##### LESIONS OF THE SKIN

(HERPES LABIALIS, FACIALIS, FEBRILIS)

Lesions of the skin are usually a manifestation of the recurrent disease; they begin with a feeling of irritation or burning pain in the area of skin involved, followed by the appearance of a group of closely aggregated reddish



papules which quickly vesiculate. These thin-walled vesicles on an erythematous base rupture, scab and heal in a week or ten days without leaving a scar; temporary depigmentation may occur in the Negro. In children the vesicles often become secondarily infected and then must be distinguished from impetigo contagiosa. The lesions tend to occur at mucocutaneous junctions, but may occur anywhere, and tend to recur at the same site.

#### TRAUMATIC HERPES

This term has been applied to the rare infections of traumatized skin. Scattered vesicular lesions begin to appear in the vicinity of the trauma; the regional lymph nodes become enlarged and tender. The clinical picture may be mistaken for that of herpes zoster since in the extremities the lesions extend centripetally as grouped vesicles. Healing may be delayed for as long as three weeks; recurrences at the site are common. During an attack of herpetic gingivostomatitis, lesions may occur on the digits of "thumb suckers" and also on the face, where they appear as scattered single vesicles in contrast to the grouped vesicles of the recurrent disease. Rarely, primary herpetic infection can occur as an isolated phenomenon on apparently unbroken skin.

#### ECZEMA HERPETICUM

(KAPOSÍ'S VARICELLIFORM ERUPTION,  
JULIUSBERG'S PUSTULOSIS VACCINIFORMIS ACUTA)

(See also p. 1313.) This complication of infantile eczema results from a widespread and usually primary infection of the eczematous skin with the herpes virus. The severity of the complication varies; the attacks may be so mild as to be overlooked without a high index of suspicion and adequate laboratory facilities, or they may be fatal. In a typical severe attack vesicles develop abruptly in large numbers over the area of eczematous skin. They continue to appear in crops for as long as seven to nine days. Isolated at first, they later become grouped and may occur on adjoining areas of normal skin. Wide denudation of the epidermis can occur in areas of confluent vesicles. Scabs eventually form, and epithelization occurs. The systemic reaction varies, but temperatures of 103° to 105° F. for seven to ten days are not uncommon. If eczema herpeticum is a manifestation of recurrent disease, antibodies are present and the systemic involvement is much less severe. Death may occur during primary in-



FIG. 150. Eczema herpeticum. Note similarity of umbilicated vesicular lesions on face to those of eczema vaccinatum (p. 504).

fection as the result of profound physiologic disturbances, associated with loss of fluid, electrolytes and protein or as the result of secondary bacterial invasion. A differential diagnosis from eczema vaccinatum (p. 504) must be made. Apart from specific differentiation in the laboratory, a history of exposure to the appropriate virus and the fact that the herpetic lesions occur in crops will usually distinguish them.

#### LESIONS OF THE MUCOUS MEMBRANES

ACUTE HERPETIC GINGIVOSTOMATITIS  
(ACUTE INFECTIOUS GINGIVOSTOMATITIS, APHTHOUS STOMATITIS, CATARRHAL STOMATITIS, ULCERATIVE STOMATITIS, VINCENT'S STOMATITIS)

(See also p. 633.) This clinical manifestation of primary infection is probably the commonest cause of stomatitis in children between one and three years of age. It can occur in adults. The symptoms may appear abruptly with pain in the mouth, salivation, fetor oris, refusal to eat, and fever, often as high as 104° to 105° F. The onset, however, may be insidious, fever and irritability preceding the oral lesions by a day or two. The



FIG. 151. Herpetic stomatitis.

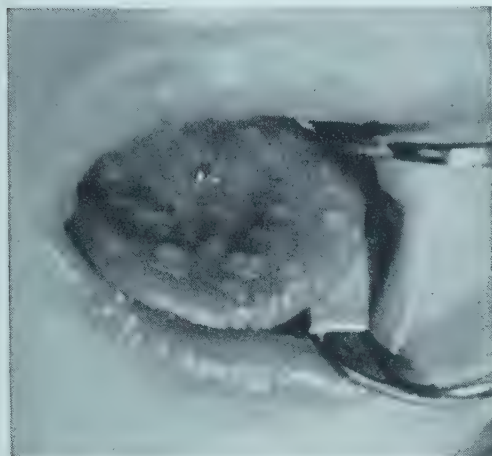


FIG. 152. Lesions of herpetic stomatitis on the tongue.

initial lesion is a vesicle, seldom seen because of its early rupture. The residual lesion is 2 to 10 mm. in diameter and is covered with a yellow-gray membrane. When this membrane sloughs, a true ulcer remains. Although the tongue and cheeks are most commonly involved, no part of the oral lining is immune.

Submaxillary lymphadenopathy and inflammation of the gums are extremely common and are most important for the differential diagnosis from other forms of stomatitis. The acute phase lasts four to nine days and is self-limited. Pain tends to disappear two to four days before healing of the ulcers is complete. In some instances the tonsillar regions are involved early, and acute tonsillitis of bacterial origin or herpangina (p. 528) may be suspected. In herpes simplex the lesions eventually spread to the tongue and/or the front of the mouth. In herpangina a careful epidemiologic history will usually reveal evidence of other cases in the vicinity.

#### RECURRENT STOMATITIS

Most recurrent stomatitis does not appear to be of herpetic origin; there is evidence that the recurrent, solitary aphthous ulcers previously thought to be herpetic are not caused by this virus. However, some involvement of the mucous membranes inside the lip may be seen with an attack of herpes labialis.

#### HERPES PROGENITALIS

**Female.** Primary herpetic vulvovaginitis may be encountered in childhood and, though uncommon, enters into the differential diagnosis of vulval lesions. The patient complains of burning pain in the genitals. The lesions resemble those in the mouth, appearing as vesicles which soon collapse and form lesions covered with a yellow-gray membrane. These become eroded into superficial, painful ulcers (Fig. 153). There is associated enlargement of the inguinal nodes, and a low grade fever is common. The lesions heal spontaneously; treatment consists of sitz baths for cleanliness.

**Male.** Herpes progenitalis of males is rare in childhood. Primary infection, manifest by a cluster of tiny vesicles surrounding a reddened meatus, has been described in association with stomatitis. In the adult, recurrent herpes appears as clusters of small erosions



FIG. 153. Primary herpetic vulvovaginitis. Note the similarity of the lesions to those of herpetic gingivostomatitis. (From Scott, Coriell, Blank and Burgoon: *J. Pediat.*, Vol. 41.)



(eroded vesicles) on the glans or corona, sometimes associated with typical herpetic vesicles on the shaft.

#### LESIONS OF THE EYE

Conjunctivitis and keratoconjunctivitis may occur as manifestations of either a primary or a recurrent infection. The conjunctiva appears congested and swollen with little, if any, purulent discharge. In the primary infection the preauricular node is enlarged and tender.

The corneal lesions are protean, but dendritic ulcers are almost pathognomonic. The diagnosis may be suspected clinically by a history of recurrence and/or by the appearance of herpetic vesicles on the lids. Proof can be obtained by isolating the virus from the eye and, in a primary attack, demonstrating a rise of antibodies in the serum against the herpes virus. In the differential diagnosis the highly contagious epidemic keratoconjunctivitis (shipyard conjunctivitis) caused by adenovirus type 8 must be considered.

#### DISEASE OF THE CENTRAL NERVOUS SYSTEM HERPETIC MENINGOENCEPHALITIS

The central nervous system is occasionally the site of a primary infection which may take the form of meningoencephalitis, encephalitis or encephalomyelitis (for discussion of clinical manifestations, see p. 547). Encephalitis may be accompanied by other manifestations of herpetic infection.

#### NEONATAL HERPETIC INFECTION

Herpetic infection may occur in the newborn infant, especially the premature. Transmission is from a primary infection in the mother as a rule.

The onset is usually from the fifth to the ninth day of life with fever or hypothermia, lethargy, dyspnea, vomiting, increasing jaundice and, at times, convulsions and circulatory collapse. Vesicular lesions of the skin, mucous membranes or conjunctivitis may or may not be present. Hepatosplenomegaly may occur. Involvement of the esophagus may lead to accumulation of thick yellow mucus in the pharynx, and severe bleeding may accompany liver failure. At autopsy characteristic inclusion bodies can be found in many organs, particularly the liver, where there is evidence of necrosis (herpetic hepatitis). A terminal infection with *Pseudomonas pyocyanea* is common.

#### GENERAL FEATURES OF HERPETIC INFECTIONS

**Etiology.** *Herpesvirus hominis* is a sphere 100 to 150 millimicrons in diameter. Of the common laboratory animals, it can infect rabbits, guinea pigs, hamsters and mice. Suckling mice are particularly susceptible. It grows on the chorio-allantoic membrane of the developing hen's egg, producing characteristic small, oval, superficial pocks. It infects various types of tissue cultured cells, especially rabbit kidney, human amnion and HeLa cells.

**Epidemiology.** Burnet has pointed out that this virus is primarily a parasite of man, which has developed an extremely compatible relationship with its host. About 70 per cent of the population are infected for most of their lives, but the host is rarely disabled and hardly ever killed by this infection. Infants up to four months of age show evidence of passive immunity. Most susceptibles become infected before the age of six years. Clinical manifestations are infrequent until the second year of life, when the peak incidence occurs, although, even then, not more than 15 per cent of infected children manifest clinical signs. Once infected, the majority of people continue to carry the virus in a latent state and maintain an almost constant level of circulating antibodies. It has been shown that the level of antibodies may fall after a primary infection, and several subclinical re-infections may occur before a stable antibody level is established. Carriers may distribute virus with or without the presence of a manifest lesion. The nonclinical carrier state is more common in children of seven months to two years of age than in adults. Although infection is usually spread subclinically, rare instances of institutional or familial outbreaks of stomatitis have been described. Lack of sufficient contact or unusual resistance leaves a small percentage of the population uninfected with the virus during childhood, thus accounting for the uncommon primary clinical infections of adults. It seems probable that close proximity is required to introduce the virus; for instance, sexual contact is associated with infection in adults. Trauma is a factor in some cases of stomatitis (e.g., teething) and in primary infections of the skin.

**Pathology.** The pathologic changes vary with the tissue infected. In general, a specific lesion is characterized by the presence of intranuclear inclusion bodies. These are

homogeneous masses lying in the midst of a severely disorganized nucleus in which the basichromatin has margined to the nuclear membrane. In the neighborhood of the specific lesion there is always evidence of an acute inflammatory reaction. In the *skin and mucous membranes* the typical lesion is a unilocular vesicle. This is formed by breakdown of epidermal cells which have undergone ballooning degeneration. In the skin there is a tense vesicle with the roof cells formed by the outer cells of the prickle cell layer and the keratinized cells beyond. Ballooned epithelial cells containing intranuclear inclusions can best be seen at the margins of the vesicle. The vesicular fluid contains shed infected epithelial cells, including multinucleated "virus" giant cells, and leukocytes. There is no necrosis. In the corium there are dilatation of capillaries and infiltration with both mononuclear and polymorphonuclear cells. In the mucous membrane, owing to maceration, there is early leakage of the vesicular fluid, resulting in a collapsed vesicle, mainly filled with fibrin, the roof cells of which are edematous. These form the gray membrane seen over the lesion. *In the brain* there are petechial hemorrhages and some areas of necrosis in the cortex and subcortical white matter; in the meninges there is congestion and infiltration with mononuclear cells. In the neighborhood of these areas, cells containing characteristic inclusion bodies are found. There is vascular engorgement and perivascular cuffing with lymphocytes. In *disseminated herpes* large areas of necrosis occur in the liver, lungs, adrenal cortex, kidneys, spleen and bone marrow which contain cells with characteristic inclusions.

**Clinical Laboratory Data.** No specific diagnostic aid is obtained from laboratory examinations, other than from viral tests (p. 384). There is a moderate polymorphonuclear leukocytosis in acute herpetic gingivostomatitis, eczema herpeticum and meningoencephalitis. In meningoencephalitis there is a cellular increase in the cerebrospinal fluid up to 1000 cells per cubic millimeter, most of which are lymphocytes; the protein level is elevated, and the sugar is within normal levels. Characteristic giant cells may be found in scrapings from fresh lesions of the skin or mucous membrane.

**Diagnosis.** The diagnosis is based on any two of the following: (1) a typical clinical picture; (2) isolation of the virus; (3) development of specific neutralizing antibodies; (4) demonstration of characteristic cells or

histologic changes in scrapings or biopsy material.

**Course and Prognosis.** Primary infection with the herpes virus is a self-limited disease, usually lasting one to two weeks. Fatalities may occur in the newborn or from meningoencephalitis or severe eczema herpeticum, but the prognosis is usually good. There may be frequent recurrent attacks, but they seldom cause more than a temporary inconvenience, except in the eye, where they may eventually cause scarring of the cornea and blindness.

**Treatment.** There is no specific therapy, but symptomatic and supportive therapy are of great importance. In infants, especially, eczema herpeticum and stomatitis may lead to severe dehydration and shock, requiring replacement of fluids and electrolytes. The use of antibiotics is of value to prevent or treat secondary infections. Application of one of the cationic detergents such as Ceepryn 1:4000 solution to the vesicles or its use as a mouth wash may be helpful; 2.5 per cent suspension of Aureomycin, used as a mouth wash, may relieve pain in older children. Pontocaine, 1 per cent, may be applied to the lesions in the mouth of infants before eating, if this can be done easily, or benzocaine lozenges may be chewed by older children.

The intake of food and fluid must be facilitated by acquiescing to the child's whims. Ice-cold fluids or semisolids are often accepted when other food is refused. Frequent recurrences may be the result of emotional disturbances, which may respond to psychotherapy.

The treatment of the ocular manifestations should be in the hands of a skilled ophthalmologist. *Cortisone must not be used*, since corneal perforation is a sequel.

**Prophylaxis.** Children with eczema should be kept from contact with manifest herpetic infection.

T. F. McNAIR SCOTT

#### REFERENCE

Scott, T. F. McNair: Diseases Caused by the Virus of Herpes Simplex; in Rivers, T. M., and Horsfall, F. L., Ed.: *Viral and Rickettsial Infections of Man*. Philadelphia, J. B. Lippincott Company, 1958.

#### VARICELLA AND HERPES ZOSTER

Recent work of Weller and his co-workers has clearly confirmed the earlier suggestions that these two diseases are different clinical manifestations of the same etiologic agent.



Evidence of the identity of the two is based on the following factors: (1) *Epidemiologic*. Since the observations of Bokay (1888) there have been frequent reports that exposure of susceptibles to a patient with herpes zoster could result in an outbreak of chickenpox (e.g., in a children's ward). (2) *Electron microscopic*. The elementary bodies (*Herpesvirus varicellae*) obtained from vesicles of the two diseases are indistinguishable, both being described as brick-shaped bodies averaging 210 by 238 millimicrons in diameter. (3) *Microbiologic*. The infectious agent from each disease can be grown in tissue culture of human embryonic skin and muscle, or human foreskin, maintained with bovine amniotic fluid medium, and each agent produces an identical focal area of cytopathogenicity. The agents multiply in the same way by spreading peripherally from infected cells to contiguous uninfected cells without appearing in the fluid medium. The infected cells in each instance contain intranuclear inclusion bodies characteristic of the herpesvirus group. Both agents can produce chickenpox in human volunteers, and neither agent can be transmitted to lower animals or grown in the embryonated hen's egg. (4) *Serologic*. Antibodies developing in the blood of patients recovering from varicella react equally with the agents derived from varicella and herpes zoster vesicles. These reactions have been demonstrated by means of the fluorescent antibody and the complement fixation techniques.

**Etiology.** The common causative agent is now designated as *Herpesvirus varicellae*. The reasons for different clinical manifestations of the two diseases are not completely explicable. It seems probable that varicella is the primary response of a completely susceptible host, while herpes zoster may be the response of a partially immune one; such reinfection could come from an outside source or from reactivation of the virus which has been latent.

**Pathology.** The *skin lesions* of both diseases are identical and characteristic of the herpesvirus group and cannot be distinguished from those of *Herpesvirus hominis* (herpes simplex), under which heading they have been described (see p. 493). Although not usual in cases of average severity, necrosis with hemorrhage can be found in the mucous membranes of the mouth, trachea, esophagus and intestine, where the lesions resemble those of herpes simplex.

Internally, the pathologic findings vary

somewhat in the two diseases. In fatal cases of *varicella* intranuclear inclusions can be found in the endothelium of the blood vessels; the vessel walls may actually undergo necrosis. The wide distribution of these lesions suggests that the infection is blood borne. Intranuclear inclusions have also been found in most organs of the body, including the salivary glands, the nervous system, and in the cells of the myenteric plexus of the stomach and intestine. In the brain perivenous demyelination occurs similar to that of other postinfectious encephalitides; necrosis of nerve cells and leptomeningitis have been described. In *herpes zoster* the characteristic lesions are in the nervous system, particularly in the dorsal root ganglia. Early in the disease the cells of the dorsal ganglia of the affected dermatome contain intranuclear inclusions. Shortly thereafter the ganglia show only necrosis of cells, sometimes associated with hemorrhage. As the disease progresses evidence of inflammation and degeneration is found in the posterior roots and in the peripheral portions of the nerves. Unilateral and segmental necrosis of the nerve cells in the posterior horn may be found (cf. poliomyelitis, which involves the nerve cells of the anterior horn). Leptomeningitis occurs in the region of the involved nerves. Intranuclear inclusions have been found in the sympathetic ganglia, the neurilemma cells of the nerve twigs in the corium and in the myenteric plexus.

## VARICELLA

### (CHICKENPOX)

Varicella is characterized by the appearance on the skin and mucous membranes of successive crops of typical vesicles generally accompanied by a mild constitutional reaction. William Heberden in 1767 was the first to distinguish chickenpox from smallpox. The term "chickenpox," derived from *cicer*, a chicken pea, was introduced by Morton at the end of the seventeenth century.

**Epidemiology.** Varicella is extremely contagious, and therefore its incidence is mainly during childhood. The most common age for infection is from two to six years, but it can occur at any age, including the newborn period. The disease can apparently be transmitted by direct droplet infection or be airborne in the form of droplet nuclei. Air disinfection by ultraviolet light can materially decrease the spread of the disease. Epidemics of chickenpox have been initiated by exposure to herpes zoster. Patients are in-



FIG. 154. Skin lesions of chickenpox. Note the varying stages of development (macules, papules and vesicles) present at the same time. (Courtesy of Dr. P. F. Lucchesi.)

fectious from twenty-four hours before to six or seven days after the eruption, at which time the vesicles have dried up. Scabs do not appear to be infectious. Second attacks are exceedingly rare, although over 70 per cent of patients with herpes zoster have had chickenpox. In epidemics featuring both zoster and chickenpox, the former tends to appear in older members of the population, whereas the latter tends to occur in children.

**Clinical Manifestations.** The incubation period varies from eleven to twenty-one days, and is between thirteen and seventeen days in the majority of instances. At the end of the incubation period prodromal symptoms, except in the mildest cases, precede the characteristic rash by twenty-four hours. There may be slight fever, malaise or anorexia, accompanied at times by a scarlatiniform or morbilliform rash. It is characteristic of the specific rash to appear rapidly. Typically, it begins as crops of small, red papules which almost immediately develop into clear, often oval, "teardrop" vesicles on an erythematous base. These vesicles are usually not umbilicated. The contents become cloudy within about twenty-four hours. The vesicles are easily broken and become scabbed. Occasionally they dry before becoming cloudy. Except for the mildest type of case in which few lesions occur, crops of widely scattered vesicles continue to erupt for three or four days, starting on the trunk and later spreading to the face and scalp, with minimal, if any, involvement of distal parts of the extremities. There is some tendency for the lesions to be concentrated in areas of skin pressure or irritation, but not to the same extent as in smallpox. Characteristically, at the height of the disease the eruption consists of papules, early and late vesicles, and crusts present at the same time (Fig. 154). Pruritus is a con-

stant and annoying characteristic of the rash. Vesicles may also be found on mucous surfaces and are common in the mouth, where they may resemble the lesions of herpetic stomatitis. Less commonly, lesions are found on the genital mucous membranes and on the conjunctiva and cornea, where they are potentially dangerous to sight. Rarely laryngeal involvement has been recorded.

Generalized lymphadenopathy occurs, and enlargement of the suboccipital and posterior cervical nodes may result from secondarily infected scalp lesions.

The disease varies in severity from patients with few lesions and little evidence of systemic illness to those with many hundreds of lesions who may be seriously ill with temperatures ranging from 103° to 105° F. Systemic manifestations occur only during the first three to four days, when the rash is erupting. The rash rarely coalesces and rarely becomes gangrenous or hemorrhagic. Bullous lesions may occur.

Recovery from the disease occurs with the development of circulating antibodies which become detectable between four and seven days after appearance of the exanthem. The level of antibodies reaches a peak about the end of the third week and then declines, so that after five years it is low.

**Laboratory Data.** There may be a mild leukocytosis, but no specific cytologic or serologic changes have been described. Scraping of the floors of fresh vesicles will reveal the presence of virus giant cells (see Herpes Simplex, p. 494).

**Diagnosis.** This is not difficult in the average case. Most important is the distinction between chickenpox and smallpox, which may be exceedingly difficult in patients suffering from mild smallpox or severe chickenpox. The following clinical points should be borne in mind: (1) The rash of chickenpox begins on the trunk and spreads toward the periphery, while that of smallpox tends to spread from the periphery toward the trunk. (2) The lesions of smallpox tend to be most frequent in areas of pressure or tightness of the skin, as over the bridge of the nose and the wrist, or at the belt line, whereas those of chickenpox do not have this tendency to the same extent. (3) The lesions of chickenpox are more superficial and are not umbilicated, whereas the lesions of smallpox tend to be deeper and more "shotty" to the touch and are usually umbilicated. (4) The lesions of chickenpox are present in all stages of development at a given time, whereas those of



smallpox are more or less in the same stage at each phase of the disease. (5) The prodromal symptoms of chickenpox are short (one to two days) and usually mild; those of smallpox are longer (three to four days) and may be severe with high fever which drops with the appearance of the rash.

**Complications.** These are rare, and can be considered under three categories. (1) *Bacterial infection* was the most common in the preantibiotic era when streptococci and staphylococci, introduced by scratching, resulted in erysipelas, furuncles and septicemia. (2) The location of the lesions can be important; vesiculation of the larynx may result in laryngeal edema, and of the cornea in discoid keratitis. (3) The severity of the *viremia* determines the systemic pattern. Pneumonitis of an interstitial variety is usually found in fatal cases, and mostly in adults. Roentgenographically it may appear as a bilateral nodular infiltration; in nonfatal cases it clears with the skin lesions. Myocarditis has also been reported. Central nervous system involvement can manifest itself in various ways, such as meningoencephalitis, with fever, changes in sensorium and convulsions; acute cerebellar ataxia, and optic neuritis with temporary loss of vision. Neurologic manifestations may appear from three days before to twenty days after the appearance of the rash. The mortality in patients with neurologic manifestations is 5 to 11 per cent. Among those that recover sequelae are few. The cerebrospinal fluid may be normal, although occasionally there is a mild lymphocytosis.

The *increasing use of steroids* has introduced a hazard previously unknown. Patients who contract chickenpox while on steroid therapy are not able to develop antibodies and therefore run the risk of a prolonged or fatal illness in which involvement of the central nervous system, lungs and other viscera occurs.

**Prognosis.** The prognosis is good; fatalities are rare in childhood, except in children under steroid therapy.

**Treatment.** There is no specific treatment. Symptomatic treatment should be directed to alleviating itching and preventing secondary bacterial infections. Scratching deepens the superficial lesions, so that the corium becomes involved and scarring results. The fingernails should be kept short and clean, and infants should wear mittens. The child's clothing and bed linen should be changed daily, and a soap and water bath once or twice daily is

indicated to diminish the risk of bacterial infection. Itching may be relieved by starch baths and calamine lotion (U.S.P.), to which 0.25 per cent menthol is added. Sedation should be used as necessary. Treatment for secondary infection should be with systemic antibiotics, although antibiotics infrequently used systemically may be applied in ointments (e.g. polymyxin, bacitracin).

If the patient is on steroids at the time of his infection, the dose should be reduced to that amount which would provide him with approximately his physiologic requirements (i.e., 1 mg. of cortisone per kilogram per day).

**Prophylaxis.** There is no reliable and generally applicable method of prophylaxis. Gamma globulin is ineffective in protecting susceptibles. Convalescent serum taken within the first six months after onset of the disease contains a high level of antibodies and should be effective, but is impracticable for general use. Ultraviolet light disinfection of air will reduce the incidence of the disease in schools, but it is important to remember that the disease is much milder in children, and no generalized attempt to reduce the incidence of the disease during childhood should be undertaken.

#### HERPES ZOSTER (SHINGLES)

Herpes zoster is an acute infection characterized by crops of vesicles, usually confined to a dermatome and accompanied by neuralgic pain in the area of the affected dermatome. The clinical features of the disease have been known from antiquity.

**Epidemiology.** Herpes zoster is relatively uncommon under ten years of age, after which its incidence increases steadily with each succeeding decade. Second attacks of zoster are rare, less than 1 per cent in one study of 206 patients, but a history of a previous attack of chickenpox is to be expected. The severity of the disease increases with age. There is no sex or race predilection. The disease is classified as spontaneous (primary) and symptomatic (secondary), depending upon whether there seems to be a trigger mechanism such as trauma, leukemia or administration of heavy metals.

**Clinical Manifestations.** Herpes zoster has a pre-eruptive and a post-eruptive phase. In the last days of the incubation period, which appears to be from seven to twenty-one days, the patient usually has pain and tenderness along the involved dermatome. There is often

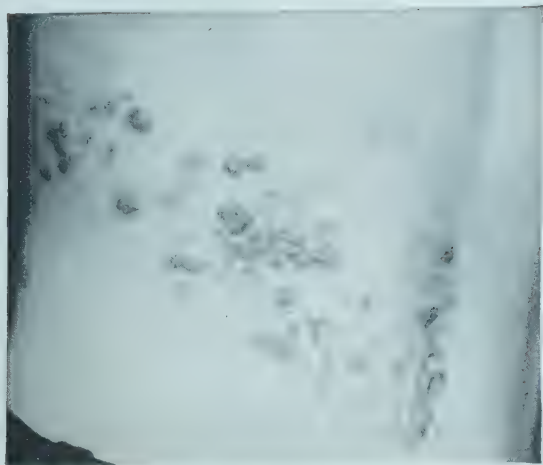


FIG. 155. Herpes zoster. (Courtesy of Dr. Carroll S. Wright.)

generalized malaise and fever. Within a few days a crop of red papules appears on the skin of the dermatome; the individual lesions quickly vesiculate (Fig. 155), become pustular, dry up and scab in the course of five to ten days. The lesions tend to appear first at a point nearest the central nervous system. Thus, in the common thoracic zoster, the dorsal part of the dermatome supplied by the shorter posterior branch of the intercostal nerve is usually involved first. Successive crops of lesions continue to appear for seven days, extending along the course of the nerve. The eruption clears in seven to fourteen days in over 90 per cent of patients under twenty years of age, but when vesicles continue to appear for seven days, healing may be delayed up to five weeks. The lesions, except in rare instances, are unilateral. Fever, pain and tenderness usually continue throughout the period of progression. The regional lymph nodes are invariably enlarged. Secondary bacterial invasion of the vesicles may occur. Under the age of twenty years almost 90 per cent of patients have involvement of dermatomes between the second dorsal and second lumbar areas. However, cephalic zoster, involving the fifth and seventh cranial and the upper three cervical nerves, which occurs in over 30 per cent of older patients, may also occur in children.

Infection associated with the distribution of the fifth nerve may involve the cornea (zoster ophthalmicus) and may lead to permanent damage; involvement of the maxillary and mandibular divisions results in lesions of the tongue and fauces; of the geniculate ganglion, in vesicles on the external ear, often accompanied by paralysis of the seventh nerve (Ramsay Hunt syndrome). Rarely paralysis

may accompany sensory changes elsewhere. In children chickenpox may occasionally manifest itself early in a dermatomic distribution shortly before the rash becomes generalized. Rarely in elderly adults true zoster with prodromal pain may be followed in a few days by a generalized rash.

**Laboratory Data.** Examination of the cerebrospinal fluid often reveals a mild lymphocytosis. Scrapings of the floors of vesicles in their initial stage will reveal virus giant cells (see Herpes Simplex, p. 494).

**Diagnosis.** Diagnosis may be difficult before development of the rash; the pain may resemble that of pleural or peritoneal origin, depending on the site of the lesion. Once the rash has appeared, its distribution and characteristics along with the pain make the diagnosis relatively simple. Occasionally, herpes simplex may simulate the distribution of zoster.

**Course and Prognosis.** In children the course is usually mild, and the ultimate prognosis is good.

**Complications.** Postherpetic pain does not occur in children. Keratitis and uveitis may follow fifth nerve involvement, and secondary bacterial infection is possible in any of the lesions.

**Treatment.** There is no specific therapy. Symptomatic treatment consists in preventing, as far as possible, secondary bacterial infection by cleanliness and prevention of scratching (see Varicella). If infection has occurred, suitable systemic or local antimicrobial therapy should be considered. Pain, seldom a serious problem in children, can usually be controlled with aspirin and codeine.

Steroid therapy is of value in the treatment of zoster ophthalmicus, in sharp contrast to the danger of its use in ophthalmic infection with the virus of herpes simplex. Treatment should be by an ophthalmologist.

**Prophylaxis.** The possibility that herpes zoster may follow exposure to chickenpox should be kept in mind. Conversely, since chickenpox can follow exposure to herpes zoster, it is unwise to admit to an open ward a child suffering from the latter disease.

T. F. McNAIR SCOTT

#### REFERENCES

- Stokes, J., Jr.: Varicella and Herpes Zoster; in Rivers, T. M., and Horsfall, F. L., Eds.: *Viral and Rickettsial Diseases*. Philadelphia. J. B. Lippincott Company, 1958.
- Weller, T. H.: *Observations on the Behaviour of*



Certain Viruses That Produce Intranuclear Inclusion Bodies in Man. Harvey Lectures 1956-57. New York, Academic Press, Inc.

## SMALLPOX

(VARIOLA)

Smallpox is an acute communicable viral disease characterized by a papulovesicular, pustular rash and usually by severe systemic symptoms. Vaccination, introduced a century and a half ago by Jenner, has provided a method of control. There appear to be two stable types of smallpox virus, variola major and variola minor, which usually can be distinguished by the severity of the disease they cause.

**Etiology.** The smallpox virus is stable. It can be dried under relatively unfavorable conditions and remains viable for months, as, for example, in house dust. The virus is a typical "pox virus," the elementary body being flattened and brick-shaped with a central mound-like protrusion. It measures on an average 244 by 302 millimicrons (*cf. Herpesvirus varicellae*). The virus grows readily on the chorio-allantoic membrane, where it produces characteristic pocks. In the rabbit it produces a keratoconjunctivitis after corneal inoculation (Paul's test).

**Epidemiology.** The disease is transmitted readily to susceptibles, probably by way of the respiratory tract. Fomites and letters can also spread the disease. The finding of elementary bodies in the crusts of lesions and on the bedclothes of a patient supports the air-borne theory. No age or sex is immune, but the colored races appear to be more susceptible than the white. Second attacks are extremely rare. Smallpox epizootics in monkeys have been reported in association with epidemics in human beings, and the virus can be transmitted to this host experimentally. The great danger of spread of the disease is from mild sporadic cases which may go unrecognized; such cases may be misdiagnosed as chickenpox. Laboratory assistance should be sought whenever there is suspicion of smallpox.

**Pathology.** Specific changes are found in the skin, mucous membranes and many of the organs. The typical skin lesion starts with changes in the capillaries of the corium and is characterized by dilatation, endothelial proliferation and perivascular mononuclear infiltration. In the adjacent epidermis the cells swell and the characteristic Guarnieri bodies make their appearance. These are spherical

bodies lying close to the nucleus, consisting of collections of virus elementary bodies, and range in size from 2 to 8 microns; they are seldom seen in routine sections. The swollen cells rupture, forming a vesicle divided into lobulations by thin septums of partially ruptured cellular membranes and thicker septums formed of the resistant ducts of sweat glands. The cells beneath the vesicle undergo a ballooning type of degeneration. As the vesicle enlarges through involvement of neighboring cells, it extends to the corium. The characteristic early umbilication is caused by edema and enlargement of the degenerating cells at the margin of the vesicle and by proliferation and thickening of the epidermal layer. Umbilication disappears as the fluid increases, but reappears as desiccation and crusting begin. Healing occurs without scarring except on the face, where necrosis of sebaceous glands characteristically occurs, and in other areas where there has been secondary bacterial infection.

In the mucous membranes of the respiratory and digestive tracts, changes occur coincidentally with those of the skin and consist initially in localized and then diffuse necrosis of the superficial cells and congestion and hemorrhage in the tunica propria. Grossly, these lead to the appearance of a diffuse pseudomembrane in the pharynx by the third or fourth day which disappears without scarring by the third week. Bronchitis and bronchopneumonia are common. In the liver, spleen and bone marrow the basic lesion appears to be in the reticuloendothelial cells and consists in necrosis and proliferation. In patients dying with hemorrhagic smallpox a decrease in megakaryocytes and in cells of the granulocytic series is seen in the bone marrow. In the kidneys of such patients there is an interstitial nephritis. An orchitis occurs during the papulovesicular stage, consisting in hyperplasia of the vascular endothelium followed in order by necrosis of the interstitial cells and of the seminiferous tubules. In boys the lesions resemble ischemic infarctions.

**Clinical Manifestations.** The typical case of smallpox is readily recognized, but mild cases may be misdiagnosed as chickenpox, or missed altogether. The incubation period is usually twelve to fourteen days, but may be as long as sixteen to twenty-one days in previously vaccinated persons and at times in variola minor.

**Variola major.** In a typical case the prodromal symptoms are severe and usually start abruptly. The initial clinical manifestations

include headache, chills or chilliness, aching of the back and limbs, and fever, which mounts rapidly to 106° or 107° F. In children there may also be vomiting, drowsiness, convulsions or coma. Often delirium occurs, and the patient is prostrated.

During the first two days transient rashes are common, which may resemble scarlet fever or measles or may be petechial. They tend to be most prominent over the upper thighs and buttocks (the "bathing drawers" distribution of the French clinicians) and disappear rapidly by the third or fourth day, when the raised macules of the typical cutaneous lesion begin to appear over the face. Widespread prodromal rashes and the early appearance of macules presage a severe attack with confluent lesions.

There is usually diminution in severity of symptoms as the rash becomes papular, and the temperature may even become normal and remain so until the pustular stage, when there is usually a secondary rise. The individual lesions appear in a single crop and progress at the same rate, unlike the multiple crops occurring in chickenpox. Initially the papules are 2 to 4 mm. in diameter and are firm and "shotty." Within about twenty-four hours the size of the papules increases, and vesicles appear. They tend to be umbilicated in the early and again in the late stages. Some of the vesicles are superficial, and others are deeper and less readily recognized. A small red areola develops about each vesicle.

About the fifth or sixth day of the disease the vesicles become cloudy, and the pustular stage begins. The individual lesion has a greenish or grayish-yellow color, and an elevation slightly greater than its diameter. About the ninth day of the disease the lesions begin to dry, and the areolas disappear. They are usually crusted over by the end of the second week, and the scabs drop off about the end of the third or fourth week. The scabs persist longest on the palms and soles, where they are known as "seeds" and may have to be enucleated with a needle.

The cutaneous areas chiefly involved in the early stages are those where the skin is tight, such as the wrists and the prominences of the face; the more exposed extensor surfaces of the forearms and upper arms are then involved, leaving the more protected flexor surfaces and the axilla relatively free. The rash then spreads to the thorax. In severe cases the abdomen and the legs are heavily covered; in milder cases they may be only slightly involved. Concurrently with the skin

lesions, the mucous membranes of the mouth, eyes and often the larynx become involved.

A striking feature of the disease, in contrast to chickenpox, is the profusion of lesions on the face, including the lips, and the presence of a relatively large number of lesions on the palms and soles. When the lesions become confluent, there is considerable edema of the face, so that there is difficulty in closing the eyes and mouth. The lesions on the mucous membranes also tend to be confluent.

The degree of scarring depends on the extent and severity of the eruption, and is usually greatest on the face. Intense pigmentation of the skin persists for a variable time after the scabs have fallen. In the fatal cases death usually occurs during the second week of the disease.

*Hemorrhagic smallpox* may occur in two forms: *vesicular hemorrhagic smallpox*, in which hemorrhages occur in the lesions, although death may occur before the vesicular stage develops; and "*true hemorrhagic or black smallpox*," in which a diffuse hemorrhagic rash begins on the second or third day of prodromal symptoms, followed by ecchymoses and hemorrhages into the mucous membranes. The temperature may be subnormal, although the symptoms are severe. Death may occur before the characteristic rash of smallpox develops.

*Variola minor (alastrim)*. This form differs from *variola major* chiefly in being less severe and rarely causing death. It apparently breeds true and never develops into *variola major*; it is thought by some to be a distinct disease entity.

*Varioloid*. Smallpox modified by previous vaccination is usually termed "varioloid." Although varioloid lesions appear in a single crop and progress in a manner similar to those of more severe smallpox, they are entirely discrete, and the prodromal symptoms are mild. There is no secondary rise of temperature, and premature involution of many of the lesions occurs.

*Abortive type*. In persons who have been vaccinated shortly before exposure to smallpox a condition known as "*variola sine eruptione*" may occur. Macules or papules may involute with great rapidity, or there may be no eruption at all, and the patient has only a mild, febrile illness.

**Laboratory Data.** A neutropenia is characteristic of the early stages of the disease. In hemorrhagic smallpox this may be marked and associated with a reduction of platelets. Large lymphocytes are characteristically



present in small numbers. During the pustular stage a polymorphonuclear leukocytosis occurs. There is prolongation of the prothrombin time and a decrease in fibrinogen associated with the hemorrhagic type, probably dependent on extensive liver damage.

**Diagnosis.** Diagnosis can be made on clinical grounds in a typical case or during an epidemic. In a doubtful case the patient should be isolated and viral studies obtained.

**Complications.** Pyogenic infections of the skin and bacteremia, particularly with the *Streptococcus*, were common before the availability of antibacterial agents. An enanthem of the larynx may lead to edema of the glottis and perichondritis of the laryngeal cartilages. Bronchopneumonia occurs as a terminal event in almost all fatal cases. Rarely osteomyelitis may occur as a result of direct viral invasion or of secondary bacterial infection. In the former, pain and tenderness appear during convalescence in an afebrile patient. Roentgenographically, there is widespread destruction of bones, even in those clinically uninvolved. Healing takes place without specific therapy. Central nervous system involvement is rare; symptoms usually begin five to thirteen days after the appearance of the rash and resemble those of other postinfectious encephalomyelitides.

**Prognosis.** The case fatality rate varies with the type of the disease and the age of the patient. The rate during epidemics of variola minor is less than 1 per cent, while an overall rate of about 10 per cent may be expected in epidemics of variola major. The case fatality rate is considered to be about 5 to 6 per cent in discrete smallpox, 60 per cent in confluent smallpox and 80 per cent or over in hemorrhagic smallpox. The mortality rate is greatest in children under five years of age and in persons over forty-five years of age.

**Treatment.** There is no specific treatment, but symptomatic treatment and nursing care are of extreme importance. The patient's room should be light and well ventilated; some odor-killing device should be used. Severe cases of confluent and hemorrhagic smallpox should be treated for shock and dehydration by proper use of intravenous fluids, blood and plasma. Prophylactic antibacterial therapy should be given from the beginning. Nutrition must be maintained by tube feeding if necessary. Potassium permanganate baths (1:5000) or wet dressings may be helpful for extensive skin lesions of the confluent variety. Lesions of the eyes require frequent irrigation; this therapy should be supervised by an oph-

thalmologist. Crusts in the nose may be loosened with swabs moistened with oil. Rinsing of the mouth with one of the cationic detergents, such as Ceepryn or Zephiran, may be beneficial. Sedation, including morphine, should be given as indicated. In the milder cases the general methods of treatment as outlined under Chickenpox are adequate (p. 497).

**Prophylaxis.** Vaccination is the only form of satisfactory prophylaxis, although vaccinia hyperimmune gamma globulin given after exposure may modify the disease.

Patients should be strictly isolated until all the crusts have dropped off. It would seem reasonable to use available methods of controlling air-borne spread of the disease, such as oiling of bedclothes, ultraviolet light or glycol vapors; in addition, the usual isolation precautions should be taken. Fomites, books, letters, and the like, must be sterilized, preferably by heat.

In the public health management of a smallpox epidemic the following steps, scrupulously enforced, can usually be relied on to control the spread of the disease, without the need for mass vaccination with its administrative problems and potential dangers: (1) listing of contacts; (2) surveillance of contacts for three weeks for any evidence of illness; (3) vaccination of contacts, preferably within twenty-four hours of exposure. Vaccination must produce reliable evidence of a take, and must be repeated if negative or doubtful.

T. F. McNAIR SCOTT

#### REFERENCES

- Bertcher, R. W.: Osteomyelitis Variolosa. *Am. J. Roentgenol.*, 76:1149, 1956.
- Bras, G.: The Morbid Anatomy of Smallpox. *Documenta de Medicina Geographica et Tropica*, 4:1, 1952.
- Downie, A. W.: Small Pox; in Rivers, T. M., and Horsfall, F. L., Eds.: *Viral and Rickettsial Infections in Man*. Philadelphia, J. B. Lippincott Company, 1958.
- Kempe, C. H.: Variola and Vaccinia; *Diagnostic Procedures for Virus and Rickettsial Diseases*. American Public Health Association, 1956.
- Murray, L. H., and Bradley, W. H.: Smallpox in 1947. *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service, Medical Research Council*, London, 7:96, 1948.
- Rolleston, J. D.: *Acute Infectious Diseases*. 2nd. ed. London, Wm. Heinemann, Ltd., 1929.

#### VACCINATION AGAINST SMALLPOX

The use of cowpox virus for vaccination against smallpox was the first successful de-

velopment of a method for the protection of human beings against a serious epidemic disease. Although used by Benjamin Jesty, a Dorsetshire farmer, in 1774 to protect his own family, it was Dr. Edward Jenner in 1798 who conclusively proved that the inoculation of human beings with material from cowpox led to immunity to smallpox. The relation between the cowpox used for vaccination by Jenner and the present vaccinia virus is obscure. Cowpox and variola belong to the "pox" group of viruses which affect many species of animals, each animal having its own specific pox infection which as a rule is not transmissible to another host. However, cowpox is sufficiently related to the human "pox" virus, variola, that it can and does affect man with a specific disease of the skin of the hands on close contact. Vaccinia virus, which is a stable "pox" virus distinguishable in the laboratory from cowpox and variola, has been evolved from them. The sources of vaccinia virus used in various parts of the world probably vary, some being derived from cowpox and some from variola.

**Age of Initial Vaccination.** It is preferable to perform vaccination during the first year of life. The principal advantages are as follows: (1) Constitutional effects tend to be less than at later ages; (2) encephalomyelitis is practically unknown as a complication; and (3) immunity develops before there is likelihood of exposure to smallpox. Vaccination can be performed in the newborn period, but is usually postponed until the fourth to eighth month of life. At the time of vaccination the infant or child should be in good general health. Vaccination should not be performed in young premature infants or in any child during hot weather or immediately after severe infections, nor in children with eczema, impetigo or other skin lesions which might result in secondary infections. A child who has a sibling or close contact with another child with eczema should not be vaccinated unless they can be separated for the period of activity of the vaccinia lesion or the eczematous child protected by hyperimmune gamma globulin.

When vaccination has not been performed in infancy, it should be one of the initial prophylactic procedures whenever the child is placed under medical supervision. Most states now require vaccination against smallpox before entering school. Pregnant women should *not* be vaccinated during the first trimester.

**Type of Vaccine.** The usual type of vaccine is obtained from the pulp of vesicles of vaccinated calves, which is diluted 1:5 in 50 per cent glycerin-saline solution containing 1 per cent phenol. It is distributed in capillary glass tubes. The marketed vaccine is not completely free of bacteria, but, by law, must contain less than fifty bacteria per dose and no pathogens. It is considered potent for three months if kept below 5° C., but deteriorates rapidly at room temperature. Avianized vaccine prepared from vaccinia-infected chorio-allantoic membranes of embryonated hens' eggs is equally effective.

**Site of Vaccination.** Vaccination should be performed on the skin over the insertion of the deltoid muscle or on the posterior axillary fold. The latter site is exposed to a minimum of trauma, and the scars are inconspicuous. Vaccination on the thigh is more exposed to contamination in the infant and proves more incapacitating during the height of the reaction in older persons..

**Method of Vaccination.** Although there is good evidence that there is direct correlation between protection against the disease and the number and extent of the vaccination scars, the present policy, in nonendemic areas, is to make only one inoculation. Where smallpox is endemic or after exposure, two to four sites of inoculation are advocated. The technique is as follows: The skin should be cleansed with a volatile antiseptic, e.g., ether or acetone, care being taken to avoid causing abrasions in which the virus could "take." The tube of lymph should be removed from the freezing section of the refrigerator only at the moment of use, the two ends broken off after filing, and the contents expressed on the skin by means of a small rubber bulb. Introduction of the virus can be accomplished by one of two methods. (1) *The multiple pressure method* is most generally recommended in the United States. The needle is held almost parallel with the skin and the point pressed up and down against the skin through a drop of lymph in such a way that the surface cells are picked off, thus exposing the deeper-growing cells of the epidermis to the virus. Six to ten pressures over an area of about  $\frac{1}{8}$  to  $\frac{1}{4}$  inch in diameter are usually sufficient for primary vaccination after the age of six months. In very young infants and for revaccination, however, thirty pressures are recommended. The area should show erythema, but not blood. (2) *The scratch*



*method* is generally recommended in the British Isles and consists in making a scratch, with a minimum of trauma, with a sterile needle through a drop of vaccine lymph. The scratch should be about  $\frac{1}{4}$  inch long and deep enough to get through the skin without drawing blood, although the appearance of a drop or two is of no significance.

In each method the lymph is rubbed into the site with the haft of the needle, the excess is wiped off, and the remainder allowed to dry.

**Type of Reaction.** There are, in general, three types of reaction: (1) primary take, (2) accelerated take or vaccinoid reaction, and (3) "immune" or "immediate" reaction.

**Primary take.** This is the reaction of the nonimmune person. There is little reaction at the site except a fading erythema until the third to fifth day, when a red, slightly itching papule appears. This rapidly vesiculates within about twenty-four hours and becomes surrounded by a red areola. The vesicle grows in size and becomes umbilicated and pearly-gray, surrounded by an area of erythema and induration. The reaction reaches its height about the ninth or tenth day, when the vesicle may be as much as 1 cm. in diameter, and is easily ruptured by minor trauma; the area of erythema and induration may be ten times as large. At this time the area is hot and painful, and the regional lymph nodes are enlarged and painful. There may be enlargement of the spleen. There are systemic symptoms, such as fever which starts as a low grade one at the appearance of the vesicle and increases to as much as  $104^{\circ}$  F. or higher at the peak of the reaction, when there may be chills. Headache is common, as is general malaise. These symptoms may last three or four days. There is little change in the leukocyte count. After the peak of the reaction the vesicle undergoes desiccation, the central umbilication becoming larger and darker. The scab drops off about the twenty-first day, leaving a pink, pitted scar which slowly fades to white and remains as the only evidence that successful vaccination has been performed.

**Vaccinoid or accelerated reaction.** This is the reaction of the partially immune person. The lesion goes through the same general stages as does the primary take, but more rapidly. The greater the immunity, the more rapid is the evolution. A papule may become vesiculated within two days and reach the peak of its reaction in less than a week. The size of the reaction is smaller than with

the primary take, and there are few, if any, general signs or symptoms.

**"Immediate" reaction.** This type of reaction, often termed *immune reaction*, is usually characteristic of a solid immunity, but it can also occur in a susceptible person as a result of sensitivity to virus protein. It is important, therefore, not to accept this reaction at its face value, but to test for immunity by at least one more vaccination with a vaccine of known potency. Unless there is a circumscribed, deep-seated, indurated swelling of the skin about three days after the inoculation, which then subsides without vesiculation, the person should not be considered immune.

In some persons repeated attempts at vaccination fail. It is possible that an occasional person is truly resistant, but smallpox has occurred after many failures to secure a vaccination take. Probably such factors as potency of virus or technique of application are responsible for most of the failures.

**Revaccination.** Infections with smallpox are almost unknown within five years of successful vaccination. For routine purposes, therefore, revaccination should be performed every four years (leap year routine). In addition, revaccination must be performed whenever there is contact with a case of smallpox. Under these circumstances a positive "take" is of such importance that at least two "insertions" should be made. The important factor is the time of appearance of the reaction, so that every effort should be made to use potent material and get good contact with the appropriate skin cells. Local skin immunity to vaccination can exist without systemic immunity; so the site of revaccination should be at a location other than the original one.

**Care of Site of Vaccination.** Maintenance of dryness and a free flow of air about the vesicle is essential. Shields should never be used. A relatively sterile surface may be maintained on the entire area surrounding the reaction by sponging gently with alcohol at least twice daily, being careful to leave the surface of the vesicle intact. If the vesicle ruptures because of excessive tension of trauma, the area should be sponged with alcohol three to four times daily and loosely covered with a piece of gauze attached to the skin above and below by adhesive tape placed well outside the indurated area. When the dressing is changed, it should be cut off and the fresh one taped on over the original adhesive tapes. These should not be removed

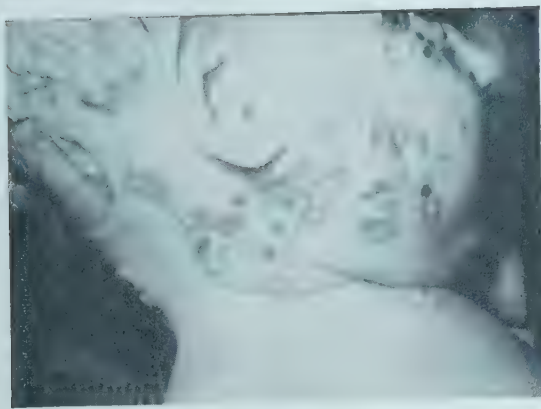


FIG. 156. Eczema vaccinatum.

until the inflammation has subsided, so that secondary vesicles in the adhesive abraded areas are avoided.

### COMPLICATIONS

**Pyogenic Infections.** As a result of scratching or neglect, the vaccination site can become contaminated with various pathogens such as staphylococci and streptococci and give rise to cellulitis, scarlet fever or septicemia. The size of the scar is always increased by such contamination. Vaccine lymph can be contaminated with tetanus spores; however, tetanus has occurred only when a tight shield or other occlusive dressing has been applied so as to exclude air from the vaccination site.

**Nonspecific Skin Rashes.** These rashes appear to be due to hypersensitivity to virus protein and fall into the category of erythema multiforme. They usually appear seven to eleven days after the inoculation, and most frequently have a maculopapular, urticarial or papular form, but occasionally characteristic iris lesions and bullae may occur. The mucous membranes may be involved, and the picture then is one of erythema multiforme pluriorificiale, and the patient may be seriously ill. Such rashes have been noted in one of 4000 to 5000 vaccinees.

### COMPLICATIONS RELATED TO THE VIRUS

**Multiple or Unusual Sites of Vaccination.** By means of scratching, the virus can be spread by auto-inoculation to abrasions in other parts of the body. Occasionally, vaccination by contact with a vaccinated person occurs in unusual sites such as the lip, tongue, penis, vulva, or on traumatized skin anywhere.

**Generalized Vaccinia.** This is fortunately rare, occurring in about one in 100,000 vac-

inations. Three clinical categories are recognized: (1) *Generalized vaccinia* per se due to a slow development of antibodies. It varies in severity and duration. In some patients satellite vesicles keep appearing about the primary inoculation for a few days to several weeks after the usual time of antibody appearance (seventh to tenth day). Viremia, which is not demonstrable after uncomplicated vaccination, occurs, and other scattered lesions may be found in distant parts of the body. In most patients antibodies eventually appear, and the patient recovers. (2) *Prolonged or progressive vaccinia, or vaccinia gangrenosa.* In such instances the patient is incapable of making antivaccinal antibodies at all. There is spreading necrosis at the site of the vaccination, and metastatic necrotic lesions occur throughout the body, including the bones, death ensuing after many weeks or months of illness. Some of these patients have agammaglobulinemia. (3) *Eczema vaccinatum.* Inoculation of vaccine virus into a wide area of traumatized skin results in a widespread "take" with subsequent viremia. These patients are covered with umbilicated vesicles, and the mortality in infants may be as high as 30 to 40 per cent. The picture may resemble that of eczema herpeticum (see p. 491), from which it must be distinguished by the absence of recurring crops of vesicles, by epidemiologic factors, by history of contact with a vaccinated person or a primary take, and by suitable laboratory techniques.

**Postvaccinal Encephalomyelitis.** This is one of the postinfectious encephalitides. It appears usually eleven to fourteen days after vaccination, but tends to appear in less than ten days in infants. The clinical pattern varies and may be mainly encephalitic, encephalomyelitic, myelitic or meningitic. It has an incidence of approximately 1:100,000 vaccinations in the United States, although its incidence is reported at higher rates in parts of Europe. The highest incidence of morbidity and mortality is in children ranging in age from five to fifteen years; 10 per cent of cases and 20 per cent of deaths have been in infants under two years of age. It is rare under one year of age. The case fatality rate is approximately 50 per cent, most of the deaths occurring in patients with the encephalitic pattern. There is no evidence that a particular batch of vaccine lymph is involved, and there appears to be no correlation with the size or severity of the local reaction or the number of inoculations. Encephalitis ap-



pears to be less common and less severe after revaccination than after primary vaccination.

**Treatment of Complications.** Bacterial complications should be treated with appropriate antibiotics. Absence or delay of antibody production can be overcome by administration of hyperimmune vaccinal gamma globulin. This can be given as a single dose of 0.6 ml. per kilogram prophylactically to contacts with eczema or to eczematous subjects at the time of vaccination, if vaccination is mandatory. For therapy of generalized vaccinia per se a similar dose is usually sufficient. For eczema vaccinatum one or two treatments may be required. For progressive vaccinia doses must be repeated every week or two until healing is proceeding favorably and vaccinia virus can no longer be demonstrated in the lesions.

T. F. McNAIR SCOTT

## REFERENCES

- Kempe, C. H., Berg, T. O., and England, B.: Hyperimmune Vaccinal Gamma Globulin. *Pediatrics*, 18:177, 1956.
- Marsden, J. P.: Vaccination against Smallpox—A Critical Review of the Present Position. *Bull. Hyg.*, 21:555, 1946.
- Ministry of Health Memorandum on Vaccination against Smallpox. London, H. M. Stationery Office, 1956.

## MUMPS

### (EPIDEMIC PAROTITIS)

**Definition.** Mumps is an acute contagious viral disease characterized by painful enlargement of the salivary glands, chiefly the parotids, and by a constitutional reaction.

**History.** Mumps was recognized as early as the fifth century B.C. by Hippocrates, who mentioned the complication of orchitis. In 1790 Hamilton also noted the orchitis of mumps and the frequent involvement of the central nervous system. Since the beginning of the twentieth century the meningoencephalitis which occurs in apparent and inapparent mumps has been fully recognized, as well as the secondary inflammation of the thymus, pancreas and ovaries. In 1945 Habel and also Levens and Enders demonstrated growth of the virus in the amniotic sac of the chick embryo.

**Etiology.** Mumps is caused by a virus that can be transmitted from filtered salivary secretions of infected persons to the rhesus monkey; injection into Stensen's ducts produces the typical swelling within five to seven days. After such reactions the monkeys are immune to the disease. On subsequent injections of active virus into Stensen's duct of the same animal, swelling of the gland

occurred within twenty-four to forty-eight hours. This is termed an immune response; swelling subsides rapidly without spreading to the opposite gland. Enders and his co-workers demonstrated that the antigen or virus reaches its greatest concentration in the parotid gland of the monkey approximately three days before the usual parotid enlargement of mumps.

The virus is approximately 90 to 135 millimicrons in diameter and passes through Berkefeld V and N filters. It can be readily grown in the amniotic sac of the chick embryo and after several passages is present in large amounts in both the amniotic and allantoic sacs. It may also be grown in tissue cultures of HeLa cells and of several other human or simian cells. Owing to characteristic changes in the HeLa cells, neutralization tests may be carried out with such infected tissue cultures. The test may be read in three days, and although it is the best test for immunity it is not as practical as the quicker complement fixation test. The virus also agglutinates chick erythrocytes, but inhibition of agglutination has not been so satisfactory a test for antibodies to the virus as the complement fixation test. For this test Henle, Henle and Harris used two antigens, one a small soluble antigen, S antigen, obtained best from the chick membranes and separated from the virus by ultracentrifugation; the other a large antigen, V antigen, attached to the virus. Antibodies to S antigen in practically all instances appear first and rise to a considerable titer before the appearance of anti-V antibodies, then usually disappear within six to twelve months from the time of onset of mumps. The anti-V antibodies, appearing later, increase to a similar extent and decrease in four to six months to a level of 1:4 or 1:8, and tend to remain at such a level through life in most persons who have had apparent or inapparent mumps. By the use of a single specimen of serum obtained during or after the occurrence of suspected mumps or mumps meningoencephalitis, it is usually possible to determine by these two antigens the presence of active or recent mumps infection.

A skin test using antigen obtained from inactivated infected monkey parotid gland or preferably from chick allantoic fluid has been developed by Enders and his co-workers. It becomes positive two to three weeks after the onset of mumps. In character, time of response, and information obtained, this reaction is similar to the tuberculin test; a

reaction is not considered positive unless its diameter is at least 10 mm.

**Epidemiology.** The disease is worldwide, occurring endemically and also epidemically in the late winter and spring at approximately seven- to eight-year intervals. The sexes are equally susceptible. Transplacental immunity is apparently effective in infants up to about the sixth or seventh month of age.

By means of the complement fixation test, it has been demonstrated that a considerable number of persons have subclinical or inapparent infections. Furthermore, it is estimated that there is no enlargement of salivary glands in about 50 per cent of cases of mumps meningoencephalitis, and orchitis in adult men is not infrequent as the sole localized manifestation of mumps. In both world wars epidemics of parotitis involved mainly men from rural areas.

Far more intimate contact is required for the spread of mumps than of measles and chickenpox. Each new case of mumps infects only a small number of the susceptible population, so that epidemics of mumps tend to follow a pattern of slow rise and slow fall. Air-borne spread of the mumps virus is probably much less common than transmission by direct contact, fomites or droplet hits. Subclinical or inapparent cases must spread the disease in many instances. The portals of entry are probably the mouth, nose and eyes.

The person with mumps apparently becomes infective a few days before and remains infective during the entire period of the swelling of the glands. Thus quarantine should be maintained for about ten days from the beginning of the swelling.

Inasmuch as immunity is usually permanent, and in view of the far greater tendency of adult males to suffer epididymo-orchitis, with the attendant danger of sterility, planned exposure of boys to the disease before puberty would appear to be a sensible procedure. Atrophy of the testicle follows pressure necrosis because of lack of elasticity of the tunica albuginea, which will not permit the inflamed testicle to swell. The ovary has no such limiting membrane and can swell in the presence of inflammation and edema. Thus sterility secondary to mumps occurs at times in men, but probably not in women.

**Pathology.** Much of pathologic data is from infected monkeys; the changes in man, however, appear to be similar. The salivary ducts are swollen, edematous and obstructed,

and the acinar epithelium shows cloudy swelling and a tendency to necrosis. Both fibrinous and serous interstitial exudates are present. The tubules and glandular epithelium show edema and an extensive infiltration of leukocytes with a desquamation of epithelial cells. In the involved testes, congestion, small hemorrhages and necrosis of the epithelium in the seminiferous tubules occur, with interstitial tissue changes similar to those in the parotid. Pancreatic involvement results at times in islet degeneration and fat necrosis, as well as in the interstitial changes mentioned.

**Clinical Manifestations.** The incubation period approximates seventeen to twenty-one days. In large epidemics the cases may be divided roughly into five groups: (1) those with a short course whose signs and symptoms are insignificant; (2) those in which the disease is full-blown with salivary swelling, but no complications; (3) those with severe mumps with the complications of epididymo-orchitis or meningoencephalitis, or both; (4) no apparent symptoms, but with typical responses of antibodies; and (5) those with meningoencephalitis or orchitis without involvement of the salivary glands. Approximately 75 per cent of all cases of apparent mumps in children belong to the full-blown type without complications. Involvement of the gonads is rare before puberty.

The average case in children has a prodromal period of one to two days, with fever, anorexia, headache, vomiting and generalized aches and pains. The headache is often particularly marked and is probably associated with mild meningoencephalitis. Finkelstein in successive cases of apparently uncomplicated mumps found a large number with pleocytosis. The temperature usually rises slowly to 102° or 103° F. as the disease becomes full-blown, but at times there is only slight or no fever. In cases complicated by epididymo-orchitis or meningoencephalitis, or both, temperatures of 105° or 106° F. are occasionally seen.

After the prodromal period one or both glands begin to enlarge. Mumps is bilateral in approximately 70 to 80 per cent of instances. A few days to a week or more may intervene between the swellings of the two sides. A distinctive "puckering" feeling appears at the angle of the jaw in the early stage and is increased by application to the tongue of sour liquids such as lemon juice or vinegar. This sign, when present, may be of considerable assistance in diagnosis. The



swelling of the gland is also distinctive in that a brawny type of edema occurs about the gland, the borders of which are not discrete, in contrast to the discrete swelling typical of lymphadenitis, in which the node is usually easily outlined. The lobe of the ear is in the center of the swelling, which usually cannot be separated by palpation from the angle of the jaw. Pressure is painful, and it is often difficult to open the jaw. The swelling reaches its maximum in about three days, remains at its peak for approximately two days, and then slowly recedes. The extent of the swelling varies considerably, but at times is sufficient to distort completely the outline of the face and head. The submaxillary and sublingual glands may be involved separately or with the parotids in any combination.

During the prodromal phase slight redness of the orifices of Stensen's or Wharton's ducts, when present, has diagnostic significance. The amount of saliva is usually unchanged, although the mouth may be dry or salivation may be extreme. Gellis described a few cases with edema over the upper part of the sternum apparently due to pressure on the lymphatics in the neck.

In uncomplicated mumps, as a rule, there is a low white blood cell count, with a relative lymphocytosis. In meningoencephalitis orchitis the white cell count is a little higher with a somewhat larger number of polymorphonuclear cells.

**Diagnosis.** Other types of infection in the parotid gland, often pyogenic in origin, are most frequently confused with parotitis. The possibility of a small stone in Stensen's duct at times must be ruled out. The method of distinguishing lymphadenitis is discussed under Clinical Manifestations. Mixed tumors of the parotid gland and Mikulicz's syndrome must also be considered in the diagnosis. The value of the complement fixation test has been discussed under Etiology.

**Complications.** Epididymo-orchitis almost never occurs before puberty, and oophoritis is even less common. Approximately 80 per cent of the cases of epididymo-orchitis appear during the first eight days of mumps, but a few occur a considerable time after the parotitis has subsided. It appears to make little difference whether patients are kept in bed during convalescence. The onset is usually with a chill, recurrence of fever and swelling of the testis. Pain over the renal area or in the lower abdomen, bilateral or unilateral, may precede or accompany orchitis. Occasionally this pain, if on the right

side, may suggest appendicitis. Support of the testes and application of an ice bag are of assistance. Incision of the tunica albuginea is highly effectual in the relief of pain and probably in the prevention of atrophy and loss of function.

Meningoencephalitis is a frequent complication and may occur in the absence of parotitis. The severity is not indicated by the number of cells in the cerebrospinal fluid. The symptoms are similar to those of other types of encephalitis (see p. 547). If death does not occur in the early stages, and it rarely does, recovery may be fairly rapid and is usually complete.

Other nervous complications include multiple neuritis, transverse myelitis and ascending or Landry's type of paralysis. Subarachnoid hemorrhage and hemiparesis with grossly bloody cerebrospinal fluid have been reported. Unilateral deafness is a rare complication.

Mumps pancreatitis is also extremely rare in children, although many complain of epigastric pain and vomit. In such cases it is difficult to be certain whether the pancreas is involved. In doubtful cases determination of serum or urine amylase has been of assistance. Occasionally the thymus, thyroid and breast are involved. Pericarditis, myocarditis and involvement of the spleen, prostate, kidneys and vulvovaginal glands have also been reported.

**Prophylaxis.** The potential danger of mumps in the adult as compared to the child accentuates the need for production of permanent immunity before puberty, whether by the disease—apparent or inapparent—or by one of the methods of active immunization. Two methods are now under trial: (1) parenteral injection of formalized virus from infected chick allantoic fluid and (2) the spraying of attenuated virus into the mouth. The latter method is also being tested in infants during their phase of transplacental immunity and in persons who have previously received the formalized vaccine. The formalized vaccine has appeared to develop some degree of immunity when given in two doses of 1 ml. each, four to six weeks apart, followed by a booster dose six to twelve months later. The protection is provided in a majority of instances for at least eight months. Inapparent infection in vaccinated persons may convert a transitory immunity into a permanent one.

Passive protection by gamma globulin from convalescents or by unfractionated convales-

cent plasma or serum is of doubtful value. Gamma globulin from pooled plasma apparently is not protective.

**Treatment.** The patient should be kept in bed during the period of fever and swelling. Heat to the swollen area may be of some comfort; ice is less comfortable, as a rule. A soft diet and liquids are preferable to solid food. The use of convalescent gamma globulin appears to have some value in preventing orchitis.

JOSEPH STOKES, JR.

## REFERENCES

- Adams, F.: *The Genuine Works of Hippocrates*. New York, Wood, 1891, Vol. 1, p. 294.
- Enders, J. F.: Mumps: Techniques of Laboratory Diagnosis, Tests for Susceptibility and Experiments on Specific Prophylaxis. *J. Pediat.*, 29:129, 1946.
- Enders, J. F., and others: Attenuation of Virulence with Retention of Antigenicity of Mumps Virus after Passage in the Embryonated Egg. *J. Immunol.*, 54:283, 1946.
- Enders, J. F., Kane, L. W., Maris, E. P., and Stokes, J., Jr.: Immunity in Mumps. V. The Correlation of the Presence of Dermal Hypersensitivity and Resistance to Mumps. *J. Exper. Med.*, 84:341, 1946.
- Finkelstein, H.: Meningoencephalitis in Mumps. *J.A.M.A.*, 111:17, 1938.
- Gellis, S. S., McGuinness, A. C., and Peters, M.: A Study on the Prevention of Mumps Orchitis by Gamma Globulin. *Am. J. M. Sc.*, 210:661, 1945.
- Gordon, J. E., and Heeren, R. H.: The Epidemiology of Mumps. *Am. J. M. Sc.* 200:412, 1940.
- Habel, K.: Vaccination of Human Being against Mumps: Vaccine Administered at the Start of an Epidemic. I. Incidence and Severity of Mumps in Vaccinated and Control Groups. II. Effect of Vaccination upon the Epidemic. *Am. J. Hyg.*, 54: 295, 312, 1951.
- Henle, G., Henle, W., and Harris, S.: The Serological Differentiation of Mumps Complement Fixation Antigens. *Proc. Soc. Exper. Biol. & Med.*, 64: 290, 1947.
- Nicolle, C., and Conseil, E.: Reproduction expérimentale des oreillons chez le singe. *Compt. rend. Soc. de biol.*, 75:217, 1913.
- Wesselhoeft, C., and Vose, S. N.: Surgical Treatment of Severe Orchitis in Mumps. *New England J. Med.*, 227:277, 1942.

## EPIDEMIC INFLUENZA

**Definition.** Influenza is an acute communicable viral disease primarily affecting the respiratory tract. It occurs in great pandemic waves usually separated by several decades, during which interpandemics or epidemics of less severity occur at two to four year intervals.

**Etiology.** Two viral agents have apparently been responsible for most of the sharp out-

breaks of respiratory infection resembling influenza since 1933: influenza A virus, identified by Smith, Andrewes and Laidlaw; and influenza B virus, identified independently by Francis and by Magill in 1940. Subsequently two additional types of influenza virus have been isolated and identified as C and D; they are apparently responsible for milder diseases than those caused by viruses A and B. Pandemic influenza, similar in worldwide prevalence, but not in severity, to that of 1918-19, occurred in 1957, starting in central China, western Europe and in certain other areas about the same time. The causative virus was shown to be a mutant strain—Asian strain—of type A influenza virus, to which immunity could not be produced by vaccines containing known strains of type A virus. Persons born before 1890 were usually found to have antibodies to the Asian strain, thus suggesting an antigenic relation of the new mutant to the virus responsible for the pandemic of 1889-90. For the first time in 1957 it was possible to determine that rapidly fatal cases in a pandemic were not necessarily the result of superimposed bacterial infection, but resulted in many instances from the antigenic quality of the virus itself.

Influenza viruses A and B are serologically distinct, but each type has a number of strains which have antigenic differences, and cross immunity has not been produced.

Preparations of virus, purified as far as possible, contain ribose nucleic acids as well as protein, carbohydrate (the polysaccharides: mannose, galactose and glucosamine units) and water. The viruses are most stable in a pH range of 6.5 to 7.9. Their infectivity is lost when they are heated to 56° C. for thirty minutes, when irradiated with ultraviolet light or when treated with formaldehyde. They will remain active when stored at 76° C. in sealed glass ampules for an indefinite period if the preparation is properly buffered. The viral bodies contain considerable amounts of toxic material.

Inhalation of the active viruses A and B by susceptible human beings will cause sharp influenzal attacks without complications, if such studies are conducted in the absence of pathogenic bacteria or with control of them by previously administered antibacterial agents. After such experimental infections and the natural infection with either virus, neutralizing and complement-fixing antibodies increase rapidly, reaching their peak within approximately two to three weeks, and



then slowly diminish to their previous levels in approximately one year. A fourfold increase of antibodies in comparative tests of acute and convalescent serums may be regarded as indicating infection with the virus tested.

The agglutination of chick red cells by both viruses and the inhibition of this phenomenon by previous addition to the viruses of an immune serum were developed independently by Hirst and Hare as a means of determining the presence and amounts of antibodies in unknown serums. By careful control (i.e., the amount of virus, the concentration of red blood cells and the titration end point) the antibody content of unknown serums can be measured by dilution of the serums to the point at which inhibition of the chick red cell agglutination no longer occurs. This method of measuring antibody formations is more exact and less cumbersome than the virus neutralization test, but not as accurate as the complement fixation test. The soluble antigen is the same for all type A strains (swine, A, A.' Asian); the soluble antigen of type B is quite different from that of type A.

In both pandemic and epidemic influenza the secondarily invading bacteria are of sufficient importance to be considered of etiologic significance, particularly since the mortality in both types of outbreak is, to an extent, dependent on such invaders. *Hemophilus influenzae*, the hemolytic *Streptococcus*, the *Pneumococcus* and the *Staphylococcus aureus* are the more frequent invaders. The last is perhaps the most serious one, owing to the frequency of antibiotic resistant strains.

**Epidemiology.** Influenza is probably the only remaining pandemic disease over which no effective control has been established. The pandemic of 1918 is estimated to have caused approximately 22 million deaths throughout the world in about three months, approximately 500 million additional persons being attacked.

Recently obtained serologic data relating to the pandemics of 1889, 1918 and 1957, together with identification of different strains of influenza A virus from various epidemics since 1930, strongly suggest, but do not prove, a pattern of recurrent outbreaks of influenza A infections which depends primarily upon mutant strains of virus and secondarily upon the accumulation of susceptible hosts, especially among the young and

middle-aged. Recurrent epidemics from the same strain may occur every three to four years following a pandemic as sufficient numbers of susceptible hosts accumulate, but a subsequent pandemic does not occur until a new mutant strain of virus again becomes widespread. The pandemic usually occurs in three waves of approximately equal incidence separated by an interval of several months, the last one being the most severe.

Epidemic influenza occurs in sharp outbreaks similar to the first wave of pandemic influenza and generally with few complications and a low mortality. The morbidity is usually about 30 to 35 per cent of the population. Epidemics usually occur in the late winter or early spring, but at times in the early winter or late fall. Epidemics from strains of A virus tend to recur every year or two, while those of influenza B thus far have recurred less frequently. They have rarely occurred simultaneously in the same geographic area. In a single epidemic the strains of virus isolated are usually closely related antigenically.

Little is known about the method of spread of either pandemic or epidemic influenza. Shope calls attention to the simultaneous occurrences of outbreaks in the pandemic of 1789-90 in places widely separated by many weeks of the customarily slow travel of that period. Such outbreaks occurred simultaneously on land and on slow sailing vessels six to eight weeks at sea.

The virus may spread by the air-borne route; whether this route is more important than the more commonly accepted ones of direct contact or direct "droplet hits" has not been determined. The viruses of influenza are in the upper respiratory tracts of patients from the first to the fifth day of disease. They have not been found in the blood stream.

Both sexes and all races appear to be equally susceptible. Young adults and children over five years of age appear to be more susceptible than infants and older persons. Experimental infection of human beings has indicated a direct relation between the height of serum antibodies and the resistance to infection. A large number of inapparent infections occur in any epidemic, as indicated by the rise of antibody titers in persons who have had no symptoms. No possible reservoir of the viruses for interepidemic survival has been found, nor have carriers been discovered. Sporadic cases may be the link between

epidemics, since the seasons of high incidence of respiratory diseases succeed each other in the two hemispheres.

**Pathology.** Uncomplicated influenza in man may be considered analogous to the disease in ferrets, in which there is a severe inflammatory reaction in the mucous membrane of the upper respiratory tract with a loss of ciliated epithelium. Regeneration in ferrets occurs by relatively rapid development of epithelium of a more squamous type over a period of several weeks with slower regeneration of the columnar epithelium. During this transitional period the epithelium is resistant to further influenzal virus infections and returns to normal status within a month or so.

In severe cases in man hemorrhages with serosanguineous exudate often occur in the pharynx, larynx, bronchi and bronchioles, with edema of the entire bronchial tree and often of the alveoli. The alveolar ducts and bronchioles may be dilated and their walls frequently covered with a hyaline membrane, which also partly or completely covers the walls of the alveoli. There is necrosis of the mucous membrane, and emphysema is usually present in localized areas.

The pathologic picture may be considerably altered by bacterial pathogens. When several different organisms are present, the pathologic changes are less uniform than when there is a single pathogen. With the *Pneumococcus* there is typically a lobular pneumonia tending to become confluent; with the influenzal bacillus there are severe destructive changes in the bronchioles and interstitial pneumonia, often leading to bronchiectasis; with the *Micrococcus pyogenes*, variant *aureus*, an overwhelming infection characterized by hemorrhagic edema and multiple pulmonary abscesses; and with the hemolytic *Streptococcus*, an interstitial reaction with hemorrhagic edema and frequently with pleurisy and empyema.

**Clinical Manifestations.** Since the symptoms of pandemic and epidemic influenza are similar except for severity and extent of complications, they are considered jointly. Experimental infections of human susceptibles have simulated the milder cases of epidemics.

The incubation period is usually about thirty-six to forty-eight hours. The onset is sudden with a chill or a chilly sensation, frequently in children with a convulsion; a sharp rise in temperature ranging from 102° to 106° F.; flushing of the face, neck and

chest; headache; vertigo; a dry sore throat; and pains in the back and extremities. A short, dry, hacking cough usually is present soon after the onset and rapidly increases in frequency and severity. It often becomes paroxysmal and resembles the cough of pertussis. In young children vomiting and diarrhea may be the principal manifestations at the onset. The accompanying prostration may be extreme and is related not only to the severity of the disease, but also to the lack of complete bed rest from the onset of symptoms. The fever is often diphasic, with the two peaks separated by a period of twenty-four to forty-eight hours.

The mucous membranes of the throat appear dry and red with no exudate; those of the nose are red, but usually there is little or no discharge except when purulent sinusitis is a late complication. The conjunctivas are injected. Epistaxis is common. The pulse is usually rapid and often weak, as are the heart sounds when the cardiac muscle is seriously affected. Often the skeletal muscles are painful on pressure, and movements of the eyeballs cause considerable discomfort.

The usual increase in leukocytes during the early stages of the disease is soon replaced by a leukopenia with a relative lymphocytosis. Often in the later stages there is a slight increase in monocytes, although complicating bacterial infection may alter this picture. Blood cultures are sterile, and the erythrocyte sedimentation rate is increased.

The milder uncomplicated cases clear almost as rapidly as they start, rarely lasting more than three or four days.

In severe infections which extend into the lower respiratory tract fine moist rales may soon be detected bilaterally, and these may rapidly spread over the entire lung area with diminution of breath sounds, or a tendency to bronchial breathing if consolidation occurs. As the cough increases in frequency it becomes productive, often sanguineous at first and later mucopurulent. Diminution of breath sounds resulting from edema of the bronchial tree and alveoli is far more common than the localized consolidation of lobular pneumonia, and frequently the breath sounds almost disappear as patchy edematous and atelectatic areas are interspersed with areas of emphysema. In the extremely severe infections which occur frequently in pandemics these changes are extensive, and the patient shows evidence of severe anoxia. Myocardial involvement results in distention of the right side of the heart, passive congestion



of the liver, and, finally, extensive pulmonary edema and cardiac failure. Death occurred frequently in the 1957 pandemic with only one quarter to one third of the lungs involved, apparently as the result of the direct toxic effect on the vital nerve centers.

When secondary bacterial infections are present, the symptoms depend to a considerable extent upon the type of organism involved, as indicated under Pathology.

**Diagnosis.** During epidemics or pandemics the diagnosis is not difficult, owing to the uniformity of the clinical manifestations. The simplest diagnostic test is that of Hirst and Hare (p. 509); when the nature of an epidemic has been established by this test, succeeding cases with a typical pattern are not easily mistaken. The complement fixation test, however, appears to be a more reliable diagnostic measure. The isolation of virus by intra-amniotic inoculation of throat washings treated with penicillin and streptomycin is helpful.

**Complications.** In few other diseases are the complications such an integral part of the severe forms of the infection. Many of them have been mentioned under Clinical Manifestations and may more properly be termed "clinical variations."

Otitis media, mastoiditis, purulent sinusitis, pneumonia, bronchiectasis, pulmonary abscess, and empyema are the more common respiratory variants of the severe infections. Less common ones are pneumothorax and mediastinitis. Rare nonrespiratory complications include hematoma from rupture of the rectus muscles of the abdomen, epistaxis, intestinal hemorrhage, polyneuritis, postinfluenzal psychoses, nephritis, subcutaneous or intramuscular abscess, endocarditis, myocarditis, pericarditis, thrombophlebitis, meningitis and hemorrhagic encephalitis. Some cases of bronchiectasis in adults possibly result from severe influenza in childhood. Chronic bronchitis and pulmonary fibrosis may also be sequels.

**Prophylaxis.** There are no known methods of increasing general resistance to influenza. Avoidance of fatigue and chilling and of large assemblies of people, however, is important. Specific resistance may apparently be increased by various types of influenzal virus A and B vaccines, including those derived from allantoic fluid, either concentrated or unconcentrated. Febrile and local reactions to the vaccines have resulted from the toxic properties of the viruses they contain and are proportional to the amount of virus N pres-

ent. In rare instances persons allergic to chick embryo proteins may have anaphylactic reactions. New strains of influenza A, i.e., A' and Asian, which have appeared recently have complicated the production of an effective vaccine, since the older strains, such as PR8, will not protect against the other prime strains of virus. Current strains can be incorporated to produce successful vaccines. The serum antibodies can be increased within seven to ten days by such vaccines; if large quantities are available, they may be useful against a pending epidemic. In general, the response to vaccines has been inversely proportional to the original level of antibodies in the person vaccinated.

Methods of disinfecting air, such as ultraviolet light, may possibly assist in preventing the spread of virus by the air-borne route within crowded spaces. Patients with influenza should not be placed in open wards without means of disinfecting the air, owing to the danger of bacterial infection from patient to patient. Isolation may be of value in preventing such complications. The value of masks in preventing the spread of secondary bacterial invaders is limited.

**Treatment.** No specific remedy is available. The use of convalescent or immune serums is still on an experimental basis. Complete bed rest from the earliest evidence of disease is absolutely essential and should be continued long into convalescence. The sulfonamide drugs and antibiotics are indicated for such complications as pulmonary abscesses, empyema and pneumonia. The fluid intake should be ample, and the quantity may be increased by use of fruit juices, lemonade and ginger ale. Acetylsalicylic acid and codeine may be used for discomfort and cough.

JOSEPH STOKES, JR.

#### REFERENCES

- Burnet, F. M., and Clark, E.: Influenza. A Survey of the Last 50 Years in the Light of Modern Work on the Virus of Epidemic Influenza. Monographs from the Walter and Eliza Hall Institute of Research in Pathology and Medicine, No. 4. Melbourne, Macmillan Company, 1942.
- Francis, T., Jr.: Transmission of Influenza by a Filterable Virus. *Science*, 80:457, 1934.
- : A New Type of Virus from Epidemic Influenza. *Science*, 92:405, 1940.
- : Factors Conditioning Resistance to Epidemic Influenza. *Harvey Lectures*, 37:69, 1941–42.
- Francis, T., Jr., Pearson, H. E., Salk, J. E., and Brown, P. N.: Immunity in Human Subjects

- Artificially Infected with Influenza Virus, Type B. *Am. J. Pub. Health*, 34:317, 1944.
- Greenfield, J. G.: Acute Disseminated Encephalomyelitis as a Sequel to "Influenza." *J. Path. & Bact.*, 33:453, 1930.
- Henle, W., and Henle, G.: Interference between Inactive and Active Viruses of Influenza. I. The Incidental Occurrence and Artificial Induction of the Phenomenon. *Am. J. M. Sc.*, 207:705, 1944.
- : Studies on the Toxicity of Influenza Viruses. *J. Exper. Med.*, 84:623, 639, 1936.
- Hirst, G. K.: The Agglutination of Red Cells by Allantoic Fluid of Chick Embryos Infected with Influenza Virus. *Science*, 94:22, 1941.
- McClelland, L., and Hare, R.: The Adsorption of Influenza Virus by Red Cells, and a New in Vitro Method of Measuring Antibodies for Influenza Virus. *Canad. Pub. Health. J.*, 32:530, 1941.
- Scadding, J. G.: Lung Changes in Influenza. *Quart. J. Med.*, 6:425, 1937.
- Shope, R. E.: Swine Influenza: Filtration Experiments and Etiology. *J. Exper. Med.*, 54:373, 1931.
- Smith, W., Andrewes, C. H., and Laidlaw, P. P.: A Virus Obtained from Influenza Patients. *Lancet*, 2:66, 1933.

## RABIES

### (HYDROPHOBIA)

**Definition.** Rabies is an acute viral disease of the central nervous system which is ordinarily transmitted to man by the bite of a rabid dog or occasionally a rabid cat or a rabid wild animal. In general, it is characterized by extreme excitation, severe and painful spasm of the muscles of the pharynx and larynx at the sight of food or liquids, which accounts for the name "hydrophobia," and finally by generalized paralysis and death within a few days.

**History.** Rabies is one of the oldest recorded diseases in Europe and Asia. Democritus in 500 B.C. and Aristotle in 322 B.C. described rabies; Celsus in A.D. 100 advised cauterization of bites by rabid dogs, and Galen in A.D. 200 advised surgical excision of the bite. Apparently rabies had not occurred in North and South America before colonization.

In 1804 Zinke infected a normal dog with saliva from a rabid dog. Pasteur in 1881 to 1884 demonstrated the infective agent in the central nervous system of rabbits and named it a virus, from the Latin word for poison. There followed the development in his laboratories of the fixed virus and the study of vaccination with attenuated virus. Fermi in 1908 treated infected nervous tissue with phenol for use as a vaccine. In 1903 Negri demonstrated the inclusion bodies now known by his name. In 1921 Haupt found the vampire bat to be a symptomless carrier of the virus, a finding of great epidemiologic importance.

**Etiology.** The rabies virus is neurotropic and travels by the injured peripheral nerves

to the central nervous system. This natural virus is termed "street virus" and has a variation in incubation period which in general appears to be related to the distance of the injury from the head, the severity of the bite, and the amount of virus in the wound. The "street virus" invades the salivary glands and usually is transmitted in saliva. The "fixed virus" is the term applied to natural virus modified by repeated intracerebral passages in laboratory animals. This virus has a four-to six-day incubation period and does not invade the salivary glands. The natural or "street virus" through multiple passage in the chick embryo loses its pathogenic properties and may be used without inactivation for vaccination. The virus is about 100 to 150 millimicrons in diameter, and, although it passes through bacteria-retaining porcelain filters, it is filtered with some difficulty through Seitz EK filter pads. Although ultraviolet radiation, sunlight, mercuric chloride and formalin inactivate the virus readily, it is quite resistant to phenol and fairly so to chloroform and ether. It is killed in an hour in watery solution at 56° C., but may be readily preserved by desiccation from the frozen state.

**Epidemiology.** Two categories of rabies have been suggested by Johnson: the sylvatic, existing in wild animals; and the urban, prevalent in domestic dogs. Sylvatic rabies is well recognized among the wolves of Canada, the Arctic, and of such smaller countries as Iran, as well as among foxes, coyotes, skunks, and more recently bats in the United States, Central and South America.

Symptom complexes in animals which in the past were not associated with rabies, such as "running fits" of dogs and paralytic syndromes in dogs and other animals, may be of rabid origin. Rabies appears to be increasing among dogs in the United States, although in human beings the number of deaths annually has been less than 100. In certain areas outside the United States the paralytic form of rabies has been more frequent and may indicate a variation in the antigenicity of the virus, although immunologically all strains of virus isolated have been similar. In Trinidad both man and cattle have been infected by vampire bats, which apparently are carriers and not victims of the disease. The disease apparently has been transmitted from a rabid lactating dog to her litter by way of the milk, but there is no record of the transmission of rabies from a rabid cow to man by this same route.



**Pathology.** Fresh virus from a rabid dog will cause widespread degeneration and necrosis of neurons. Demyelination and degeneration of the axis cylinders are present in the white matter. The areas chiefly involved are the red nucleus, substantia nigra, pons and particularly the nuclei of the cranial nerves in the medulla. Here neuronophagia and infiltration with mononuclear cells are extensive. The pathognomonic change in the neuronal cytoplasm and dendritic processes is the Negri body, which is apparently an inclusion body. It has eosinophilic cytoplasm with a basophilic granular corpuscle in the center. Since the neurons of the salivary glands at times show similar changes with Negri bodies, it is conceivable that the rabies virus enters the saliva by this route.

**Clinical Manifestations.** Since prophylaxis against the disease in man depends to a great extent upon an understanding of the early manifestations in the dog, they are described first.

*In the dog* symptoms may be considered under two general types, although it is not possible to separate them completely.

1. The "furious" type results from increased excitation of the central nervous system, with fever, hyperesthesia and lack of appetite. The evidences of disease depend to a great extent upon the nature and training of the dog. The more aggressive dog will begin to snap and become excited and dangerous early in the course of the disease. The gentle dog in the early stages will more frequently seek seclusion and refuse food or will become excessively affectionate, after which it becomes agitated and restless. This is usually followed by irritability and snapping at strangers and a little later by snarling or snapping at imaginary objects and chasing and biting other animals. Finally, if free, it will run for miles, snapping at or biting all living things in its path until it falls paralyzed to the ground.

2. The "dumb" or paralytic type, despite its frequency (approximately 20 per cent), is rarely recognized by the dog's owners, primarily because no agitation or excitement is seen. The course is far more rapid, paralysis occurring in any group of muscles, but particularly in the lower jaw and in the muscles of deglutition. In such cases the tongue hangs out of the mouth, continuously dripping saliva; sympathetic persons, suspecting a foreign body in the dog's throat, may expose their hands to the infective saliva in an effort to relieve the dog. Rapidly extending paralysis soon results in death; occasionally dogs die suddenly without signs of illness, and encephalitis with Negri bodies is found at autopsy.

*In man* the incubation period is approximately four to eight weeks, but may be months and, rarely, as long as a year. It may also be shorter than four weeks when the lacerations are about the head or neck, ap-

parently because of the greater laceration and the larger amount of virus thus introduced, rather than because of short distance from the laceration to the central nervous system.

The majority of clinical cases are characterized by three stages. In the *prodromal* phase, numbness, formication, tingling, burning or a sensation of cold may be felt about the wound and along the involved nerve trunks, followed by mild excitation with irritability, restlessness, dilatation of pupils, salivation, lacrimation, perspiration and insomnia or, at times, drowsiness and depression.

In the *second* phase the excitation rapidly increases, and there is apprehension and even terror. The neck becomes stiff, and there is delirium and twitching or mild convulsive movements. At this stage the sign appears which has characterized the disease, i.e., the strangulating and intensely painful spasm of the throat at any attempt to swallow food or liquids and even at the sight of them (hydrophobia). Slight noises may initiate these spasms, and the extreme hyperesthesia of the skin also facilitates their initiation through tactile stimuli. At such times the patient is unable to breathe, and the body remains in a tonic convulsion during which death may occur. The temperature is usually elevated to 103° to 105° F., but may be considerably lower. Blood-tinged vomitus or excessive saliva may give the impression of "frothing."

Within one to three days the patient passes rapidly into the *terminal* phase with increasing paralysis, cessation of spasms, coma and death within another day or two.

The paralytic form of the disease, which is far less common, begins with numbness or severe pains in the nerve trunks supplying the involved area, followed shortly by flaccid paralysis of the part, which extends first to the opposite side of the body, and then slowly ascends in a manner similar to Landry's paralysis, terminating with involvement of the respiratory and circulatory centers.

Ordinarily, in each form there is a polymorphonuclear leukocytosis, often as great as 20,000 to 30,000 cells per cubic millimeter. The cerebrospinal fluid usually has a slight increase of protein and occasionally of cells, up to 30 to 100 mononuclear cells per cubic millimeter.

**Diagnosis.** The only organic disease for which rabies may be mistaken is *tetanus*, which has no cellular response or increase of protein in the cerebrospinal fluid and has a characteristic trismus. Another differenti-

Table 74. Indications for Specific Postexposure Treatment\*

Nature of Exposure	CONDITION OF ANIMAL		
	At Time of Exposure	During Observation Period of 10 Days	Recommended Treatment
I. No lesions Indirect contact only	Rabid	—	None†
II. Licks			
1. Unabraded skin	Rabid	—	None†
2. Abraded skin and abraded or un- abraded mucosa	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately. Stop treatment if animal is normal on fifth day after exposure‡
	(d) Rabid, escaped, killed or unknown	—	Start vaccine immediately
III. Bites			
1. Simple exposure	(a) Healthy	Healthy	None
	(b) Healthy	Clinical signs of rabies or proved rabid	Start vaccine at first signs of rabies in animal
	(c) Signs suggestive of rabies	Healthy	Start vaccine immediately. Stop treatment if animal is normal on fifth day after exposure‡
	(d) Rabid, escaped, killed or unknown; or any bite by wolf, jackal, fox or other wild ani- mal	—	Start vaccine immediately
2. Severe exposure (Multiple; or face, head or neck bites)	(a) Healthy	Healthy	Hyperimmune serum immediately; no vaccine as long as animal remains normal
	(b) Healthy	Clinical signs of rabies or proved rabid	As in III, 2, (a), but start vaccine at first sign of rabies
	(c) Signs suggestive of rabies	Healthy	Hyperimmune serum immediately, followed by vaccine. Vaccine may be stopped if animal is nor- mal on fifth day after exposure
	(d) Rabid, escaped, killed or unknown. Any bite by wild animal	—	Hyperimmune serum immediately, followed by vaccine

Hyperimmune serum to be effective must be given within 72 hours of exposure.

These indications apply equally well whether or not the biting animal has been previously vaccinated.

\* Prepared by Expert Committee on Rabies of World Health Organization.

† Start vaccine immediately in young children and patients when a reliable history cannot be obtained.

‡ Alternative treatment would be to give hyperimmune serum and not start vaccine as long as animal remains normal.

ating feature of tetanus is the lack of strangulating spasms of the muscles of deglutition. Occasionally a person who has been bitten suffers a hysterical state simulating rabies, but this is not difficult to differentiate from the organic disease.

**Prognosis.** No recovery from rabies has been recorded.

**Prevention.** The most important prophylactic measure is control of dogs. In England, the Scandinavian countries and Canada, rabies has been nearly eliminated by precautions in the general handling of dogs. Stray dogs should be eliminated, and all other dogs should be muzzled, confined or on leash. A dog bitten by a rabid animal should either



be killed or isolated immediately for at least six to eight months. Vaccination of such a dog may be carried out successfully only if a sufficient number of injections is given, the customary single prophylactic injection of rabies vaccine in dogs being totally inadequate. The disappearance of a dog after biting an animal or man should be regarded with suspicion, since a dog frequently seeks seclusion before death from rabies. Suspicion should also be attached to a previously gentle dog whose behavior suddenly changes. Any dog which has bitten a person, but which has no sign of rabies, should be kept under surveillance.

Suggestions for prophylactic therapy are detailed in Table 74.

*Passive immunization* with hyperimmune antirabies serum is now accepted as an essential part of prophylaxis to be used immediately prior to vaccination. It may be that use of the serum may permit a shortening of the vaccine course from three to two weeks, thereby lessening the danger of paralytic complications.

The vaccine is usually given in doses of 2 cc. daily for fourteen days, starting immediately after the bite, or for twenty-one days if the bite has occurred on the head, neck or shoulders. It is injected subcutaneously into the abdominal wall, the area for injection being varied from day to day in order to avoid severe local reactions.

An acute myelitis with paralysis resulting from vaccination is a rare but serious complication which may be lethal. About 80 per cent of those who recover do so completely. It occurs about one to four weeks after the start of vaccination. The vaccines in which the virus has been destroyed are less likely to cause this complication than those containing active virus, though probably the reaction is due primarily to the heterologous tissue of the rabbit cord rather than to the virus itself. Adults are more susceptible than children to such myelitis.

**Treatment.** Although the usual treatment of the rabid animal's bite has been to cauterize it with fuming nitric acid, the possible advantages are outweighed by the disadvantages of pain and scarring, particularly in view of the more recent success with injection of antirabies serum in the area immediately adjacent to the wound. Bites and abrasions exposed to the animal's saliva should be thoroughly cleansed, first with soap and water, and finally with a 1 per cent solution of Zephiran chloride.

Active treatment, once the disease has developed, is of little avail. Sedatives should be used in large doses, and the patient's room should be kept quiet and dark to avoid all stimuli. Anesthesia for the convulsions is necessary as the disease progresses. Attendants should be vaccinated and must also be careful to avoid the danger of being bitten by the patient.

JOSEPH STOKES, JR.

## REFERENCES

- Casals, J., and Palacios, R.: Complement Fixation Test in the Diagnosis of Virus Infections of the Central Nervous System. *J. Exper. Med.*, 74:409, 1941.
- Fermi, C.: Ueber die Immunisierung gegen Wutkrankheit. *Ztschr. f. Hyg. u. Infektionskr.*, 58: 233, 1908.
- Hurst, E. W., and Pawan, J. L.: An Outbreak of Rabies in Trinidad, without History of Bites, and with Symptoms of Acute Ascending Myelitis. *Lancet*, 2:622, 1931.
- Johnson, H. N.: The Significance of the Negri Body in the Diagnosis and Epidemiology of Rabies. *Illinois M. J.*, 81:382, 1942.
- : Experimental and Field Studies of Canine Rabies Vaccination. *Proc. 49th U. S. Livestock San. Assn.*, 1945, pp. 99–107.
- Koprowski, H., and Cox, H. R.: Studies on Rabies Infection in Developing Chick Embryos. *J. Bact.*, 54:74, 1947.
- Negri, A.: Beitrag zum Studium der Aetiologie der Tollwuth. *Ztschr. f. Hyg. u. Infektionskr.*, 43: 507, 1903.
- Pasteur, L., Chamberland and Roux: Sur une maladie nouvelle, provoquée par la saliva d'un enfant mort de la rage. *Compt. rend. Acad. sci.*, 92:159, 1881.
- : Méthode pour prévenir la rage après morsure. *Compt. rend. Acad. sci.*, 101:765, 1885.
- Pawan, J. L.: The Transmission of Paralytic Rabies in Trinidad by the Vampire Bat (*Desmodus rotundus murinus* Wagner). *Ann. Trop. Med.*, 30: 101, 1936.

## YELLOW FEVER

**Definition.** Yellow fever is an acute infectious viral disease with severe constitutional symptoms accompanied by hepatitis with jaundice, hematemesis, nephritis and degenerative changes in the cardiac muscle. Although it has occurred during the summer in the temperate zones, it is essentially a disease of the tropical zones.

Immunologically the strains of yellow fever virus may not differ, but clinically a differentiation appears necessary between *jungle yellow fever* and the more common *urban yellow fever*, for which *Aedes aegypti* acts as a vector. Jungle yellow fever occurs

occasionally in man in close contact with the jungle in the absence of *Aedes aegypti*. In jungle yellow fever in South America the virus has been found in mosquitoes of the genus *Haemagogus* and in *Aedes leucocelaeus*, while in Africa it has been found in *Aedes simpsoni* and *A. africanus*.

**History.** Carlos Finlay in 1881 first suggested that the mosquito, *Aedes aegypti*, was the vector, and the classical experiments of Reed, Carroll, Agramonte and Lazear in 1900 and 1901 verified its essential role in the disease and the need for mosquito control and established the virus as the etiologic agent.

**Etiology.** The virus of yellow fever is approximately 20 millimicrons in diameter, being one of the smallest isolated. Affinity or tropism of the virus for host cells is of two main types: neurotropism, an affinity for nervous tissue, and viscerotropism, an affinity for the liver, kidney and heart. Under natural field conditions the virus is pantropic. Both viscerotropism and neurotropism of the virus can be greatly reduced by repeated passage in tissue cultures, whereas neurotropism is increased and viscerotropism practically disappears after repeated intracerebral passage of the virus in mice.

Man and the rhesus monkey (*Macaca mulatta*) are highly susceptible to the pantropic strain of virus found in the field, the severe lesions in both occurring in the liver, heart and kidneys as a result of the viscerotropic properties of the virus. In the laboratory the neurotropic strain developed from intracerebral mouse passage produces, when injected intracerebrally in the *Macaca mulatta*, a usually fatal encephalitis with absence of hepatitis and other visceral lesions. Other animals differ considerably in their susceptibilities to these viral tropic properties.

**Epidemiology.** In transmission of the more common form of the disease the aegypti mosquito bites an infected person during the first three days of the disease when the virus is circulating in the blood. After nine to twelve days of incubation of the virus in the mosquito a susceptible host is bitten who acquires the disease after a further incubation period of approximately three to six days.

Another, less common method of infection has been suggested in the laboratory without transmission by an insect vector. While the virus is circulating in the blood of monkeys it can apparently be transmitted from one animal to another through the intact skin. The passaged neurotropic virus may also be

transmitted to both mice and monkeys by intranasal instillation.

A few African outbreaks of urban yellow fever have occurred in areas contiguous to endemic areas of jungle yellow fever, such as in Nigeria in 1946. In Central America jungle yellow fever has been slowly spreading north from Panama since 1948 in epidemic form. Urban yellow fever has not been present in the Western Hemisphere since 1934 and has never been reported in the Orient.

**Pathology.** On gross appearance the body reveals severe jaundice, combined usually with petechial hemorrhages or ecchymotic areas of the skin. There may be black, bloody vomitus in the nose and mouth which is also usually present in the stomach in considerable amounts. The primary visceral changes are in the liver, which is normal in size or slightly enlarged and has a deep yellow stain.

The typical microscopic lesion of the liver is an acute, midlobular fatty degeneration and necrosis of the parenchymatous cells, with normal cells immediately surrounding the central vein of the lobule and the portal vein. The architecture of the liver is preserved, and in healing no cirrhosis occurs. Certain acidophilic areas of hyaline necrosis widely scattered in the parenchymatous cells are termed "Councilman bodies." Superficial hemorrhages are often seen in the mucous membranes of the stomach, particularly in the pyloric end, and in the intestines. Although the spleen is approximately normal in size, there is usually degeneration of the malpighian corpuscles. Both the tubular epithelium of the kidneys and the cardiac muscle show involvement similar to that in the liver. The brain at times shows perivascular hemorrhages.

**Clinical Manifestations.** The majority of infections are so mild that they do not show the classic picture and are frequently missed.

The acute onset following the incubation period is similar, in the more severe cases, to a sharp attack of epidemic influenza except for lack of cough and evidences of upper respiratory tract infection. Headache, chills, backache, pains in the limbs and flushing of the face all appear suddenly and in a severe form, and photophobia and conjunctival injection are prominent. Initially, jaundice is absent or only slight. As a rule, during the first two or three days the temperature rises rapidly to 103° to 104° F. with an increasing pulse rate, and then diminishes relatively



more slowly than the pulse rate in what is frequently a temporary remission. During this period, albuminuria develops with pain and tenderness in the epigastrium, and there is vomiting without blood. The leukocyte count slowly decreases.

In the succeeding stage the temperature is again elevated, and the early signs and symptoms are replaced by prostration and depression; the face has a pale, cyanotic appearance, and there is a slowly increasing jaundice, which is rarely extreme. Hemorrhages into the skin and often into the gums usually appear at this time with epistaxis, a dry, brown tongue and a decreasing pulse rate to less than 50 per minute in spite of high fever (Faget's sign). Degenerative changes in the heart result in cardiac dilatation and a low blood pressure. The urine contains large amounts of albumin and casts. There is usually vomitus of a dark brown material, and the leukocyte count often drops to 3000 cells, from which it rises slowly as the patient recovers. In severe and often in fatal cases bile appears in the urine, or at times there is anuria followed by convulsions or coma.

If recovery occurs, improvement starts about the fifth or sixth day, and the temperature often is normal by about the eighth day. When convalescence begins, progress is continuous without complications. There is permanent immunity to the disease.

**Diagnosis.** There may be considerable confusion in diagnosis in the milder cases. Leptospirosis is particularly difficult to differentiate clinically. Infectious and serum hepatitis are usually far slower in development and subsidence. Somewhat more severe cases of yellow fever may initially be confused with influenza, malaria or dengue.

Such diagnostic difficulties can best be resolved by neutralization tests performed on mice with acute and convalescent serums, the latter being obtained about three weeks after the onset. Blood obtained from the patient during the first three days of disease and injected intracerebrally into susceptible mice will cause encephalitis in the mice if the yellow fever virus is present. The examination of acute and convalescent serums is more practical, since in the mouse-brain test, after further passage of the encephalitic mouse brain, a neutralization test must finally be carried out before the presence of the yellow fever virus can be confirmed.

**Prognosis.** It is probable that the over-all case fatality rate is not over 5 per cent, but

in any outbreak the fatality rate of recognized cases may be high, up to 50 per cent or more.

**Prophylaxis.** The strain of active yellow fever virus termed 17D, which has become avirulent after many passages on tissue cultures, may be used for vaccination of those likely to be exposed to the disease. Vaccines developed from this strain have been extremely effective in preventing yellow fever. They afford immunity within one week of injection which lasts for at least six years.

Urban communities should use methods to rid themselves of the *aegypti* mosquito by the districting and weekly inspection with a flashlight of all homes and their surroundings. The larvae may thus be found and eliminated. Netting should be used to prevent access of *Aedes aegypti* to the patient, and the room and house should be sprayed with an insecticide such as DDT.

**Treatment.** Specific therapy is lacking. Complete bed rest is essential to lessen the danger of cardiac failure, and sufficient fluids must be provided for the formation of urine. In order to prevent irritation of the gastric mucosa, solid food should be avoided. If vomiting is extensive, fluids should be administered parenterally in large amounts. Parenteral fluids should include glucose, saline and amino acid solutions, blood or plasma and the water-soluble vitamins. Because of diminution in prothrombin and fibrinogen, vitamin K should also be given and, if possible, plasma concentrates which contain the coagulating materials. Codeine may be used for vomiting. An ice cap should be kept at the head, and for excessively high temperatures the body should be sponged with cool water. Good oral hygiene is essential.

JOSEPH STOKES, JR.

#### REFERENCES

- Carter, H. R.: Yellow Fever, an Epidemiological and Historical Study of Its Place of Origin. Baltimore, Williams & Wilkins Company, 1931.
- Fox, J. P., Kossobudski, S. L., and Fonseca da Cunha, J.: Field Studies on the Immune Response to 17D Yellow Fever Virus. Relation to Virus Substrain, Dose, and Route of Inoculation. *Am. J. Hyg.*, 38:113, 1943.
- Reed, W., Carroll, J., Agramonte, A., and Lazear, J. W.: Yellow Fever: A Compilation of Various Publications. U.S. 61st Cong., 3rd sess. Senate, Dec., No. 822, Washington, D. C., 1911.
- Whitman, L.: The Multiplication of the Virus of Yellow Fever in *Aedes aegypti*. *J. Exper. Med.*, 66: 133, 1937.

## LYMPHOGRANULOMA VENEREUM (LYMPHOGRANULOMA INGUINALE)

**Etiology.** Lymphogranuloma venereum is caused by a virus\* which is relatively large and stains with aniline dyes. Among the laboratory animals susceptible to this virus are mice, hamsters, rabbits, guinea pigs and monkeys. The virus is successfully grown on the chorio-allantoic membrane and in the yolk sac of the chick embryo. Antigen obtained from this source is used for skin tests and for complement fixation tests. As a result of infection, man develops circulating antibodies and skin sensitivity to the virus. The virus is closely related to those of meningo-pneumonitis of mice and of psittacosis and is one of the causes of atypical pneumonia.

The majority of children with lymphogranuloma venereum acquire the disease from nonsexual contact. The virus usually enters through an abrasion in the penis or the vulva or may penetrate the urethra, resulting in a mild urethritis.

**Clinical Manifestations.** Inguinal node enlargement is the most prominent manifestation of the disease and may be the first and only sign, since the primary lesion is rarely discovered in children. Cervical and axillary lymphadenopathy has been described following mouth and hand lesions. Rectal and anal strictures, common in adults, are infrequent in children. This is explained by the site of the primary lesion. The lymph drainage from the vulva, clitoris and urethra is to the inguinal nodes, and drainage from the vaginal mucosa, the site of most primary lesions in the adult female, is to the lymph nodes around the rectum.

The lymphadenopathy is chronic; the nodes frequently suppurate and give rise to multiple fistulas. Joint involvement has been observed, roentgenographically, in children. The joint space was slightly increased, and there was a slight, diffuse bony rarefaction. Erythema nodosum is an infrequent complication.

Parinaud's oculoglandular syndrome, a unilateral conjunctivitis followed by a chronic enlargement of the parotid and anterior cervical glands, may be caused by the virus of lymphogranuloma venereum as well as by a variety of other infectious agents.

**Diagnosis.** Lymphogranuloma venereum may be suspected, but the diagnosis cannot be established without the aid of laboratory

tests. These are a skin test (Frei) with inactivated virus and a complement fixation test. The Frei test is performed by injecting 0.1 cc. of the antigen (Lygranum) intradermally into the flexor surface of the forearm; a similar amount of control material is injected in the other arm. A positive test consists of a firm papule 5 mm. or more in diameter, which appears within forty-eight to seventy-two hours, with a negative or only slight reaction at the site of the control inoculation. The test usually becomes positive three to eight weeks from the time infection occurred and then may continue to be positive for many years. Transient positive reactions have been reported in the course of psittacosis and atypical pneumonias and in patients with syphilis.

**Treatment.** The drugs of choice are the tetracyclines. Penicillin and chloramphenicol are much less effective. Therapy should be maintained for ten to fourteen days.

## INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is a generalized infection whose only essential sign is, at some time in its course, an increase in the mononuclear elements of the blood. The disease occurs most frequently in the spring and fall, occasionally in outbreaks of fairly large proportions, although its communicability is usually low. It occurs most often in older children and young adults, although no age group or race is immune. The etiologic agent has not been identified, but is probably a virus. The disease has been transmitted from man to the monkey and the rabbit.

**Clinical Manifestations.** The incubation period is considered to be approximately eleven days. The onset may be insidious or acute. The most consistent clinical manifestations are generalized malaise, fever and sore throat. The last may appear early or late in the course of the disease. Fever is a fairly constant finding and may persist for several weeks; it is usually characterized by morning remissions. Enlargement of lymph nodes may occur early or late in the disease, but most frequently appears during the febrile phase. The posterior cervical nodes are usually the first to enlarge; any or all of the regional nodes can be involved. The salivary glands are rarely enlarged. The enlarged lymph nodes are usually nontender and rarely suppurate. The enlargement may disappear quickly or persist for weeks to months. The spleen is palpable in about 50 per cent of

\* This agent is classified in Bergey's Manual as a rickettsia.



cases, usually by the end of the first week of illness, and may remain enlarged for a long time.

Skin rashes occur in 9 to 18 per cent of cases and usually appear between the fourth and tenth days of the disease in the form of a discrete macular eruption (Fig. 157) which is most prominent over the trunk. They may assume a petechial, vesicular, morbilliform or scarlatiniform appearance. The hands, thighs, legs and feet are rarely involved.

Jaundice is evidence of hepatic involvement, but present evidence indicates that the liver is frequently involved without discernible jaundice. The possibility of confusing infectious mononucleosis with infectious hepatitis is especially likely in view of the lymphocytosis which frequently accompanies the latter disease.

Central nervous system manifestations consist in headache, stiffness of the neck, blurring of vision, mental confusion and, rarely, convulsions. The cerebrospinal fluid may be normal, or there may be an increase in mononuclear cells and in protein content.

Pericarditis with characteristic clinical manifestations and electrocardiographic changes may occur during the acute phase and prolong the convalescence.

**Diagnosis.** The laboratory aids are the changes in the monocytes in the peripheral blood and a positive heterophile antibody test.

The characteristic hematologic alteration is in the lymphocytes, which vary greatly in size and shape; they have been divided into three groups by Downey and McKinlay.

Type I cells are most common. Their nuclei are oval or lobulated and are usually eccentrically placed. The cytoplasm usually stains a deep blue, with an irregular, mottled appearance, except in the nuclear indentation, where it stains pink with fine carmine granules. Type II cells are somewhat larger, and their nuclei have more regular shapes and certain coarse, distinct chromatin strands. The cytoplasm is somewhat smoother, lighter staining and less mottled, with irregular strands of deep blue-staining material extending out from the nucleus to the periphery of the cell. Type III cells resemble lymphoblasts of lymphocytic leukemia; their nuclei tend to be regular in shape, but disproportionately large. The chromatin pattern is more delicate with one to three nucleoli occasionally present. The small amount of cytoplasm may be quite basophilic.

The total leukocyte count is usually elevated, but may be normal or low. The polymorphonuclear cells are often increased initially, but in the fully developed case a rela-

tive reduction in granulocytes is characteristic. The rise in lymphocytes usually begins on the fourth or fifth day, and by the seventh or tenth day these cells constitute 60 to 90 per cent of the total leukocytes. In rare instances thrombocytopenia with purpura and prolonged bleeding time, agranulocytosis and anemia may be encountered.

The heterophile antibody test of Paul and Bunnell usually becomes positive (60 per cent or more of cases) during the first week of the disease or shortly thereafter and may remain positive for varying periods of time. Since the titer of agglutinins may reach a peak quickly and subside rapidly, a positive test may be easily missed. Falsely positive heterophile antibody tests may occur in patients who have received horse serum and rarely in other acute infections. The Barrett modification of the Paul-Bunnell test makes the heterophile antibody reaction even more specific. There are three types of heterophile antibodies in human serums which agglutinate sheep red blood cells: (1) The type found in human serums after horse serum injection is absorbed by either ox erythrocytes or guinea pig kidney. (2) The type found in infectious mononucleosis is absorbed by ox erythrocytes, but not by guinea pig kidney. (3) The type found in normal serums is absorbed by neither. Thus the spe-

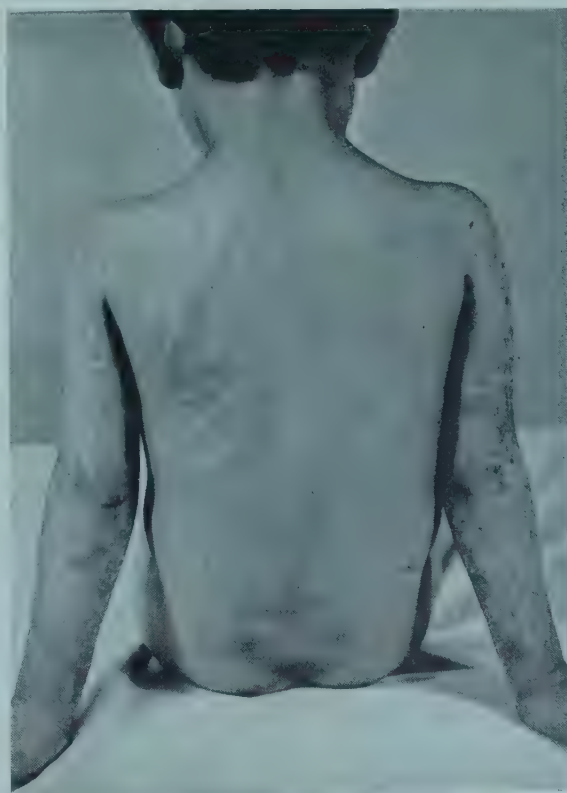


FIG. 157. Morbilliform rash in mononucleosis.

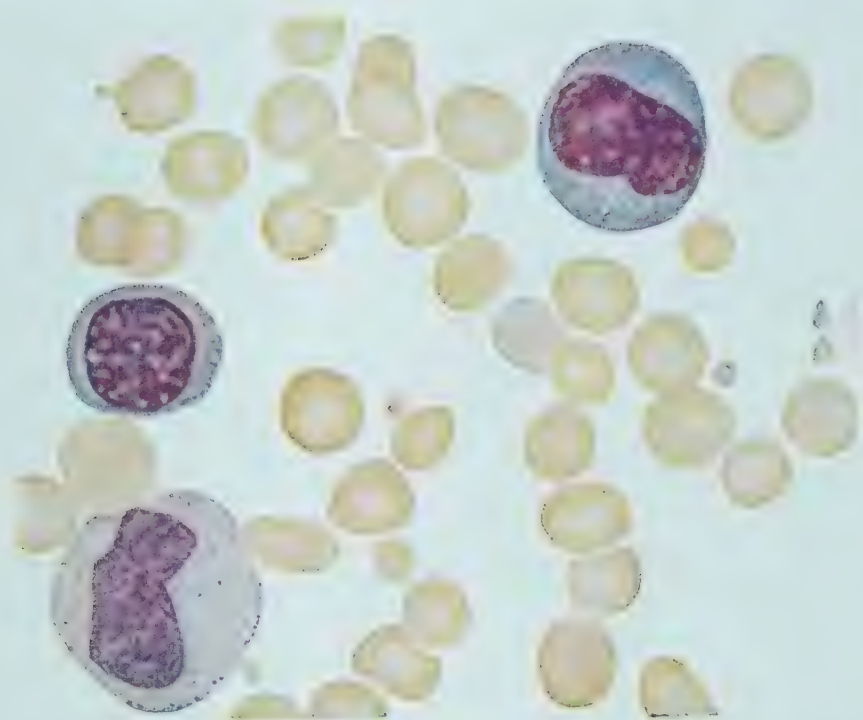


FIG. 158. Peripheral blood smear from a patient with infectious mononucleosis. In the lower left corner is a normal monocyte; the 2 lymphocytes are Downey type I cells, commonly encountered in this disease. The nucleus, which often is eccentrically placed, is lobulated with the chromatin arranged in coarse clumps. The cytoplasm stains a deep blue; there is a characteristic lighter perinuclear area most pronounced in the hilus of the nucleus. (Blackfan and Diamond: *Atlas of Blood in Children*. New York, Commonwealth Fund.)

cific antibody can be titrated. By this test, titers of 1:40 or higher are considered diagnostic. By the usual technique 1:64 or higher is considered significant.

Patients with infectious mononucleosis may show a falsely positive complement fixation (Wassermann and/or Kahn) test for syphilis, which usually appears during the second week of the disease and becomes negative within two weeks, though it may persist longer. Patients in whom a rash develops appear more likely to have a falsely positive serology than do those who do not have an eruption.

**Prognosis.** The prognosis is good even in the rare cases when central nervous system manifestations are marked. Weakness and easy fatigability may persist for a long time. There are no sequels of significance with the exception of rare cases of chronic hepatitis. Fatalities have occurred in young adults from rupture of the enlarged spleen.

**Treatment.** There is no specific therapy. Bacterial complications are not common, and should be treated appropriately. The convalescent period is likely to be prolonged, though less in children than in adults; an initial period of fourteen to twenty days in bed may be indicated in the average case.

Subsequent increases in activity should be gradual, being based on evidences of fatigue and the patient's temperature. A generous intake of protein and vitamins is indicated.

SYDNEY S. GELLIS

#### REFERENCE

Parrott, R. H., and Cramblett, H. G.: Nonbacterial Infections Affecting the Nasopharynx. *Pediat. Clin. North America*, 4:126, 1957.

#### ACUTE INFECTIOUS LYMPHOCYTOSIS

This infection, originally thought to be a variant of infectious mononucleosis, was described and named by Carl Smith in 1941. The outstanding characteristic is the increase in the total number of lymphocytes in the peripheral blood and in the bone marrow which persists over relatively long periods of time. Initially it was thought that there were few or no clinical manifestations. Subsequent observations, however, have disclosed a variety of symptoms and signs, such as fever, nasopharyngitis, abdominal complaints, skin rashes, and mild meningoencephalitic manifestations.

**Etiology.** Bacteriologic and viral studies have not disclosed a causative agent.



**Epidemiology.** On the basis of institutional epidemics and the occurrence of multiple cases in families, the disease is considered to be infectious. The incubation period is estimated to be twelve to twenty-one days. Most cases have been in children less than ten years of age. The disease has been observed in the Americas and in Europe. Nothing is known about the development of immunity.

**Pathology.** Microscopic examination of lymph nodes has shown degeneration of the lymph follicles and proliferation of the reticuloendothelium of the sinuses.

**Clinical Manifestations.** In the majority of the cases observed there are no symptoms and no abnormal physical findings, or they are so mild that they escape attention. In a few instances there are fever and variable, but short-lived, complaints at the onset. These complaints include upper respiratory infections with throat manifestations predominant, vomiting, irritability, abdominal pain and diarrhea and, infrequently, signs referable to the central nervous system. The abdominal signs may infrequently be severe enough to suggest an acute surgical emergency. Several instances are recorded in which the clinical pattern was that of a meningoencephalitis, and one instance in which there was paralysis, similar to that occurring in poliomyelitis, and a slight increase in the cerebrospinal fluid cell count. A mild, generalized morbilliform rash of several days' duration, similar to that in infectious mononucleosis, has been observed. Slight enlargement of the lymph nodes or spleen has been observed, but is apparently infrequent.

**Laboratory Data.** The only characteristic finding is the high white blood cell count, which may range from 22,500 to 120,000 per cubic millimeter, the lymphocytes varying from 62 to 97 per cent. The lymphocytes are normal in appearance and are mainly of the small variety. There may be a slight eosinophilia. There is no abnormality of the erythrocytes or platelets.

The heterophile agglutination test is negative. The bone marrow contains an increased number of normal or postmature lymphocytes; otherwise it is not abnormal. The changes apparently persist longer in the bone marrow than in the peripheral blood.

**Diagnosis.** The disease must be differentiated from infectious mononucleosis, acute leukemia, infections associated with a lymphocytosis, principally pertussis, and rarely

from acute abdominal conditions and meningoencephalitis of other causes.

*Infectious mononucleosis* can be distinguished only by a positive heterophile agglutination test and by demonstration in the peripheral blood of the abnormal lymphocytes typical of the disease. The clinical pattern of infectious mononucleosis, however, is likely to be much more severe, being characterized by fever, malaise, sore throat, enlargement of lymph nodes and often of the spleen, and occasionally by a rash and jaundice.

*Acute lymphatic leukemia* may cause some difficulty initially, but the presence of abnormal lymphoblasts in both leukemic and aleukemic phases of leukemia, diminution of erythrocytes and platelets, leukemic invasion of the bone marrow, and the progressively downward course combine to make a clear differentiation.

Extremely high lymphocytic counts are occasionally observed in *pertussis*, but usually with the more severe cases, so that the characteristic clinical manifestations are usually adequate to determine the diagnosis.

*Acute abdominal conditions* which would require operation apparently can occasionally be simulated. In such cases the high lymphocytic count should speak for a period of watchful waiting; in acute infectious lymphocytosis the abdominal complaints can be expected to disappear.

The differentiation of a *meningoencephalitis* of other etiology presents greater difficulties. Exact diagnosis of the various viral encephalitides can be established with certainty only by laboratory means (p. 384). The possibility of confusion with poliomyelitis is suggested by the report of one case.

**Course and Prognosis.** In the few instances in which there have been abnormal symptoms they were only of a few days' duration. Otherwise the course can be measured only by laboratory data. The lymphocytosis persists for weeks, and was observed for seven months in one case. The disease is apparently exceedingly benign, no sequels having been recognized or deaths recorded.

**Treatment.** Except for symptoms present at the onset, no therapy is indicated.

WALDO E. NELSON

#### REFERENCES

- Riley, H. D.: Acute Infectious Lymphocytosis. New England J. Med., 248:92, 1953.
- Smith, C. H.: Acute Infectious Lymphocytosis. J.A.M.A., 125:342, 1944.

## CAT-SCRATCH FEVER

(BENIGN INOCULATION LYMPHORETICULOSIS; CAT-CLAW DISEASE; CAT-BITE FEVER)

Cat-scratch fever is now recognized as a relatively common disease of man, and the role of the domestic cat in its transmission seems to have been established. Observed as early as 1930 in France and in the United States, the disease as an entity has been brought to general attention comparatively recently.

**Etiology.** The etiologic agent, though not identified, is thought to be a virus of the psittacosis-lymphogranuloma venereum group. Attempts to isolate the agent from suppurative lymph node material have been unsuccessful, but transfer of the disease to monkeys and to human volunteers has been accomplished. Stained sections of primary skin lesions and involved lymph nodes from both man and monkeys show large numbers of intracellular and extracellular granule-like bodies similar to those of psittacosis.

**Epidemiology.** It appears probable that distribution is worldwide. To date cases have been reported from France, Great Britain, Canada, Australia, the United States, South America, Switzerland and India. On the basis of similarity in the type of elementary body, a possible relation between the etiologic agent of cat-scratch fever and that of feline pneumonitis has been suggested. The infectious agent of the latter is antigenically related to the psittacosis-lymphogranuloma venereum viruses. It can be isolated readily, and passage is established in mice by intranasal inoculation. A similar transfer of pus from infected nodes of cat-scratch disease has not resulted in disease in mice. Cats which transfer the agent to human subjects show no evidence of illness and have no reaction to the intradermal injection of the antigen. Their role is considered to be simply that of a vector.

**Pathology.** Examination of involved lymph nodes has revealed only nonspecific morphologic changes, classified into distinct phases: (1) an "elementary" phase of simple hyperplasia; (2) an "accentuated" phase in which, in addition to hyperplasia, areas of early cellular necrosis stain as acidophilic masses; and (3) the "ultimate" stage in which the lymph node architecture is displaced by multiple areas with central necrosis and by circumscribed foci of epithelioid cells and scattered giant cells of the Langhans type (pseudotubercles). The final phase corre-

sponds to the clinical stage when the enlarged node becomes fluctuant.

**Clinical Manifestations.** Cat-scratch fever is a nonfatal systemic illness characterized by malaise, headache, low grade fever and lymphadenitis. Though as a rule the patient does not appear acutely or chronically ill, the size of the involved lymph node, or nodes, is often striking. In most instances the history will reveal association with cats, with or without the recollection of a specific abrasion. The incubation period varies from ten to thirty days. In one volunteer subject regional adenopathy began in eight days and progressed to fluctuation in about twenty. At the height of the lymph node response a skin papule appeared at the site of the primary intradermal inoculation and persisted for several days.

The foregoing sequence appears to be characteristic of the natural infection. At the time medical advice is sought there is usually an exacerbation of redness and swelling at the site where a primary lesion is in the process of healing. This lesion tends to heal slowly and may resemble an insect bite, a small furuncle or a scab following simple trauma. The nodes involved are those which drain the area where the initial lesion occurred, commonly the epitrochlear, axillary, submandibular, cervical or inguinal ones. The skin overlying enlarged nodes may show some redness, but more often is normal in appearance. Involved lymph nodes may be hard or soft and vary in diameter from 1 to 5 cm.; on aspiration a purulent fluid may be obtained, from which no bacteria can be cultured.

Unusual clinical manifestations have included cervical adenitis thought to result from inhalation or aspiration of the etiologic agent, transient pulmonary infiltration associated with otherwise typical cat-scratch fever, and an oculoglandular form of the disease with conjunctivitis and enlargement of preauricular and cervical nodes. Purpura and skin rashes of the erythema multiforme and nodosum types have been observed. An osteolytic lesion, which healed spontaneously, has also been observed.

Central nervous system involvement, classified as encephalitis, encephalomyelitis and myelitis and radiculitis, may accompany or follow the acute phase. Onset of neurologic symptoms is usually abrupt with high fever. The cerebrospinal fluid usually has a moderate increase in both lymphocytes and in protein.

**Laboratory Data.** There are no conclusive



data; there may be a moderate leukocytosis with a slight shift to the left.

**Skin Test.** Patients with cat-scratch fever have a positive skin reaction from the intradermal injection of the antigen prepared by the Frei procedure from an involved lymph node of a known case. The following procedure is a convenient method for preparing skin test antigen.

A suppurative node is aspirated under aseptic conditions, and the material is injected directly into a sterile puncture-type vial containing 2 to 3 cc. of isotonic saline solution. The vial is shaken vigorously in order to ensure dispersion, and additional saline solution to give an approximate 1:5 dilution is immediately injected into the vial. No anticoagulant is necessary if dilution is accomplished quickly. On each of two successive days the diluted material is heated for one hour at 56° to 60° C. If this potentially antigenic material proves by routine culture to be sterile, it should be tested intradermally in volunteers to rule out nonspecific skin reactions. Since antigens of this type carry the possible risk of exposure to hepatitis, there is need for caution.

The skin test is performed by injecting intradermally 0.1 cc. of the antigen, the site being observed at intervals of forty-eight and seventy-two hours. A typical positive reaction consists of an indurated, raised, erythematous wheal 5 mm. or more in diameter which is surrounded by a zone of erythema 30 to 40 mm. in diameter. The erythema may disappear in one to two days, but as a rule the wheal can be recognized for four or five days more. A positive skin test may be ob-

tained for years following cat-scratch infection. No regional adenopathy is associated with a positive reaction to the intradermal injection of the antigen.

**Differential Diagnosis.** Cat-scratch fever is most commonly confused with simple pyogenic adenitis, but must also be differentiated from tuberculous adenitis, tularemia, rat-bite fever, Hodgkin's disease, lymphoma, fungus infections and lymphogranuloma venereum.

**Prognosis.** The prognosis in cat-scratch fever is uniformly good. The enlarged nodes regress spontaneously in one to three months after reaching their peak. In some instances fibrosis may result in persistent enlargement.

**Prevention.** At present, detection of cats carrying the infective agent is not possible, since they are apparently not ill and do not have a positive skin reaction to the antigen. Thus no control measures are apparent other than avoidance of contact with cats, and it does not seem likely that the cat is to be displaced as a household pet. Other means of transfer include abrasions by thorns and wood splinters and by fragments of bone in meat handlers. The obvious question, in such instances, is whether the persons involved had subsequent contact with cats.

**Treatment.** No therapeutic measures are known to be of benefit. Although in a few instances treatment with one of the broad-spectrum antibiotics was thought to shorten the course of the disease, the evidence is not conclusive. Occasionally drainage by aspira-



FIG. 159. Cat-scratch fever: primary skin lesion with associated cervical lymphadenitis. (Photograph courtesy of C. W. Daeschner.)

tion will hasten resolution of fluctuant nodes; the procedure does carry the risk of a draining sinus, but this usually heals with minimal scarring.

RUSSELL J. BLATTNER

## REFERENCES

- Adams, W. C., and Hindman, S. M.: Cat Scratch Disease Associated with an Osteolytic Lesion. *J. Pediat.*, 44:665, 1954.
- Armstrong, C., Daniels, W. B., MacMurray, F. G., and Turner, H. C.: Complement Fixation in Cat Scratch Disease Employing Lygranum C. F. as Antigen. *J.A.M.A.*, 161:149, 1956.
- Belber, J. P., Davis, A. E., and Epstein, E. H.: Thrombocytopenic Purpura Associated with Cat Scratch Disease: Response of Cat Scratch Disease to Steroid Hormones. *A.M.A. Arch. Int. Med.*, 94:321, 1954.
- Daeschner, C. W., Salmon, G. W., and Heys, F.: Cat Scratch Fever. *J. Pediat.*, 43:371, 1953.
- Daniels, W. B., and MacMurray, F. G.: Cat Scratch Disease: Report of One Hundred Sixty Cases. *J.A.M.A.*, 154:1247, 1954.
- Debré R., and Job, J.-C.: La maladie des griffes du chat. *Acta paediat.*, 43(Suppl. 96):86, 1954; 43:386, 1954.
- Gifford, H.: Skin-Test Reactions to Cat Scratch Disease among Veterinarians. *A.M.A. Arch. Int. Med.*, 95:828, 1955.
- Mollaret, P., Reilly, J., Bastin, R., and Tournier, P.: Documentation nouvelle sur l'adénopathie régionale subaiguë et spontanément curable décrite en 1950: La lymphoréticulose bénigne. *Presse méd.*, 58:1353, 1950.
- Mollaret, P., Reilly, J., Bastin, R., and Tournier, P.: Le virus de la lymphoréticulose bénigne d'inoculation. *Presse méd.*, 64:1177, 1956.
- Small, W. T., and Sniffen, R. C.: Nonbacterial Regional Lymphadenitis (Cat Scratch Fever): Evaluation of Surgical Treatment. *New England J. Med.*, 255:1029, 1956.
- Weinstein, L., and Meade, R. H., III: The Neurological Manifestations of Cat Scratch Disease. *Am. J. M. Sc.*, 229:500, 1955.
- Winship, T.: Pathologic Changes in So-Called Cat Scratch Fever. *Am. J. Path.*, 23:1012, 1953.

## CYTOMEGALIC INCLUSION DISEASE

Generalized cytomegalic inclusion disease is a rare systemic disease involving predominantly infants, and characterized by the presence of intranuclear and intracytoplasmic inclusion bodies in the enlarged cells of many viscera. The virus responsible for the disease has been isolated from salivary glands, liver, urine and from the aqueous humor of affected infants; a similar virus has been isolated from adenoid tissue of presumably healthy children.

The inclusion bodies are usually found in epithelial cells, but mesenchymal cells may

also be involved. Inclusion-bearing cells have been demonstrated in almost all organs of the body at postmortem examination. The tissue adjoining the involved cells may reveal no significant inflammatory response. In some instances, however, there is an associated infiltrate of lymphocytes or, less frequently, focal areas of necrosis or fibrosis. Excessive extramedullary hematopoiesis may be present, especially in the spleen and liver of infants dying during the neonatal period. The intranuclear inclusion body may occupy most of the enlarged nucleus of the affected cell, although characteristically it is separated from the nuclear membrane by a clear halo. Multiple intracytoplasmic inclusion bodies may be present, but are less constant than the intranuclear ones.

Serologic studies, which are still inadequate for diagnostic purposes, indicate that the virus responsible for the disease is widespread. Moreover, the characteristic inclusion bodies have been observed as incidental findings in the salivary glands in 10 to 32 per cent of fetuses and infants dying of a variety of causes; such a finding does not warrant the diagnosis of generalized cytomegalic inclusion disease. Similar inclusion bodies, disseminated in a variety of sites, have been encountered less frequently in infants, children or even in adults dying with debilitating diseases, e.g., fibrocystic disease of the pancreas and pertussis; the significance in such instances is not clear. It seems possible, however, that a latent viral infection may have become activated because of loss of resistance on the part of the host. Although such patients might properly be regarded as having generalized cytomegalic inclusion disease, it apparently represents only an intercurrent incident and not the primary cause of their illness.

The most constant clinical pattern associated with generalized cytomegalic inclusion disease occurs during the neonatal period. The infants are often below average birth weight and exhibit manifestations at the time of delivery or in the early neonatal period; rarely manifestations may not be apparent for several weeks. The manifestations are usually related to the hematopoietic system, liver and central nervous system, although any system may be involved. Hepatomegaly, splenomegaly, icterus, anemia, thrombocytopenia, purpura and cerebral calcification are among the more common clinical manifestations. The cerebral calcification is classically para-



ventricular in location and may be associated with microcephaly or hydrocephalus. Chorioretinitis is occasionally present, and the clinical pattern may thus be indistinguishable from that of congenital toxoplasmosis.

The *differential diagnosis* in the neonatal period includes erythroblastosis fetalis, sepsis, toxoplasmosis, congenital syphilis and such rarer diseases as generalized herpes simplex, congenital hemolytic icterus and congenital leukemia. These can usually be excluded by appropriate laboratory studies. A definite diagnosis can be established by demonstration of the typical inclusion-bearing cells in smears of the urinary sediment or less frequently in gastric washings or possibly in bronchial secretions or cerebrospinal fluid; inclusion bodies may still be demonstrable in specimens of urine obtained from infants several months of age.

In infants whose first manifestations of the disease occur in the postnatal period the clinical pattern is somewhat more varied. Evidence of interstitial pneumonitis and diarrhea are apt to be prominent symptoms. The inclusion-bearing cells may be limited to the lungs or intestinal tract or may be widely disseminated through the viscera.

Information about the natural history of the disease is still inadequate, since until 1952 the diagnosis had been made only at postmortem examination. However, the evidence indicates that the disease is a serious but not invariably a fatal one. Permanent cerebral damage, although often present in patients who survive, may be of varying degrees of severity, and rarely no permanent sequels are apparent. The prognosis for future pregnancies is apparently good; only one instance is known of infection in two infants of separate pregnancies of a given mother.

JAMES B. AREY

## REFERENCES

- Medearis, D. N., Jr.: Cytomegalic Inclusion Disease: An Analysis of the Clinical Features Based on the Literature and Six Additional Cases. *Pediatrics*, 19:467, 1957.
- Guyton, T. B., Ehrlich, F., Blanc, W. A., and Becker, M. H.: New Observations in Generalized Cytomegalic Inclusion Disease of the Newborn. Report of a Case with Chorioretinitis, *New England J. Med.*, 257:803, 1957.
- McElfresh, A. E., and Arey, J. B.: Generalized Cytomegalic Inclusion Disease. *J. Pediat.*, 51:146, 1957.
- Smith, M. G., and Vellios, F.: Inclusion Disease or Generalized Salivary Gland Virus Infection. *Arch. Path.*, 50:862, 1950.

## INFECTIOUS NEURONITIS

(INFECTIOUS POLYNEURITIS, GUILLAIN-BARRÉ SYNDROME)

Infectious neuronitis is a disease of unknown etiology characterized by a slowly progressive ascending paralysis. The disease frequently follows an acute infection and is thought by many to be the toxic effect of the original infection. Others feel that infectious neuronitis is caused by a virus; however, animal experiments have thus far failed to demonstrate such an agent. It appears likely that the clinical picture of infectious neuronitis may be caused by several different agents. The development of the Guillain-Barré syndrome has been noted in association with diphtheria.

In the usual case, signs of a peripheral neuritis develop symmetrically in the lower extremities several days after an upper respiratory infection. The muscles become tender, and deep tendon reflexes are abolished or greatly diminished; cutaneous reflexes are usually maintained. Sensory loss may be marked, but in most cases is slight. Cramping pains and paresthesias may occur. The muscles become paralyzed, and the paralysis moves upward, often involving the abdominal and thoracic muscles. Involvement of the cranial nerves is uncommon, except of the facial nerves, which is usually bilateral. Muscular atrophy is not marked in this disease, and recovery is usually complete, especially in children. The course of the disease tends to be prolonged with a gradual return of function to the paralyzed muscles. Fatalities are uncommon, but may occur as a result of respiratory paralysis.

Fever is not conspicuous in infectious neuronitis and may be absent. A diagnostic feature of importance is an increase in the protein of the cerebrospinal fluid with little or no increase in the cell count. The symmetry of paralysis and the increase in cerebrospinal fluid protein serve to distinguish this disease from poliomyelitis.

Pathologic changes are found in the peripheral nerves and nerve roots, and consist in degeneration in the myelin and in the axis cylinders. There may or may not be evidences of inflammatory reaction. No characteristic central nervous system changes are found. Visceral lesions have also been reported which consist in focal necroses in liver, kidneys and adrenals with round cell infiltration.

*Treatment* is symptomatic; no specific therapy is available. Acceleration of recovery has been reported when therapy with corti-

cotropin or cortisone was initiated early in the course of the disease.

SYDNEY S. GELLIS

## INFECTIONS BY ENTERIC VIRUSES (ENTEROVIRUSES)

Viruses which inhabit the alimentary tract and appear to be natural parasites of man include the poliomyelitis, Coxsackie and ECHO (enteric cytopathogenic human orphan) viruses. These agents, referred to as the enteroviruses, have many properties in common, including small size, relative durability as exemplified by resistance to ether, maximal prevalence in warm weather (summer season in temperate zones) and other similarities of epidemiologic pattern. Many of these viruses produce disease in man, and all induce recognizable infection in one or more of various experimental hosts, including primates, rodents, and cells in tissue culture.

Table 75. Association of Enteroviruses with Human Disease\*

<i>Enteroviruses</i>	<i>Associated Disease</i>
Poliovirus.....	Paralysis (complete to slight muscle weakness) Aseptic meningitis Undifferentiated febrile illness, particularly during the summer
Coxsackie viruses, group A.....	Herpangina Undifferentiated febrile illness, particularly during the summer Aseptic meningitis (types A-7, A-9)
Coxsackie viruses, group B.....	Aseptic meningitis Pleurodynia Undifferentiated febrile illness with pharyngitis Myocarditis or encephalomyocarditis during neonatal period and early childhood Mild paralysis (?)
ECHO viruses...	Aseptic meningitis (types 2, 3, 4, 5, 6, 9, 14, 16) Summer rash (types 4, 9, 16) Summer febrile illness Mild paralysis (?) (type 6) Summer diarrhea of infants and children (type 18 and others)

\* From "The Enteroviruses," Committee on the Enteroviruses, National Foundation for Infantile Paralysis, Am. J. Pub. Health, Vol. 47.

## REFERENCE

Crozier, R. E., and Ainley, A. B.: The Guillain-Barré Syndrome. New England J. Med., 252:83, 1955.

The associations of enteroviruses with human diseases as currently recognized are indicated in Table 75.

Poliomyelitis is discussed on page 531.

## COXSACKIE VIRUS INFECTIONS

**Etiology.** Coxsackie viruses have in common the capacity to induce fatal infections, frequently with paralysis, in suckling mice and hamsters. The route of inoculation, the strain of virus and the size of the dose, as well as the age of the host, influence the manifestations of infection. Dalldorf has classified these agents into two groups based on the features of disease induced in suckling mice. Group A viruses characteristically cause extensive destruction of skeletal muscle without lesions elsewhere. Group B viruses cause varying degrees of focal damage to skeletal muscle as well as myocarditis, fat necrosis, pancreatitis, encephalomyelitis and, less regularly, lesions in other organs. Group B viruses also induce a form of pancreatitis in mature mice in which the islets of Langerhans are spared and the acinar tissue first becomes necrotic and then is replaced by fat.

Nineteen Coxsackie viruses of group A (designated A-1 to A-19) and five of group B (designated B-1 to B-5) have been identified to date. Each of these agents is antigenically distinct and can be identified and differentiated by neutralization and complement fixation tests with specific immune animal serums, as well as by determinations of active immunity in mice or chimpanzees. Circulating antibodies can usually be detected in the human or animal host within two weeks of infection or the onset of symptoms.

A-7 and A-14 viruses induce poliomyelitis-like lesions in monkeys. Strains of virus recovered from children with paralytic disease and thought by Russian workers to represent a fourth type of poliovirus have been identified as Coxsackie virus A-7. Only two types, A-2 and A-8, have been found to multiply in chick embryos; A-4 has been grown in chick cells. Strains of all five group B and



several group A viruses grow and produce cytopathic changes in tissue cultures of trypsinized monkey kidney cells.

Coxsackie viruses are relatively small with diameters in the range of 25 to 30 millimicrons. An A-10 strain has been purified and crystallized.

Coxsackie viruses are unusually stable. Viral activity is maintained at room temperature for many days and can be preserved for a long time if infected tissues are stored in glycerin or in a frozen state. In aqueous suspensions activity disappears after exposure to a temperature of 60° C. for thirty minutes. When these viruses are suspended in milk or ice cream, higher temperatures are required for their inactivation. Like poliomyelitis viruses, these agents retain their activity through a wide range of pH (2.3 to 9.4 for one day and 4.0 to 8.0 for a week). They are not inactivated by ether, 70 per cent ethyl alcohol, 5 per cent Lysol, 1 per cent Roccal, or antibiotics, but are inactivated rapidly by tenth-normal hydrochloric acid and 0.3 per cent formaldehyde.

**Epidemiology.** Coxsackie viruses have been encountered throughout the world. Like poliomyelitis and ECHO viruses, these agents have been recovered most commonly from human feces and pharyngeal swabbings, and also from sewage and flies. Strains of all the group B types and A-9 virus have been recovered from the cerebrospinal fluid of patients with aseptic meningitis. Recovery of a Coxsackie virus from human blood, tissue or other sources has been relatively uncommon. No natural reservoir of infection other than man has been found, although flies and possibly cockroaches are able to transport these agents.

Coxsackie viruses have been recovered mainly in the summer and fall, and more frequently from children than from adults. Rates of infection may be higher in persons with poor living conditions. Some of these viruses may cause epidemics of human disease, usually in the summer and fall, but at unpredictable intervals and locations. Any one of six different group A viruses may cause herpangina. Group B viruses, especially B-1 and B-3, have been responsible for widely separated outbreaks of the syndrome pleurodynia. All of group B and A-7 and A-9 viruses can produce meningoencephalitis in man, the group B agents sometimes in association with epidemic myalgia. The infrequent production of paralytic disease by one of these agents has

been demonstrated most convincingly with A-7 virus. Group B viruses may cause myocarditis, which in newborn infants is highly fatal.

Successive infections with strains of a single type of Coxsackie virus have not been reported; immunity appears to be type specific and relatively lasting. Communicability of infection by Coxsackie viruses is similar to that in poliomyelitis.

**Pathology.** Relatively few observations have been made of pathologic changes in man. Myocarditis, encephalitis, hepatitis and, in one instance, inflammatory changes in the spinal cord have been observed in newborn infants with fatal disease attributed to a group B virus. In a few instances myositis and degenerative changes have been observed in biopsies of skeletal muscle.

**Diagnosis.** Diagnosis of infection by a Coxsackie virus is suggested by clinical and epidemiologic findings and confirmed by recovery of virus from feces, oropharyngeal swabbings, cerebrospinal fluid or, rarely, blood, and by demonstration of a related increase of specific neutralizing antibodies in serial specimens of serum obtained during the acute and convalescent phases of illness. Since infection by one of these viruses stimulates complement-fixing antibodies to heterologous strains, determinations by this technique are of limited diagnostic value.

**Prognosis.** Diseases attributed to infection by a Coxsackie virus appear in most instances to be relatively benign, self-limited and usually uncomplicated. Fatalities have occurred in newborn infants with myocarditis and encephalomyelitis and much less often in children with central nervous system involvement.

**Treatment.** No therapeutic measure is known which affects the course of infection by an enterovirus. Treatment is entirely supportive and symptomatic.

**Prophylaxis.** Effective measures to control infection by Coxsackie or ECHO viruses are not available. Attempts to limit the spread of infection within the home or an institution should be based on recognition of the fact that these agents may be distributed directly or indirectly by the oropharyngeal secretions or feces of infected persons, many of whom remain undetected. Since enteroviruses are unusually stable at ordinary temperatures and resistant to solutions commonly used as antiseptics, decontamination of objects which cannot be boiled or autoclaved, as, for example,

rectal thermometers, can be accomplished only by immersion in tenth-normal hydrochloric acid or 0.3 per cent formaldehyde.

## CLINICAL DISORDERS

### HERPANGINA

This acute febrile disease, first described by Zahorsky, was shown by Huebner and his associates to be caused by any one of six group A viruses (types A-2, A-4, A-5, A-6, A-8 and A-10). It occurs during the warm months, affects mainly children, and is characterized by distinctive faucial lesions.

After an incubation period of two to four days the illness is usually initiated by an abrupt elevation of temperature to as high as 105° F. Anorexia and dysphagia are common, and most patients over two years of age complain of sore throat. Headache and abdominal pain are encountered less often. Infrequently convulsions occur with the fever. The pharynx is usually hyperemic. The characteristic discrete lesions appear initially as white or grayish vesicles, later as shallow ulcers 1 to 5 mm. in diameter, each surrounded by a red areola. They range from one to about fifteen in number and are commonly located on the anterior pillars of the fauces, less frequently on the palate, uvula or tongue, but not characteristically on the posterior pharyngeal, gingival or buccal mucosa. These lesions are not invariably present, however. Genital ulceration attributed to infection by A-10 virus has been described in a seven-year-old-girl with herpangina. Acute parotitis complicating herpangina has also been reported. Rhinitis, cough, otitis media, sinusitis, diarrhea, generalized myalgia and meningeal irritation are not typical features of herpangina. The illness generally follows an uncomplicated course to recovery. Fever may last one to four days, and the ulcers heal within a week. The white blood cell count is usually normal or only slightly elevated.

A *diagnosis* of herpangina is suggested by the occurrence of an acute self-limited disease prevalent in the community in spring, summer or fall and characterized by typical faucial lesions which, unlike those of herpetic or aphthous stomatitis, do not occur on the gingival or buccal mucous membranes. Infection by herpes simplex virus, unlike herpangina, is usually not epidemic and causes lesions on the skin and at mucocutaneous borders. Vesicles and ulcers similar to those of herpangina are occasionally seen in ECHO viral infections. Follicular tonsillitis due to

the hemolytic Streptococcus and the pseudomembrane of diphtheria do not resemble herpangina and can be correctly identified by culture. The oral lesions of acute exanthematous diseases, leukemia and infectious mononucleosis, as well as those seen in various deficiency states and following intoxication by heavy metals, are usually readily differentiated.

### PLEURODYNIA

(EPIDEMIC MYALGIA, DEVIL'S GRIPPE, BORNHOLM DISEASE)

The disease apparently first recognized by Finsen in 1856 in Iceland is widely distributed throughout the world. It is evident that group B Coxsackie viruses, especially B-1 and B-3, can induce pleurodynia. This relationship, first suggested by Curnen and co-workers, has been established by Weller and others. Outbreaks usually occur in the summer and fall. The true rate of occurrence is not known; in Denmark, where this disease is reportable, the incidence closely parallels that of acute poliomyelitis and of typhoid fever.

The incubation period is usually two to four days. The illness begins suddenly with fever, headache and pain, commonly located in the muscles of the lower chest or upper abdomen. Characteristic sharp or stabbing pain which may be extreme is accentuated by respirations and may be present on one or both sides. Sometimes pain is localized in the lower abdomen and may simulate an acute surgical condition. Superficial tenderness and palpable swelling of muscles in affected areas may be detected. The muscles of the extremities are rarely involved. Although pleurisy may be suggested, auscultation and roentgenologic examination of the chest seldom reveal abnormalities. Splenomegaly is infrequent. The white blood cell count is not unusual.

The fever and pain subside within two or three days, but in about a fourth of the cases they recur on one or more occasions after asymptomatic intervals of two or three days. Often several members of a family are affected with somewhat different manifestations and degrees of severity. Involvement of the central nervous system may be evidenced by convulsions, encephalitic manifestations or pleocytosis of the cerebrospinal fluid. Except for occasional meningeal involvement and orchitis in mature males, complications are unusual, and the disease terminates spontaneously in recovery.



Pleurodynia must be differentiated from other causes of thoracic pain, particularly pneumonia and pleurisy, and from other causes of abdominal pain, including acute gastroenteritis, appendicitis, peptic ulcer and disease of the gallbladder. Whether a group B Cocksackie virus can cause pancreatitis in man as in mice has not been determined. The superficial quality of the pain, the absence of deep abdominal or rectal tenderness, the relatively normal leukocyte count and the absence of abnormal roentgenologic findings should aid in the recognition of infection by a Cocksackie virus. The diagnosis is favored when other typical cases are occurring in a local epidemic; it can be confirmed by recovery of the virus and by demonstration of a type-specific antibody response.

#### MYOCARDITIS IN THE NEWBORN INFANT

Recent evidence from widely separate sources indicates that group B Cocksackie viruses may induce intrauterine or neonatal infection manifest in newborn infants by acute myocarditis. The onset is sudden, most often within the first ten days of life and sometimes shortly after a brief episode of diarrhea and anorexia. Tachycardia, dyspnea and cyanosis may appear early, and lethargy, grayish pallor and mild jaundice are typical manifestations. The temperature may be depressed or elevated. The heart, liver and sometimes the spleen are enlarged. Electrocardiographic changes are characteristic of myocarditis. The cerebrospinal fluid may be xanthochromic, and the leukocytes and protein may be increased.

The clinical course may be rapidly fatal or progress to complete recovery. In fatal cases virus has been recovered from the brain and spinal cord as well as from the myocardium. Recently myocarditis and pericarditis have also been observed as features of infection by group B Cocksackie viruses among older children and adults.

#### ASEPTIC MENINGITIS

Cocksackie viruses of group B now appear to be responsible for much of the aseptic meningitis or so-called nonparalytic poliomyelitis during the summer and fall months. Strains of all the group B types 1 to 5 and A-9 virus have been recovered from the cerebrospinal fluid of patients during the acute illness.

The clinical picture of aseptic meningitis caused by a Cocksackie virus is not distinctive for the various strains. The onset may be sudden or gradual; in approximately half of

the instances it is initiated by a prodromal phase. In one patient viremia with a B-2 strain was demonstrated five days before the appearance of meningeal signs. Anorexia, malaise, fever, nausea and abdominal pain are frequent early complaints. The temperature may be elevated to 104° F. or so. Ultimately headache, drowsiness, vomiting and discomfort or stiffness of the neck or back may appear, occasionally associated with focal or generalized myalgia. Physical examination may reveal hyperemia of the pharynx and some degree of resistance to flexion of the neck and back. Persistent muscular stiffness or weakness is usually equivocal or lacking. The reflexes remain physiologic.

The white blood cell count is normal or only slightly elevated. The cells of the cerebrospinal fluid are increased, but usually not in excess of 500 per cubic millimeter, except in patients with B-5 infection, when counts may be as high as 2000. The cells are predominantly lymphocytes, but initially the percentage of polymorphonuclear cells varies from 10 to 50 per cent; protein and sugar levels are usually normal.

The course is characteristically uncomplicated and terminates in complete recovery; especially in adult patients, fatigue and irritability may persist for several months. Paralytic involvement is rare.

Differentiation of Cocksackie viral meningitis from other infections of the aseptic meningitis syndrome (p. 544) may be suggested by clinical and epidemiologic data. The diagnosis can usually be established by appropriate serologic tests and, in some instances, by recovery and identification of the responsible agent, especially from the cerebrospinal fluid. Differentiation from nonparalytic 'poliomyelitis is not possible on the basis of clinical findings; persistence of muscle spasm, however, is more suggestive of poliomyelitis.

#### ECHO VIRUS INFECTIONS

**Etiology.** ECHO viruses, some of which have been referred to earlier as "orphan" or "human enteric" viruses, now comprise nineteen different antigenic types and have in common a number of properties. They are cytopathogenic for human or monkey cells in tissue cultures. They are not neutralized by antisera for the three types of polioviruses or by antisera for Cocksackie viruses which induce cytopathogenic changes in tissue culture. In general they do not cause disease in newborn mice, although types 9 and

10 after passage in tissue culture appear to be exceptions in this respect and cause lesions in suckling mice resembling those produced by Coxsackie A and B viruses, respectively. Some of the ECHO viruses (types 1, 2, 3, 4, 6, 10 and 13) produce neuronal lesions in monkeys. After immunization of monkeys and rabbits with ECHO viruses higher titers of neutralizing antibody are found in serums from the former than from the latter; this may be another reflection of viral multiplication in monkeys. Clinically inapparent infections associated with excretion of virus and homologous antibody response have been demonstrated in chimpanzees.

ECHO viruses are not related to other viruses recovered from the alimentary tract of man by means of tissue culture. Neutralizing antibodies to ECHO viruses are found in gamma globulin and in human serum. Although these agents have been classified to date into nineteen different types, considerable variation has been recognized between individual strains of certain types, especially types 4 and 6. Some evidence suggests that types 1 and 13 are related and may be identical. Kidney cells of different monkey species vary in their susceptibility to ECHO viruses. Separation of the ECHO viruses into two groups based on the kind of plaque formation and the capacity to propagate in cultures of cells from different species of monkeys has been suggested by Melnick.

ECHO viruses are relatively small, being about the same size as Coxsackie viruses and polioviruses with the exception of type 10, which is considerably larger (approximately 75 millimicrons in diameter) and differs in additional features from other ECHO viruses. As far as has been determined, ECHO viruses appear to resemble poliomyelitis and Coxsackie viruses in respect to other physical properties, including thermal stability and resistance to inactivation by ether, common antiseptics and other antimicrobial agents.

**Epidemiology.** ECHO viruses have been encountered in many parts of the world, characteristically in the summer and fall seasons, more frequently in children than in adults, and have been recovered more readily from feces than from oropharyngeal swabbings. Some ECHO viruses are commonly present in the human intestinal tract and are found there most frequently among young children from families of relatively low socioeconomic status. A number of ECHO viruses, particularly representatives of types 4, 6 and 9, have been associated with epidemics of

aseptic meningitis in various parts of North America and Europe. Many patients with aseptic meningitis attributable to ECHO virus type 9 exhibit a transitory exanthem. A rubella-like rash and meningeal involvement have been observed during outbreaks with ECHO type 16 virus, but the two manifestations have not been noted in the same patient. In outbreaks of aseptic meningitis attributable to ECHO virus, types 4, 6 and 9, associated cases of mild or inapparent infection were recognized, and presumably many others were undetected. The high attack rate and morbidity in families indicated that infection spread rapidly, probably from person to person. In communicability of infection ECHO viruses are similar to other enteroviruses. Although the ECHO viruses appear to be natural parasites of man, biologically similar enteric viruses have been found in monkeys, cattle and swine.

**Pathology.** Almost no information is available concerning the pathologic changes caused by ECHO viruses. A virus, subsequently identified as ECHO virus type 2, was recovered by Steigman from the spinal cord of a child who died of a disease which clinically and pathologically resembled bulbospinal poliomyelitis.

**Diagnosis.** Infection by an ECHO virus may be suggested by clinical and epidemiologic evidence, but must be confirmed in the laboratory. All the ECHO viruses are cytopathogenic and can be identified by neutralization tests with specific immune serum in cultures of kidney cells from rhesus monkeys. Evidence of infection may be obtained by recovery of the virus from the feces, oropharyngeal swabbings or cerebrospinal fluid, and by demonstration of a related antibody response in the patient's serum. Recovery of virus from the spinal fluid in patients with aseptic meningitis is convincing evidence of an etiologic relation between the agent and the disease. To establish a causal relation between the virus and minor ailments is more difficult.

**Prognosis.** In most instances disease caused by an ECHO virus is self-limited and uncomplicated and progresses rapidly to complete recovery. In cases with involvement of the central nervous system muscular paralysis is an occasional complication. Fatal infection appears to be rare.

**Treatment.** See under Coxsackie virus (p. 527).

**Prophylaxis.** See under Coxsackie virus (p. 527).



## CLINICAL DISORDERS

## ASEPTIC MENINGITIS

A number of ECHO viruses can cause disease with meningeal involvement. Epidemics of aseptic meningitis in separate localities and in different years have been caused by ECHO viruses of types 4, 5, 6, 9 and 16. In individual patients with aseptic meningitis, strains of ECHO viruses, types 4, 5, 6, 9 and 14, have been recovered from cerebrospinal fluid.

In general the clinical features and laboratory findings in patients with aseptic meningitis attributable to an ECHO virus are similar to those in patients infected with a group B Coxsackie virus. There are, however, noteworthy exceptions. The occurrence of muscular weakness and paralysis with associated reflex changes resembling those of paralytic poliomyelitis has been observed in patients infected with a type 2 or a type 6 ECHO virus and suggests that either of these agents may induce neuropathy similar to poliomyelitis in man as well as in monkeys. In many patients with aseptic meningitis attributable to ECHO virus type 9 a fine or blotchy maculopapular erythematous rash is noted, most frequently on the face, during the acute stage of illness. Occasionally tiny ulcerations of the oral mucosa resembling the lesions of herpangina are also seen in infection with some of these viruses, including types 9 and 16. Cervical or generalized lymphadenopathy may be present. ECHO virus type 16 has produced aseptic meningitis in some patients and a rash (Boston exanthem) in others, but both features have not been observed in the same patient. The illness in most patients is self-limited and relatively mild, although the duration and intensity of symptoms are extremely variable.

In patients with aseptic meningitis the blood leukocyte count is usually in the normal range. In infection with types 4 or 6 virus the white cell counts in the cerebrospinal fluid are usually below 500; in cases with type 9 infection they are higher and may exceed 1000. Although polymorphonuclear cells are usually present early in the illness, the cells in type 4 infection may initially be predominantly lymphocytic. The protein content of the fluid is normal or slightly elevated, and the sugar content is normal.

Aseptic meningitis due to an ECHO virus must be distinguished mainly from similar disease resulting from infection by a different virus, especially another virus of the ECHO

group, or a Coxsackie, poliomyelitis or mumps virus. In patients with lymphadenopathy and/or a rash leptospiral infection and infectious mononucleosis have to be considered. The possibility of dual viral infection, especially in patients with muscular weakness or paralysis, must always be kept in mind.

## OTHER ILLNESSES

The role of ECHO viruses in other forms of illness has not been clearly established. The association between ECHO virus type 16 and *Boston exanthem* has been mentioned. This mild disease, affecting mainly children, has clinical similarities to rubella, but can be differentiated by its relatively short incubation period of three to eight days, absence of characteristic lymphadenopathy and a different seasonal incidence. An association between type 18 and possibly other ECHO viruses with diarrhea of infants in the summer months has been noted and an etiologic relationship suggested. As with other minor illnesses, this relationship is difficult to establish with certainty.

EDWARD C. CURNEN

## REFERENCES

*Coxsackie*

- Curnen, E. C.: Human Disease Associated with the Coxsackie Viruses. *Bull. New York Acad. Med.*, 26:335, 1950.
- Dalldorf, G., Melnick, J. L., and Curnen, E. C.: The Coxsackie Group; in Rivers and Horsfall, ed.: *Viral and Rickettsial Infections of Man*. 3rd ed. Philadelphia, J. B. Lippincott Company, 1958.
- Parrott, R. H.: The Clinical Importance of Group A Coxsackie Viruses. *Ann. New York Acad. Sc.*, 67:230, 1957.
- Rhodes, A. J., and Beale, A. J.: Aseptic Meningitis: Evidence for the Etiologic Role of Coxsackie B and "Orphan" Viruses. *Ann. New York Acad. Sc.*, 67:212, 1957.

*ECHO*

- Committee on the Enteroviruses, National Foundation for Infantile Paralysis: The Enteroviruses. *Am. J. Pub. Health*, 47:1556, 1957.
- Melnick, J., and Sabin, A. B.: The ECHO Virus Group; in Rivers and Horsfall, ed.: *Viral and Rickettsial Infections of Man*. 3rd ed. Philadelphia, J. B. Lippincott Company, 1958.

## POLIOMYELITIS

Poliomyelitis is an acute viral infection occurring sporadically and in epidemics and characterized by varying degrees of neuronal injury with special localization in the anterior horns and the motor nuclei of the brain stem.

There is a wide range in the clinical manifestations from inapparent infection to complete flaccid paralysis of many muscle groups with the possibility of death from asphyxia and involvement of vital centers in the brain stem.

**History.** Epidemics of paralytic poliomyelitis have been described only in the past century, but there is some evidence that sporadic cases were recognized earlier. The first reference in the medical literature appeared in 1789 (Underwood in England). During the nineteenth century the disease was regarded as a rare affliction of infants, and a small group of isolated cases were accumulated by Heine in 1840 in Germany. The *epidemic* form was not clearly described until 1890 in Europe (Medin in Stockholm) and 1894 in America (Caverly in Vermont). In 1908 Landsteiner produced paralysis in the monkey by intraperitoneal injection of human spinal cord tissue from fatal cases, and the filtrable nature of the virus was established in 1910. A crucial observation was made in 1931 by Burnet and Macnamara that not all poliomyelitis virus strains are immunologically alike. The most significant contribution has been the cultivation of the virus in tissue cultures by Enders, Weller and Robbins. Their findings opened many conceptual and practical areas previously closed by the prevailing notion of the strict neurotropism of poliovirus. Vaccine production has been the most widely heralded of these.

**Etiology.** Three serologic types of virus have been isolated: type 1 (Brunhilde), type 2 (Lansing) and type 3 (Leon). To date *large epidemics* of paralytic poliomyelitis have been caused by type 1, smaller epidemics by type 3, and isolated cases by type 2. Two or more of the types have been recovered during an epidemic, although type 1 has predominated in mixed outbreaks. Many people have been *infected* by all three types as reflected by trivalent antibodies in their serum. The occurrence of two attacks of clinical disease each due to a different serologic type of virus is rare but documented.

Poliovirus is small and hardy and resists many chemicals, including sulfonamides, antibiotics, ether, phenol and glycerin. On electron micrographs the virus appears as a spherical particle. The virus is destroyed by desiccation, strong oxidants such as hydrogen peroxide and potassium permanganate and by the chlorine concentrations generally used in urban water supplies. Under suitable conditions formalin or ultraviolet light may extinguish the infectivity of the virus without abolishing its antigenic capacity, an important point in vaccine research.

Man appears to be the sole virus reservoir in nature, although virus may be recovered from sewage and flies. Until recently the virus

was experimentally demonstrable only by inoculating primates; the response of the chimpanzee is believed to be the closest to that of the natural infection in man. Virus can now be demonstrated in cultures of primate tissues.

For a time infection in rodents could be produced only with strains of the type 2 group, but now members of the other types are capable of infecting them, and one member of the type 2 family has been adapted to grow in the chick embryo. These findings illustrate an important concept, namely, that a strain of virus while retaining its family denomination may undergo changes in pathogenic properties even under natural conditions. Certain strains of poliovirus are more pathogenic for man and monkey than other strains of the same type, a fact which may account for some of the variations in severity in patients and in epidemics.

Recent evidence suggests that ECHO (enteric cytopathogenic human orphan) and Coxsackie viruses may produce a clinical picture indistinguishable from that of nonparalytic and even paralytic poliomyelitis. ECHO and Coxsackie viruses and poliovirus are now grouped together as *enteroviruses*.

**Poliomyelitic infection versus poliomyelitic disease.** Human infection with poliovirus is much more common than poliomyelitic disease. Certain properties of the viruses which cause infection are known from laboratory studies. Less clear are the factors of host-virus relationships which determine the varying clinical consequences of poliomyelitis infection.

**Epidemiology and Public Health Measures.** Epidemics of paralytic disease are seasonal, occurring mainly in the summer and early fall months in the temperate zones, which are the areas most afflicted, e.g., United States, Canada, the United Kingdom, Scandinavian countries, Australia and New Zealand. Significant epidemics have occurred, however, in the Arctic and on tropical islands.

Outbreaks of paralytic poliomyelitis have occurred in winter months in temperate zones. Mild unrecognized cases and their contacts maintain a continuous pool of virus throughout the year. Transmission is largely by personal contact through unrecognized alimentary contamination. Flies, sewage, drinking water, food and milk are potential vectors of infection, but their role appears small. Virus may be recovered from pharyngeal swabs of patients and their contacts for a short time, but the role of pharyngeal drop-



lets in transmission of infection is not clear. It is unwise to assume spread of virus by a single route, even though the predominant one is the oral-fecal circuit.

There is considerable variation in community control measures. The clinical disease when recognized is reportable in most places, usually in two categories, as paralytic and nonparalytic infections. Isolation is recommended by the American Public Health Association for one week from the date of onset or for the duration of fever, if that is longer. Although strict quarantine in urban areas is frustrating and seldom practiced, susceptibles should be kept from known cases and household contacts for two weeks. It has been suggested that poliovirus is not always broadcast widely. Control of personal contacts may therefore be an important factor in limiting spread of virus, especially if vaccination is successful in reducing the incidence of poliomyelitis. The greatest communicability occurs during the latter part of the incubation period and the first week of the acute illness.

The incubation period is usually seven to ten days, but there are extremes of three to thirty-five days. During epidemics it is wise to keep children with unexplained febrile illnesses in bed pending diagnosis.

During epidemics elective operations should be postponed, particularly those of the nose and throat and teeth. Children subjected to tonsillectomy during an outbreak suffer the bulbar type of poliomyelitis approximately ten times as often as the unoperated. If a crucial indication for tonsillectomy arises during an epidemic, it may be wise to administer gamma globulin prior to operation. Tonsillectomy done *at any time* substantially increases the possibility of the bulbar form of the disease should poliomyelitis be contracted in later years.

Evidence indicates that intramuscular injections of certain irritating substances such as alum-precipitated combined antigens of pertussis and diphtheria, given when poliomyelitis virus is widespread, may result in paralysis of the injected limb. Some health officers postpone all but urgent inoculations during epidemics of poliomyelitis.

Although much attention is frequently devoted to environmental sanitation, such efforts do not appear to influence the course of an established epidemic. Swimming pools are often held under suspicion as a locus of infection in view of the opportunities for pharyngeal-fecal contamination. The aggrega-

tion of susceptible children with intimate contact in such places may be important, as may be the tendency for chilling and fatigue from unsupervised play activity.

It is safe to treat patients with poliomyelitis in general hospitals, provided precautions are observed as for typhoid fever.

**Immunity. *Passive immunity.*** Relatively small amounts of injected antibody protect monkeys against oral and intramuscular inoculations of virus. Since many adults have had unrecognized poliomyelitic infections, pools of adult serum (gamma globulin fraction) contain antibody to the three types of virus. A relatively small amount of antibody is capable of preventing or lessening the extent of paralysis. It is presumed that the injected antibody neutralizes the virus during the stage of viremia (see Fig. 160). The practical application of gamma globulin prophylaxis to exposed persons carries many uncertainties and has largely been abandoned.

***Active immunity—naturally acquired.*** The presence of type-specific poliomyelitis antibodies in the serum of many persons with no history of poliomyelitic disease is evidence of the frequent occurrence of nonapparent infections. Poliomyelitis antibody has been found in varying percentages of sampled populations in all parts of the world. Where the attack rate of manifest paralytic poliomyelitis is low in countries with poor sanitation, it is assumed that oral entry of virus occurs early in life, while the infant still has protection from the transplacental passive antibody of an immune mother, and active or passive-active immunity is acquired. In countries with good sanitation there has been a shifting age pattern, infectivity rates being highest in the five- to nine-year groups.

***Active immunity—artificially acquired.*** There are four possible approaches to this phase of control of poliomyelitis: (1) A killed virus vaccine. Formalinized tissue-culture vaccine (Salk) is available. Such a vaccine should be as free as possible of extraneous sensitizing materials. (2) A living, stable, laboratory-developed nonvirulent mutant strain of virus for oral or intramuscular administration. This approach has been the object of important studies by Koprowski and by Sabin. (3) A live virus under protective cover of injected antibody (gamma globulin). There are no examples of this approach in other human viral infections; it has been used successfully in veterinary medicine. (4) Discovery of a virus in the animal kingdom which is antigenically closely related but not

dangerous for man; an example is the original cowpox virus of Jenner.

**SALK-TYPE VACCINES.** The best available and most widely tested vaccine is a formalin-treated monkey-kidney tissue culture filtrate containing the three serotypes of poliovirus. Current practice is to give three injections of 1 ml., respectively; the first two with an interval of one month, and the third seven months after the second. The duration of effective protection and the required frequency of booster injections are under study, as is the question of improving the effectiveness of the vaccine without lessening its safety. The "Cutter incident" in 1954 with the transmission of poliomyelitis from certain batches of vaccine has not recurred. The *Mahoney* strain is used as the prototype 1 virus strain in American and Canadian vaccines; the *Brunenders* strain, which appears devoid of *Mahoney's* property of peripheral invasiveness, is used in the British vaccine.

**Pathogenesis.** Much of the knowledge of the pathogenesis of poliomyelitis has been obtained from experimental disease in other primates. When virus is *fed* to chimpanzees, they seldom become paralyzed. The usual response is the brief appearance of virus in the blood some days later, then in the stools, where it may remain for some weeks, and finally immunity as detected by the development of type-specific antibody. If autopsied, those chimpanzees which had no apparent disease have scattered poliomyelitic lesions in their central nervous systems.

In man the virus generally enters the body through the oropharyngeal route and multiplies in sites unknown, probably in the alimentary tract and in its related lymph nodes and other reticuloendothelial structures. Type-specific antibody is formed; if the response is of sufficient speed and magnitude, the virus particles are neutralized, no clinical disease occurs, and immunity to that type of poliovirus ensues. In this infectivity-antibody contest the virus may proliferate and become invasive before sufficient antibody is formed.

If virus gains direct access to nerve structures or to the blood-lymphatic system, direct infection of the central nervous system may occur. Thus bulbar poliomyelitis occurring soon after tonsillectomy may be due to virus gaining direct access to the medulla through several cranial nerve filaments. Subcutaneously injected virus may follow nerve pathways and cause paralytic consequences initially in the injected limb, as it did in 1935 with the trial of incompletely inactivated

vaccines and in the "Cutter incident" of 1954. There is no evidence that biting insects "inject" poliovirus into man, as they do with the virus of yellow fever.

Factors other than humoral antibody may affect the outcome of the contest between the virus and its human host. These host factors operate at the cellular level, affecting the rate and perhaps the sites of virus multiplication. The occurrence of paralysis has been high in certain families even when not living in the same epidemic area. The role of constitutional physique and nutrition is not certain, but paralytic attacks seem to occur in the robust active child perhaps even more than in the marantic one. The influence of hormonal factors and of stress is evidenced by such observations as (1) the incidence of paralytic disease being higher in pregnant women than in others of similar age; (2) the increased clinical severity of disease with increasing age; (3) the deleterious clinical effect of such stresses as muscular exhaustion, chilling and surgical procedures once the virus has entered the body; and (4) cortisone making certain forms of experimental poliomyelitis more severe.

Clinically the process may terminate at any of the stages shown in Figure 160.

Primary resistance to poliomyelitis apparently depends upon the presence of type-specific neutralizing antibodies. Serologic tests for determining individual antibody level are not readily available, nor is there a skin test for detecting immunity.

**Pathology. Neuropathology.** Unlike most viral infections of the central nervous system, the neuropathology of poliomyelitis is usually pathognomonic; only certain cells and areas of the neuraxis are susceptible to the virus. There is little histologic evidence of meningeal reaction.

Neuronal damage is due directly to virus multiplication. The clinical picture is dependent upon the number and location of involved neurons. The earliest changes consist in lysis of Nissl bodies in the cytoplasm, margination of the chromatin, acidophilic necrosis of the neuron followed by neuronal death, and finally neuronophagia, i.e., invasion by scavenger cells, including polymorphonuclears, plasma cells, lymphocytes and macrophages. Neighboring small vessels reveal perivascular cuffing. Some interstitial glial infiltration occurs, but edema is not an important feature.

Not all affected neurons are killed. The injury may be reversible, and restoration of



function may occur within three to four weeks after onset.

Histologic sections generally reveal more widespread lesions than would be estimated from the clinical findings. Considerable destruction of scattered neurons occurs without clinical disability. Each functionally related neuronal group has a margin of safety which must be exceeded before dysfunction of a vital center and paralysis appear.

The regions in which neuronal lesions occur are (1) spinal cord (anterior horn cells chiefly; to a less degree the intermediate and dorsal horn and dorsal root ganglia); (2) medulla (vestibular nuclei, cranial nerve nuclei and the reticular formation which contains the vital centers); (3) cerebellum (nuclei in the roof and vermis only); (4) midbrain (chiefly the gray matter, but also the substantia nigra and occasionally the red nucleus); (5) thalamus and hypothalamus; (6) the pallidum; and (7) cerebral cortex (motor cortex). The virus spares the following areas, although they are invaded by the viruses of the arthropod-borne encephalitides: (1) the entire cerebral cortex *except* the motor area, (2) the cerebellum *except* for the vermis and deep midline nuclei, and (3) the white matter of the spinal cord. It is the *distribution* of lesions which permits a histologic diagnosis of poliomyelitis.

In relating the neuronal changes to clinical findings the most obvious relationship is the *flaccid paralysis* (cranial and peripheral). The ensuing muscular atrophy is due to denervation plus the atrophy of disuse. The pain, spasticity, nuchal and spinal rigidity and hypertonia of early illness are probably due to lesions of the brain stem, spinal ganglia and posterior columns. The vestibular nuclear lesions may account for the vomiting. When certain vital centers of the medulla are sufficiently involved, dysfunction is reflected clinically by respiratory arrhythmias, blood pressure and vasomotor fluctuations, cardiac arrhythmias, and the like.

**Extraneural pathology.** Although the virus seldom causes lesions outside the central nervous system, secondary lesions do occur elsewhere. The neurophysiologic mechanisms governing other structures are subtle and far reaching. When nervous control of ventilation is disturbed, secondary bronchopulmonary changes occur, viz., aspiration pneumonia, atelectasis and purulent bronchitis, owing to the inability to cough and to interference with thoracic movements. The cardiovascular changes may result in hypertension,

cardiac failure and pulmonary edema. Long-term immobilization leads to negative nitrogen and calcium balances with urinary lithiasis, renal failure, hypertension with encephalopathy and convulsions; thrombophlebitis and pulmonary embolism are less common than might be expected. Treatment itself may cause untoward complications, such as urinary tract infection from improper catheterizations, decubitus ulcers and psychotic disturbances; the virus does not affect the intellectual structures of the cerebral cortex. Ulcerations in the alimentary tract may result in serious bleeding and occasional perforation. Respiratory failure results in anoxic changes and respiratory acidosis.

**Clinical Manifestations.** The diagnosis of acute poliomyelitis rests upon clinical grounds; there is no generally available diagnostic laboratory test. Careful history, close examination of the unclothed patient, and recollection of conditions which may mimic poliomyelitis will obviate most diagnostic pitfalls.

When a susceptible person has had effective contact with poliovirus, one of the following responses may occur: (1) *silent infection*, i.e., asymptomatic and inapparent; (2) *abortive poliomyelitis*; (3) *nonparalytic poliomyelitis*; (4) *paralytic poliomyelitis*. One response may blend into a more severe form. This feature may result in a biphasic course ushered in by a minor febrile illness, a symptom-free interlude of a few days succeeded by a major episode (Fig. 160). Evidence suggests that the order of frequency of the four types of response to poliovirus is that just enumerated, the paralytic response being the least common. Each type of response may result in durable immunity to the immunologic type of virus involved.

**Abortive poliomyelitis.** This presumptive clinical diagnosis is applicable only during obvious poliomyelitis outbreaks, especially in patients known to have been exposed to a clearly recognizable form of the disease. A brief febrile illness occurs, with one or more of the following symptoms: malaise, anorexia, nausea, vomiting, headache, sore throat, constipation and unlocalized abdominal pain. The following are *uncommon* in abortive poliomyelitis: coryza, cough, pharyngeal exudate, diarrhea, localized abdominal tenderness and rigidity. A definitive diagnosis without tissue culture studies is impossible, since the findings are those which precede or accompany a variety of acute disorders. The fever seldom exceeds 103° F., and examina-

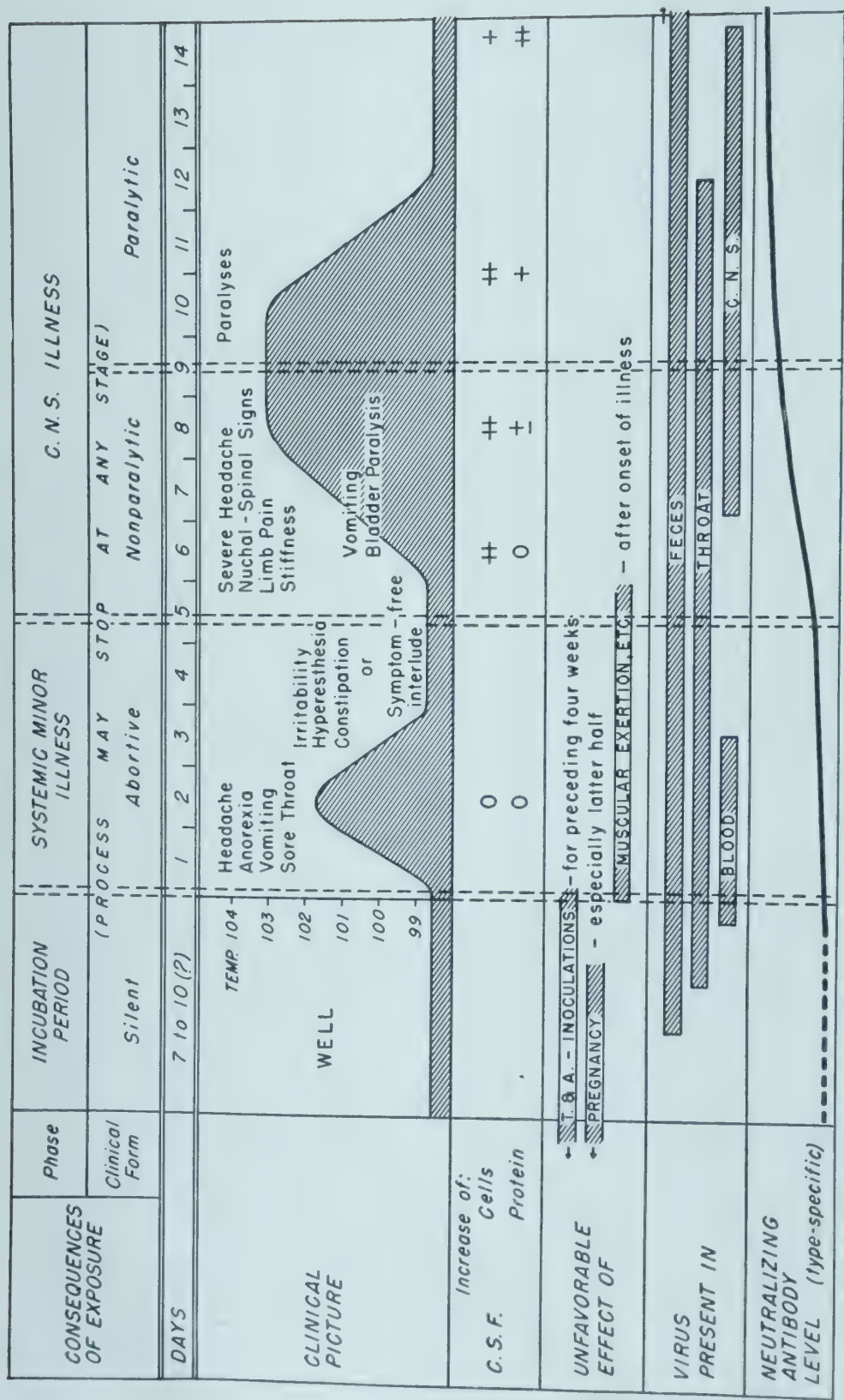


FIG. 160. Schematic representation of major findings in the typical course of clinically biphasic poliomyelitis, which occurs frequently in children, but less so in adults, who tend to have an insidious monophasic course. The evolution of the disease is often compressed into fewer days than shown diagrammatically. Note that virus is present in feces and in throat swabs for relatively long periods, but the viremia period is short. Virus appears in the central nervous system prior to paralysis and tends to disappear in about 10 to 14 days, yet continues to be excreted in the feces. Antibody is present at onset of symptoms and continues to rise. Muscular fatigue does not affect the course adversely unless continued after onset of the minor illness phase, but the influences of tonsillectomy, inoculations and pregnancy are exerted earlier.



tion of the pharynx shows little despite the frequent complaint of sore throat.

During poliomyelitis outbreaks patients presumed to have the abortive clinical form should have complete rest for about a week after defervescence and should be examined carefully about two months later to exclude muscular involvement previously undetected.

**Nonparalytic poliomyelitis.** The subjective symptoms are those enumerated for abortive poliomyelitis, except that headache, nausea and vomiting are more intense, and there is soreness and stiffness of the posterior muscles of the neck, trunk and limbs. Fleeting paralysis of the bladder is not uncommon, and constipation is frequent. Approximately two thirds of the children have a short symptom-free interlude between the first phase (minor illness) and the second phase (central nervous system or major illness) (Fig. 160). This two-phase course is less common in adults, in whom the evolution of symptoms is more insidious. Nuchal and spinal rigidity is a necessity for the diagnosis of nonparalytic poliomyelitis during the second phase.

**DETECTION OF NUCHAL-SPINAL SIGNS.** The signs are first sought by *active tests*. The child is asked to sit up unassisted. If this causes undue effort, if the knees flex upward and he writhes a bit from side to side in sitting up and then places his hands on the bed behind him in the *tripod* supporting position, there is unmistakable spinal rigidity (Fig. 161). While he is still sitting, ask him to flex his chin to his chest and observe whether nuchal rigidity is apparent. Then from the supine position, holding the knees down gently, ask him to sit up and *kiss his knees* (Fig. 162). If the knees draw up sharply or if the maneuver cannot be adequately completed, there is stiffness of the spine due to muscle spasm.

If still uncertain, the *passive tests* should be applied. Gentle forward flexion of the occiput and neck will elicit nuchal rigidity, which may antedate spinal rigidity. Kernig's and Brudzinski's signs are sought.

Next one looks for *head drop* by placing the hands under the patient's shoulders and raising the trunk (Fig. 163). Normally the head follows the plane of the trunk, but in poliomyelitis it often falls backward limply. The frequency of the head-drop sign even in nonparalytic poliomyelitis with no subsequent residuals indicates that it is not due to true paresis of the neck flexors.

In struggling infants it may be difficult to distinguish voluntary resistance from clini-

cally important involuntary nuchal rigidity. One may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly (Fig. 164). Nuchal rigidity that persists during this maneuver may be interpreted as involuntary. When not closed, the anterior fontanel may be tense or bulging as in meningitis.

In poliomyelitis the nuchal rigidity detected in the supine position (Fig. 165, A) often disappears when the patient is turned over. The nuchal rigidity associated with purulent meningitis generally persists in either position (Fig. 165, B). This paradoxical sign, though helpful, is not pathognomonic.

**SUPERFICIAL AND DEEP REFLEXES.** In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or depressed, may *precede weakness* by twelve to twenty-four hours; hence it is important to detect them, especially in nonparalytic patients managed at home.

The *superficial* reflexes, i.e., cremasteric, abdominals, and the reflexes of the spinal and gluteal muscles, are usually the first to be diminished. The status of the spinal and gluteal reflexes helps in forecasting paralysis; they are elicited by tapping segmentally downward on each side of the spine and buttocks. These reflexes may disappear even before the abdominal and cremasteric ones.

Changes in the *deep* tendon reflexes, whether exaggerated or depressed, generally occur eight to twenty-four hours after depression of superficial reflexes and indicate impending paresis of the extremities. There is absence of tendon reflexes with paralysis. Objective evidence of sensory defects 'does not occur in poliomyelitis.

**DIFFERENTIAL DIAGNOSIS.** A wide variety of diseases must be considered in an alert, febrile patient with meningeal signs whose muscle power and reflexes appear intact. In such a patient, when the cerebrospinal fluid reveals pleocytosis, no organisms and a normal sugar level, the differential diagnosis must include all causes of the *aseptic meningitis syndrome*, of viral, leptospiral, fungus, protozoan, helminth or neoplastic etiology (p. 544). Serologic procedures may be helpful in excluding many of these diseases. The diagnosis of nonparalytic poliomyelitis is made by exclusion of other conditions and the epidemiologic probability.

In their early stages *tuberculous* and *purulent meningitis* may simulate nonparalytic



FIG. 161. Tripod sign: characteristic position associated with stiffness of the spine.



FIG. 162. Kiss-the-knee test: ability to complete the maneuver only by flexing the knee. Note tense appearance of the hamstrings.



FIG. 163. Head-drop sign: the head fails to continue in the plane of the body when the shoulders are elevated. This child had nonparalytic poliomyelitis. Tripod and head-drop signs appear in nonparalytic and paralytic poliomyelitis.



FIG. 164. Testing nuchal rigidity in uncooperative, struggling infant: Place the shoulders at the edge of the table, supporting the occiput manually. Flex anteriorly. Only true involuntary rigidity persists.



A



B

FIG. 165. Supine versus prone postural test for nuchal rigidity in poliomyelitis. A. Nuchal rigidity elicited in conventional supine position. B. In prone position nuchal rigidity disappears in poliomyelitis, but generally persists in pyogenic meningitis. (From A. J. Steigman: Diagnosis and General Care of Acute Poliomyelitis. *Pediat. Clin. North America*, Vol. I, No. 1A.)

poliomyelitis. A lumbar puncture should be done; in addition to bacterial smears and cultures and a cell count, particular attention should be paid to the sugar content, since it is not depressed in the viral infections. Headache, fever and stiffness of the neck and back

with tender extremities may occur in *acute rheumatic fever*, *rheumatoid arthritis* and in *serum sickness*; the cerebrospinal fluid is normal, however, as it also is in the *meningismus* which may accompany the early stages of pneumonia, dysentery, typhoid,



pyelitis and other infections. *Acute tonsillitis* and other conditions associated with cervical adenitis may cause a child to hold his head and neck immobile; this should not be confused with true nuchal rigidity.

**Paralytic poliomyelitis.** The manifestations are those enumerated for nonparalytic poliomyelitis together with weakness of one or more muscle groups, either skeletal or cranial. Symptoms of abortive poliomyelitis may be followed by a symptom-free interlude of several days and then a recurrence of symptoms, culminating in paralysis (Fig. 160). Bladder paralysis of one to three days' duration occurs in approximately 20 per cent of patients, and bowel atony is common, occasionally to the point of paralytic ileus. In infants muscular paralysis may be the first evidence noted.

**CLINICAL CLASSIFICATION.** The distribution of clinical paralysis is characteristically spotty and haphazard. To detect mild muscular weakness it is often necessary to apply gentle resistance in opposition to the muscle group being tested.

**SPINAL FORM.** There is weakness of the neck, abdomen, trunk, diaphragm, thorax or extremities.

**BULBAR FORM.** There is weakness in the motor distribution of one or more *cranial nerves* with or without dysfunction of the *vital centers of respiration and circulation*.

**BULBOSPINAL FORM.** Components of the preceding forms occur together.

**ENCEPHALITIC FORM.** In this form there are irritability, disorientation, drowsiness and coarse tremors not explained by inadequate ventilation. Even during poliomyelitis epidemics this group can be recognized *only* if some peripheral or cranial nerve *paralysis* coexists or ensues. Hypoxia, due to inadequate ventilation from respiratory insufficiency, may itself produce disorientation.

**DIFFERENTIAL DIAGNOSIS. CONDITIONS CAUSING MUSCULAR WEAKNESS.** (1) *Infectious neuronitis* (*Guillain-Barré syndrome*) is the most common and difficult differential problem in this group. Generally the fever, headache and meningeal signs are less marked; characteristically there are few cells, but elevated globulin content in the cerebrospinal fluid. Paralysis is characteristically symmetrical in distribution. Sensory changes and/or pyramidal tract signs are common, but are absent in poliomyelitis. (2) *Peripheral neuritis*—postinjectional, toxic (lead, avitaminosis, and so forth), paralytic cranial herpes zoster, postdiphtheritic neuropathies

—is excluded by history, sensory examination and related findings. (3) Arthropod-borne viral *encephalitis*, *rabies* and *tetanus* have been confused with bulbar poliomyelitis. (4) *Botulism* may closely simulate bulbar poliomyelitis; nuchal-spinal rigidity and pleocytosis are absent. (5) *Demyelinating types of encephalomyelitis* are associated with or follow the exanthems and other infections or occur as an untoward sequel of antirabies vaccination. (6) *Tick-bite paralysis* is uncommon; there is an absence of meningeal signs, and removal of the tick is followed by swift recovery. (7) *Neoplasms* originating in and around the spinal cord may rarely have a fairly abrupt onset. (8) *Familial periodic paralysis*, *myasthenia gravis* and *acute porphyria* are uncommon causes of weakness. (9) *Hysteria* and *malingering* are rare in children.

**CONDITIONS CAUSING PSEUDOPARALYSIS.** In these nuchal-spinal rigidity and pleocytosis are absent. (1) *Unrecognized trauma* as from contusions, sprains, fractures and epiphyseal separation is a common cause of diagnostic confusion. (2) *Nonspecific (toxic) synovitis* produces a limp, usually unilaterally; the hip and the knee are the most common sites. There may be low grade fever for several days. (3) *Acute osteomyelitis* has a more septic course; there is polymorpholeukocytosis, with localized signs, positive blood culture and later roentgenographic changes. (4) In *acute rheumatic fever* the clinical pattern is usually diagnostic. (5) *Scurvy* is revealed by history of inadequate intake of vitamin C and by roentgenographic changes in the bones. (6) *Congenital syphilitic osteomyelitis* of the acute painful type is found only in early infancy; serologic tests are indicated.

**Bulbar and respiratory forms of poliomyelitis.** A number of components acting together may produce insufficiency of ventilation (see Table 76). Adequate ventilation requires (1) intact neural mechanisms, including the rhythmic "drive" from the respiratory centers, and the neuromuscular integrity of the diaphragm and the intercostal muscles, (2) an open airway from the nostrils or lips to the alveoli, and (3) normal hemodynamics, especially of the pulmonary circulation.

The pathology of poliomyelitis is such that any or all three of these factors may become involved clinically. Although it may be convenient to consider the three factors separately, there is close interplay physiologically.

**Table 76. Common Sources of Hypoxia and Hypercapnia in Poliomyelitis**

1. Cranial nerves IX to XII involved, with
  - (a) Pharyngeal paralysis and pooling of secretions
  - (b) Laryngeal involvement—either spasm of laryngeal muscles or paralysis of vocal cords
  - (c) Lingual paralysis
  - (d) Tracheal accumulation of secretions due to inability to cough resulting in aspiration of vomitus
2. Vital center involvement with
  - (a) Inefficient, irregular respiration
  - (b) Cardiovascular disturbance
  - (c) Hyperpyrexia causing increased oxygen consumption
3. Cervical and spinal cord involvement causing paresis of the primary and accessory muscles of respiration
4. Pulmonary complications, viz., pneumonia, atelectasis, edema
5. Contributory factors
  - (a) Panic
  - (b) Gastric dilatation
  - (c) Sedation
  - (d) Inadequate equipment, viz., small-bore tracheotomy tubes, respirator settings, and the like

Thus obstruction to airflow due to paralysis of pharyngeal muscles with accumulated secretions may result in hypercapnia, which may stimulate the respiratory center to speed up its rate, but that particular vital center may be so diseased as to be unresponsive or may be responsive and discharge impulses at an increased rate and depth, but with incomplete response from the effector organs (the muscles of respiration) whose innervation in the cervical and thoracic spinal cord may be involved.

The most serious biochemical changes are the hypoxia and the hypercapnia. These states produce effects on many other systems, such as the cardiovascularrenal.

Respiratory insufficiency should be detected as early as possible in order to diminish its widespread effects. The objective of its management is to maintain normal levels of oxygen and of carbon dioxide in the blood; this requires the proper assessment of the factors contributing most to ventilation failure at any given time; since the situation may shift rapidly, continued clinical analysis is essential.

Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort that normal alveolar ventilation is maintained. In fact, at the beginning of respiratory muscular involvement, the in-

creased effort (associated with anxiety and fear) may actually produce overventilation, resulting in respiratory alkalosis. Such effort is fatiguing and soon leads to respiratory failure.

For clarity certain terms will be defined: (1) *Pure spinal poliomyelitis with respiratory insufficiency* refers to patients whose respiratory muscles (chiefly the diaphragm and intercostals) develop tightness, weakness or paralysis without discernible clinical involvement of cranial nerves or vital centers. The cervical and thoracic spinal cord segments are chiefly involved. (2) *Pure bulbar poliomyelitis* refers to patients with paralysis of motor cranial nerve nuclei with or without involvement of the vital centers which control respiration, circulation and body temperature. Involvement of the ninth, tenth and twelfth cranial nerves is most important, since there is paralysis of the pharynx, tongue and larynx with resultant obstruction of the airway. (3) *Bulbospinal poliomyelitis with respiratory insufficiency* refers to patients with involvement of the respiratory muscles and with coexisting bulbar paralysis.

The clinical findings resulting from involvement of the *respiratory muscles* are (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, "breathless" sentences, which can be demonstrated by asking the patient to count numbers serially; (3) increased respiratory rate; (4) movement of the alae nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements due to diaphragmatic immobility from spasm or weakness of one or both leaves; (7) relative immobility of the intercostal spaces, which may be segmental, unilateral or bilateral. When the upper extremities are weak, and especially when deltoid paralysis occurs, it is well to beware of impending respiratory paralysis, since the phrenic nerve nuclei are in adjacent areas of the spinal cord. In order to bring out minor degrees of paresis, splint the abdominal muscles manually and observe the patient's capacity for thoracic breathing. By lightly splinting the thoracic cage manually, the effectiveness of diaphragmatic movement may be assessed.

The clinical findings of *bulbar poliomyelitis* with respiratory difficulty (other than paralysis of extraocular, facial and masticatory muscles) include (1) nasal twang to the voice or cry, due to palatal and pharyngeal weakness—hard-consonant words such



as "cookie" or "candy" bring this out best; (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx and in partial immobility on holding the larynx lightly and asking the patient to swallow. (3) Accumulated pharyngeal secretions may cause irregular respiration, since each inspiration must be "planned" and cannot be "subconscious" in view of the risk of aspirating; the respirations may thus appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness. (4) Effective coughing is impossible, and constant fatiguing efforts are made to clear the throat. (5) Nasal regurgitation of saliva and fluids due to palatal paralysis with inability to separate the oropharynx from the nasopharynx during swallowing. (6) Deviation of the palate, uvula and/or the tongue. (7) Involvement of vital centers as reflected by irregularity in rate, depth and rhythm of respiration, by cardiovascular alterations which include blood pressure changes, especially upwards, alternate flushing and mottling of the skin, and cardiac arrhythmias; and by rapid changes in body temperature. (8) Paralysis of one or both vocal cords causing hoarseness, aphonia and ultimately asphyxia unless recognized by laryngoscopy and managed by tracheotomy immediately. (9) The "rope sign," an acute angulation between the chin and larynx, due to weakness of the hyoid muscles. The hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet.

**Lumbar puncture in poliomyelitis.** This procedure has diagnostic but not prognostic or therapeutic value. In *manifest* cases of poliomyelitis it is not necessary.

Although there are generally less than 500 leukocytes per cubic millimeter, the count may be higher, and rarely there may be no cellular increase. Early the cells are predominantly polymorphonuclear, but they soon become predominantly lymphocytic and decrease to normal numbers as early as ten to fourteen days after the onset. Absence of organisms on smear and culture and normal to elevated sugar content support the diagnosis of poliomyelitis. The protein content in the early stages is normal (up to 40 mg. per 100 ml.) or slightly elevated. Within two to three weeks after onset the pleocytosis diminishes, but the protein content frequently rises to as high as 300 mg. per 100 ml.

**Complications. Gastrointestinal tract.** Striking complications arise occasionally, including melena, which may be severe enough

to require transfusion and is due to single or multiple superficial erosions. Gastrointestinal perforation is rare. Acute gastric dilatation may occur abruptly during the acute or convalescent stage, causing further embarrassment of respiration; immediate gastric aspiration and external application of ice bags are indicated.

**Cardiovascular system.** Mild hypertension of a few days' or weeks' duration is common in the acute stage, probably related to lesions of the vasoregulatory centers in the medulla and to underventilation. Hypertension may appear in the later stages, owing to the protracted immobilization with resulting hypercalcemia, nephrocalcinosis and associated vascular lesions. Dimness of vision, headache and a lightheaded feeling in association with hypertension should be regarded as premonitory of a frank convulsion. Barbiturates, Dilantin or magnesium sulfate therapy is indicated, and a program favoring increased mobilization should be instituted.

Abrupt hypotension rarely occurs and can be controlled only by immediate high pressure intra-arterial or intravenous infusion.

Cardiac arrhythmias are uncommon and vary from unexplained tachycardias, which occasionally yield to digitalization, to a state of abrupt cardiac standstill, for which immediate thoracotomy and manual cardiac massage are indicated.

Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. It should be managed as an acute emergency with autonomic blocking agents for rapid reduction of blood pressure, and inhalation of oxygen bubbled through ethyl alcohol or liquid silicon for an anti-foaming effect.

Electrocardiographic abnormalities indicative of myocarditis are not rare, and varying degrees of histologic changes are observed in fatal cases. Pulmonary embolism is uncommon despite the immobilization.

**Urinary tract.** The transitory paralysis of the bladder in the acute stage has been mentioned. Skeletal decalcification begins soon after immobilization and results in hypercalciuria, which in turn predisposes to calculi, especially when urinary stasis and infection are present together. High fluid intake, a low calcium diet and administration of aluminum gels, hyaluronidase and aspirin have been suggested as preventive measures. A regimen of early active mobilization is desirable.

**Prognosis.** Over-all mortality rates are influenced greatly by the percentage of bulbo-

respiratory cases in any epidemic and by the completeness of reporting nonparalytic cases. With present methods of therapy the overall mortality in large urban epidemics in the United States approximates 5 to 7 per cent. Most deaths occur within the first two weeks after onset. Case fatality rates and the degree of disability appear to be greater after the age of puberty.

Prognosticating the degree of ultimate disability is complex. In general, the more extensive the paralysis in the first ten days of illness, the more severe will be the ultimate disability. Unexpected improvement may appear soon after defervescence and again about six weeks after the onset, a time which corresponds to functional restoration of temporarily inactive neurons. The degree of functional recovery depends also upon the adequacy and promptness of therapy as related to proper body positioning, active motion, use of assistive devices and, of great importance, the psychologic motivation to return to as full and normal a life as possible.

**Treatment.** The broad principles of management are to allay fear, to minimize ensuing skeletal deformities, to anticipate and meet complications in addition to the neuromusculoskeletal ones and to prepare the child and family for the prolonged treatment which may be required and for the permanent disability, if this seems likely. A highly individualized approach with cheerfulness, optimism and candor is of extreme importance.

Patients with the *abortive, nonparalytic* and mildly *paralytic* forms may be treated at home. No antibiotics are effective against poliovirus, and injections of human immune globulin are believed to be ineffective if given after the onset of illness.

For the *abortive* form simple analgesics, sedatives, an attractive diet and bed rest until the child's temperature is normal for several days suffice. Avoidance of exertion for the ensuing two weeks is desirable, and there should be a careful neuromusculoskeletal examination two months later to search for any minor involvement.

Treatment for the *nonparalytic* form is similar to that for the abortive one, relief being indicated in particular for the discomfort of muscle tightness and spasm of the neck, trunk and extremities. Analgesics alone are not as effective as when combined with the application of hot packs for fifteen to thirty minutes every two to four hours. Dry heat as by infra-red lamp is simpler but less

effective in relieving discomfort. Hot tub baths are sometimes useful. A firm bed is desirable and is improvised at home by placing table-leaves or a sheet of plywood beneath the mattress. A footboard should be used to keep the feet at a right angle with the legs. Muscular discomfort and spasm may continue for some weeks even in the nonparalytic form, necessitating hot packs and gentle physical therapy. Such patients should be carefully examined, preferably by a physiatrist or orthopedist, two months after apparent recovery in order to detect minor residuals which might cause postural problems of the spine and feet in later years.

Most patients with the *paralytic* form require hospitalization. A calm, quiet atmosphere is desired. The maintenance of suitable body alignment is necessary to avoid excessive skeletal deformity. A neutral position with the feet at a right angle, knees slightly flexed, hips and spine straight, is achieved by use of boards, shoes, sandbags and occasionally light splint shells. Active and passive motions are carried out by physical therapists as soon as pain has disappeared. Opiates and sedatives are permissible only if there is no impairment of ventilation present or impending. Constipation is common, and fecal impaction should be prevented.

When bladder paralysis occurs, a parasympathetic stimulant such as Urecholine (5 to 10 mg. orally; 2.5 to 5.0 mg. subcutaneously) may induce voiding in fifteen to thirty minutes; some patients do not respond, and others have nausea, vomiting and palpitation. Since bladder paresis seldom lasts more than a few days, intermittent catheterization is preferred to an indwelling catheter; rigid asepsis is necessary, and prophylaxis against urinary tract infection by therapy with a sulfonamide is desirable.

An interesting diet and a full fluid intake should be started at once unless there is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially and must be combated with clinical and culinary skill. An indwelling polyethylene gastric tube is often necessary to ensure adequate dietary and fluid intake.

The orthopedist and the physiatrist should see these patients as early in the illness as possible, and assume responsibility before fixed deformities develop. Ingenious operations have been devised to counter the skeletal effects of poliomyelitis, particularly inequal-



ity of limb length. Arrest of epiphysial growth in the more normal extremity is more commonly practiced than limb-lengthening operations.

The *management of pure bulbar poliomyelitis* consists essentially in maintaining the airway and avoiding all risk of inhalation of saliva, food or vomitus. Most patients can be treated by suitable position combined with frequent mechanical aspiration of the pharynx. Gravity drainage of accumulated secretions is favored by the head-low (foot of bed elevated 20 to 25 degrees) *prone* position with the face to one side. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal use, and soft flexible catheters may be used for nasopharyngeal aspiration.

A broad-spectrum antibiotic may be given for about a week or until any risk of aspiration pneumonia subsides, but other drugs are contraindicated. Fluid and electrolyte equilibrium is best maintained by clysis, since tube or oral feeding in the first few days may incite vomiting. After the first few days an indwelling polyethylene gastric tube may be used and sips of sterile water given from a spoon with increments as indicated by ability to swallow. In addition to close observation for respiratory insufficiency, the blood pressure should be taken at least twice daily. Hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. An occasional patient with pure bulbar poliomyelitis requires tracheotomy because of vocal cord paralysis or because of a "rope sign" with constriction of the hypopharynx.

The majority of patients with pure bulbar poliomyelitis who recover have little residual impairment, but some patients exhibit mild dysphagia and occasional vocal fatigue with slurring of speech. Generally speaking, the younger the child, the less common are these residual defects.

*Management of respiratory failure due to inadequacy of respiratory muscles* (see also p. 740). This consists essentially in providing artificial mechanical respiration, and familiarity with the equipment selected is essential. The tank respirator (enclosing the entire body except the head and neck) is mechanically more efficient than the cuirass type or the rocking bed, and is the machine of choice in the early management of patients requiring ventilation assistance. In placing a child in the respirator it is essential to conceal any sense of haste or anxiety. The child and the parents should be told what is to take

place; often the presence of the parents at the time of transfer reduces the child's terror and permits smoother synchronization to the machine. Suggestions for regulation of the respirator pressure and rate of respiration are given on pages 737 and 740 and in Figure 208. Clinical evidence of improvement is detected by disappearance of restlessness, pallor or cyanosis, by adjustment to the machine's rhythm with cessation of extra efforts with the accessory muscles, and by a relaxed appearance and ability to doze.

Fever increases the oxygen requirement and should be controlled; in desperate instances the author has used induced hypothermia to reduce oxygen need. During the early febrile days it is better to err on the side of hyperventilation when in doubt. However, if patients are hyperventilated for too long a time, they may become "addicted," making the process of weaning from the respirator more difficult.

The amount of ventilation needed to maintain normal levels of oxygen and carbon dioxide in the arterial blood may vary widely in a short time in the same patient. Since blood gas determinations are not readily obtained and since the oximeter gives no indication of carbon dioxide accumulation, close clinical supervision is required. Respiratory acidosis from accumulation of carbon dioxide may occur despite normal oxygenation abetted by oxygen therapy. The only effective way to remove this excess carbon dioxide is by augmented ventilation.

A combination of positive and negative pressures may be used with a cumulative net effect. A patient on occasion may require minus (—) 25 cm. of water pressure or more, which makes nursing difficult because of inability to maintain a tight seal at the portholes. A combination of negative and positive pressures is then preferred, as for patients with hypotension and poor cardiac filling in whom "atmospheric" pressure, e.g., minus (—) and plus (+) 10 cm. yielding net pressures of 20 cm., is preferable. As with the dose of a drug, the amount of ventilation prescribed must be "enough"; individualized judgment is required for each patient at each of frequent examinations. The thoracic cage of recumbent poliomyelitic patients acquires a lack of compliance or resistance to distensibility, so that pressures required to yield "enough" ventilation may be high.

Measurement of ventilation provides an index of when the patient requires artificial

respiration and is especially useful in establishing the degree of progress during the recovery stage (see p. 736).

**TRACHEOTOMY.** Tracheotomy is required for some patients with pure bulbar poliomyelitis, for some with pure spinal respiratory paralysis and for most patients with bulbo-spinal respiratory involvement. Numerous patients with the combined form, however, have survived without the operation, particularly when highly experienced nursing and medical attention are available constantly. During epidemics it is generally possible for a busy nurse to maintain the airway more readily in respirator patients with a tracheotomy than in those treated by oropharyngeal aspiration alone. The operation is best done with a bronchoscope in situ to maintain ventilation, if necessary by attachment of the anesthetist's manual bag. An opening of the second tracheal ring is preferred, and the largest size tube admissible is inserted in order to reduce resistance to airflow. Collar depressors are available for tracheotomized respirator patients. Standard tracheostomy tubes are often too long for these recumbent, head-low patients and may impinge upon the anterior tracheal wall, so that it may be advisable to cut 1 to 2 cm. from the distal end. Frequent but swift endotracheal aspiration is required and is facilitated by instillation of a broncholavaging solution such as saline solution with or without added antibiotics, decongestants or enzymes, such as trypsin. Humidification of air or oxygen is an important feature in preventing inspissation.

The tracheotomized patient with bulbo-spinal poliomyelitis differs from patients tracheotomized for other acute airway problems in being unable to cough, frequently for many months. Tubes should not be removed too early, but may be corked and left in place for many months until the patient has some tussive strength restored. Plastic buttons and tubes used for this purpose have the advantage of less weight and less irritation.

Electronically activated mechanical devices ("exsufflators") are being devised to produce periodically high pressures on the chest wall of respirator patients during exhalation, thus forcing the bronchial secretions toward the glottis. These intermittent cycles can be established by the use of a vacuum cleaner whose hose is inserted through a port-

hole; when a high negative pressure is built up, sudden opening of the large bedpan port will produce exsufflation. Convalescent respirator patients whose cough is ordinarily feeble can be trained to clear their bronchi several times daily by coughing while the chest is squeezed together by the attendant.

**Antibacterial prophylaxis** with an antibiotic to prevent respiratory infection is desirable for patients with respiratory difficulties. Penicillin in large doses is preferred for the initial administration, pending results from nasopharyngeal and tracheal cultures to determine the susceptibility *in vitro* of the bacteria to various antibiotics.

**Weaning a patient from dependency on a respirator** during convalescence is a part of the necessary rehabilitation. Much depends upon the initial psychologic and physical handling of the patient. The respirator should be opened periodically even if only for a few seconds, beginning on the first day of acute illness. Strong verbal reassurance is given to the patient. Gradually the pressure settings are lowered unobtrusively and the periods out of the respirator increased in duration and frequency. Cuirass respirators and the rocking bed are valuable devices in the weaning process, during which fatigue must be avoided. Speech therapists may be helpful in training these patients in breathing methods, including the glossopharyngeal one. The weaning from respirators and the total rehabilitation of the severely involved ex-respirator patient may require several years of active work plus a supervised program for life.

ALEX J. STEIGMAN

#### REFERENCES

- Debré, R., and others: Poliomyelitis. World Health Organization Monograph Series, No. 26, 1955.
- Francis, T., Jr., and others: Evaluation of the 1954 Field Trial of Poliomyelitis Vaccine. Ann Arbor, Michigan, Edwards Bros., Inc., 1957.
- Hektoen and Salmons: Bibliography of Infantile Paralysis with Selected Abstracts and Annotations, 1789-1949. 2nd ed. Philadelphia, J. B. Lippincott Company, 1951.
- Steigman, A. J.: Treatment of Acute Phase of Poliomyelitis. A.M.A. Am. J. Dis. Child., 87:343, 1954.
- Revised authoritative publications for professional personnel dealing with clinical and other aspects of poliomyelitis are available from The National Foundation for Infantile Paralysis, Inc., New York City.



## ACUTE ASEPTIC MENINGITIS SYNDROME

The above title is applied to a clinical syndrome involving the central nervous system of infants and children which may be caused by a variety of etiologic agents. The descriptions of a number of these agents and the diseases they cause are given under their appropriate headings elsewhere in the book. In this chapter an attempt is made to summarize the possible causes and diagnostic criteria of the recognized etiologic entities. An arbitrary and broad criterion is accepted as the basis for diagnosis, namely, that there is a pleocytosis without visible etiologic agents in the stained smear.

**Clinical Pattern.** The onset is variable; central nervous symptoms often occur suddenly in an apparently healthy child; there may be a history of a nonspecific grippelike illness seven to ten days previously from which recovery seems to have been complete; or the child's health may have gradually deteriorated during the preceding one to two weeks. The presenting symptoms and signs vary and depend somewhat on the age of the child. The striking complaint of the older child is headache. In the infant the presence of headache may be inferred from his irritability and resentment at being touched, or convulsions may be the initiating symptom. Anorexia, nausea or vomiting is frequently present. There is some stiffness of the neck and back, but it may be slight; the presence of Kernig's sign is variable. In the infant, bulging of the fontanel indicates increased intracranial pressure; in the older child it may be sufficient to cause fullness of retinal vessels or papilledema. Careful neurologic examination may detect localized paresis of muscle groups or localized changes in sensation.

The only consistent laboratory finding is an increase in cells in the cerebrospinal fluid, which ranges from 20 to several thousand cells per cubic millimeter. The cells are characteristically mononuclear, but many may be polymorphonuclear. The cerebrospinal fluid sugar and protein are normal or slightly elevated.

**Approach to an Etiologic Diagnosis.** The clinical pattern just described can be caused by any of the agents listed in Table 77. A careful analysis of the history is probably the most important clinical factor. The following points should be considered: (1) the age and sex of the patient; (2) the season of the year and the geographic location; (3) the

presence of similar cases or of communicable diseases in the community; (4) associated illness among animals in the community or the possibility of contact with sick or dead animals.

During the summer and early fall the possibility of *nonparalytic poliomyelitis* comes first to mind, especially if there are known cases of paralytic poliomyelitis in the community. Many of the outbreaks and cases called "nonparalytic poliomyelitis" are due to such other enteroviruses as the Coxsackie and ECHO ones (see p. 526). This is especially so when there are concomitant cases of pleurodynia and of unexplained rashes with meningismus. *Mumps encephalitis* is much more common in boys than in girls and can occur without any of the usual manifestations of this disease. A history of swimming in possibly contaminated rivers or streams should suggest the possibility of *leptospirosis*; *L. icterohaemorrhagiae*, *L. canicola* and *L. pomona* can all cause this syndrome without evidence of jaundice. Contact with dogs, cattle or pigs or with a rat-infested environment would also suggest the possibility of *leptospirosis*. A summer epidemic in the middle West or the West should raise the possibility of one of the *arthropod-borne encephalitides* and, if associated with enzootics among horses, would suggest *Eastern* or *Western equine encephalitis*. A sporadic illness might suggest *lymphocytic choriomeningitis*, particularly if there is a history of contact with mice.

In addition to mumps, the aseptic meningitis syndrome may be associated with such other communicable diseases as measles, German measles or chickenpox, or it may be the first manifestation of such diseases as herpes simplex, herpes zoster, infectious hepatitis, primary atypical pneumonia and infectious mononucleosis.

Patients with *purulent meningitis*, particularly *H. influenzae*, may have clinical manifestations that simulate this syndrome when seen early in the disease or if the clinical course has been modified by suboptimal antibiotic therapy. The cerebrospinal fluid should always be cultured even though it is clear. *Tuberculous meningitis* may present a difficult diagnostic problem. A careful evaluation of contacts, a positive tuberculin reaction and other points in the history and physical examination (see p. 469) may indi-

Table 77. Clinical Conditions Which May Induce the Acute Aseptic Meningitis Syndrome\*

Agent	Disease
I. Infectious	
A. Viral	
1. Established viral origin	
Transmitted:	
<i>Man to man:</i> Viruses of poliomyelitis, mumps, herpes simplex, herpes zoster, Cocksackie, ECHO, primary atypical pneumonia, infectious hepatitis	
<i>Rodent to man:</i> Lymphocytic choriomeningitis	
<i>Arthropod to man:</i> The arthropod-borne encephalitides, including Eastern, Western Equine and St. Louis	
2. Presumed viral origin	Infectious mononucleosis, infectious lymphocytosis
B. Bacterial	
1. <i>M. tuberculosis</i>	
2. Bacteria causing purulent meningitis	(1) Very early meningitis (2) Meningitis modified by partial suppression of organisms by suboptimal antibiotic therapy
C. Spirochetal	
1. <i>Leptospira icterohaemorrhagiae, canicola, pomona</i>	Leptospirosis
2. <i>Treponema pallidum</i>	Syphilis
D. Protozoal	Toxoplasmosis
E. Helminthic	Trichinosis
II. Postinfectious or allergic	
A. Natural infections	Rubeola, rubella, varicella, variola, mumps
B. Vaccinations	Smallpox vaccination, rabies vaccination
III. Noninfectious	
A. Meningeal irritation from contiguous lesion	Lesions within or adjacent to the central nervous system, including abscesses, granulomas, hematomas, tumors, thromboses
B. Allergy	
1. After vaccinations or infections	See under <i>Postinfectious or allergic</i>
2. Tuberculosis	Presumably a sensitivity reaction occurring in tuberculous children without actual infection of the meninges
3. Other allergic reactions	e.g., Serum sickness
C. Toxins or irritants	
1. General poisons	e.g., Lead, arsenic, bacterial
2. Intrathecal injections	e.g., Serum, antibiotics, Lipiodol or air

\* Cerebrospinal fluid shows a leukocytosis, often polymorphonuclear early and lymphocytic after the first few days, but no organisms can be detected on a stained smear. The etiologic agent is not necessarily demonstrable in the central nervous system.

cate the correct diagnosis. *Trichinosis* is suggested by a high eosinophile count in the peripheral blood and by other signs compatible with this disease. Finally the possibility must be recognized that the meningeal reaction may be noninfectious in origin, resulting from the reaction to (1) a contiguous lesion (tumor, abscess, and the like) in the brain, spinal cord or their bony covering; (2) a toxin such as lead; (3) an intrathecal injection; or (4) an allergen.

**Treatment.** Symptomatic measures for headache, fever, vomiting and muscle sore-

ness are useful. As the etiologic diagnosis often remains in doubt, hospitalized patients should be as strictly isolated as those with the most infectious of these causes, which is probably mumps, unless that diagnosis can be eliminated by virtue of a known previous attack. It is important to examine the patient carefully several weeks after apparent recovery for assessment of muscular function to detect any weakness which may have eluded recognition.

ALEX J. STEIGMAN  
T. F. McNAIR SCOTT



The limited types of response of the central nervous system to noxious influences make it impossible to distinguish the manifestations of disturbances due to inflammation (encephalitis) from those due to other causes, e.g., hypertension (encephalopathy). Although, in general, such a distinction can be made by the association of cerebral manifestations with other evidences of infection, or with a systemic illness of noninfectious origin, it is important to remember that such an association does not constitute an absolute diagnosis. For instance, a convulsion in the presence of a viral pneumonitis may not result from encephalitis due to the infectious agent itself, but from an encephalopathy associated with a physiologic disturbance such as a remediable electrolyte imbalance.

Of the groups of infectious agents that cause encephalitis, the most frequent are the viruses, so that the term "encephalitis" has almost become synonymous with viral encephalitis. Other agents, however, including bacteria, fungi and helminths, can cause encephalitis as they can the aseptic meningitis syndrome (see p. 544). The discussion will be confined to encephalitides of known or suspected viral origin.

**Clinical Manifestations.** Regardless of etiology, the central nervous system responds by reactions which are predominantly meningeal, encephalitic, myelitic or radicular. When two or more of these reactions occur together, such terms as "meningoencephalitis" or "meningoencephalomyelitis" are used.

**Meningeal.** This is the most common and is described in detail elsewhere.

**Encephalitic.** Characteristically, there is a history of sudden or insidious onset of headache, followed by drowsiness which may proceed to deep coma. Fever is usual. A convulsion may be the initial symptom; this is common in infancy, but decreases in frequency with age. Sometimes the onset is marked by hyperactivity, bizarre behavior or mental disturbance. Palsy or paresis of one or more cranial nerves, disorder of speech, ataxia, weakness of muscle groups, diplopia, alteration of reflexes and disturbances of the autonomic nervous system are usually found as single or combined signs. The cerebrospinal fluid is often within normal limits by routine tests; however, there may be a moderate leukocytosis, in which lymphocytes usually predominate after the first forty-eight hours, although a high percentage of polymorphonuclear cells may be present early.

The sugar content is usually normal, but on occasion it may be low; the protein content is either normal or moderately elevated. Recovery may be dramatically sudden within a few hours after the onset or may be delayed for days, weeks or months. Permanent residual damage may result at all ages, although the incidence appears to be much greater in very young infants and decreases with increasing age. The presence of persistent neurologic involvement is evidenced by such symptoms as convulsive attacks, hemiplegias or monoplegias, bizarre behavior patterns and mental retardation. Residual damage may not be immediately obvious, but may manifest itself later as a deficiency in motor skills or learning ability. Apart from permanent residuals, transient neurologic changes and behavior disorders may be noted shortly after apparent recovery from the acute phase.

**Myelitic.** The onset is usually insidious. There is often paresthesia of the lower extremities followed by weakness; weakness may be the initial symptom as in poliomyelitis. Sphincter disturbances are common, early manifestations. There may be a monoplegia, a paraplegia or paralysis of various muscle groups which may be symmetrical. Recovery is slow and often incomplete. In Landry's type of paralysis the lower extremities are first involved, and the paralysis ascends until it fatally affects the respiratory center, the sensorium remaining clear. The cerebrospinal fluid usually shows an increase in cells with an accompanying increase in protein. Sugar is usually normal.

**Radicular.** Root pain may be a presenting symptom as in herpes zoster, or there may be widespread peripheral neuritis, as in Guillain-Barré's syndrome.

**Pathology.** The pathology of the encephalitides can be considered under several headings: (I) rabies and von Economo's disease; (II) arthropod-borne encephalitides; (III) inclusion body encephalitides, (a) herpesvirus groups and subacute inclusion encephalitides, (b) cytomegalic inclusion disease; (IV) the demyelinating encephalitides. These divisions are useful as general guides, although there is considerable overlapping and variation of severity within each group.

**I. Rabies and von Economo's disease.** The cortex is relatively free from lesions, while the basal structures are most involved.

(a) **RABIES.** There is congestion and lymphocytic infiltration in the meninges, especially near focal parenchymal lesions in

which degeneration of nerve cells occurs. The medulla, pons and midbrain are predominantly affected. The cortex, except for the hippocampus, tends to be spared. Advanced degenerative changes may occur in the gray matter of the cord. The presence of Negri bodies in the cytoplasm is characteristic of degenerating and even of apparently normal neurons. These are eosinophilic, oval or round, and contain basophilic granules. As nerve cells degenerate, neuronophagia occurs. In severely affected areas there is hyperemia with occasional perivascular hemorrhage, and perivascular infiltration with lymphocytes and polymorphonuclear cells.

(b) VON ECONOMO'S DISEASE. Here again neuronal degeneration is the characteristic finding with satellitosis and neuronophagia. Perivascular lymphocytic infiltration occurs focally. Necrosis with liquefaction is occasionally found. The midbrain and basal ganglia are most often affected. Glial scarring may be marked, especially in the area of the substantia nigra.

II. *Arthropod-borne (ARBOR) viruses*. Characteristically, all parts of the brain, including the cortex, are involved. The striking findings are those of acute inflammation involving mainly the cerebral cortex, the thalamus and basal ganglia. The cerebellum and the spinal cord are frequently and extensively affected. The brain may be grossly hyperemic. Histologic lesions are widely scattered throughout gray and white matter. These consist of perivascular and parenchymal infiltration initially by neutrophils and later by lymphocytes; focal areas of demyelination, and foci of total necrosis of all elements with intense infiltration by polymorphonuclear cells. Punched-out areas of acute neuronal degeneration are found without inflammatory reaction. Cavitation eventually may occur in these areas. These encephalomalacic areas suggest vascular involvement, although none can be demonstrated.

III. *Inclusion body encephalitides*. The cortex is extensively involved, although the basal ganglia and cord are not spared and may sometimes predominate.

*Herpesvirus and subacute inclusion encephalitis*. The characteristic of this group is the presence of type A intranuclear inclusion bodies. These are large inclusions occurring in disorganized nuclei. They are often hard to find in sections and are more often in the oligodendria than in the neurons.

1. *HERPESVIRUS INFECTION*. (a) *HERPES SIMPLEX (HERPESVIRUS HUMANI)*. Gross softening of the brain is charac-

teristic. The meninges are infiltrated by lymphocytes, large mononuclear cells, plasma cells and, less often, neutrophils. The cortex is most involved, especially the outer layers, as if the process were extending in from the meninges; the basal ganglia and the cord are little affected. The lesions contain large numbers of nerve cells undergoing necrosis; satellitosis and neuronophagia occur, and the damaged area becomes infiltrated with macrophages or remains rarefied without cellular reaction; early gliosis may be found at the margin of the lesions; demyelination of the associated white matter may occur.

(b) *HERPES ZOSTER (HERPESVIRUS VARICELLAE)*. Intense inflammatory changes occur in the posterior root system, and the posterior gray and white matter of the cord, pons and medulla. The nerve cells of the affected posterior root ganglia show degenerative changes, but only occasionally intranuclear inclusion bodies. Inclusion bodies can be found in the nucleus of the capsular cells of the posterior root ganglia, in the sympathetic ganglia, in the neurilemma cells of peripheral nerve twigs and in the nerve cells of the myenteric plexus.

(c) *B. VIRUS (HERPESVIRUS SIMII)*. Involvement of gray and white matter of the cord may predominate. Focal areas of necrosis, perivascular cuffing and congestion of vessels are spread throughout the central nervous system. Demyelination is prominent and is secondary to the extensive necrosis.

2. *SUBACUTE INCLUSION ENCEPHALITIS*. The changes are similar to, but not as acute as, those found in herpes simplex infection. Widespread perivenous mononuclear cell infiltration is present; neuronophagia and diffuse astrocytosis occur. The basal ganglia and cord tend to be more involved than in herpetic infection (see p. 552).

*Cytomegalic inclusion disease* (see also p. 524). The affected cells in this disease grow to enormous size and contain both nuclear and cytoplasmic inclusions. The nuclear inclusions are granular, eosinophilic to basophilic and are surrounded by a halo. The cytoplasmic inclusions are numerous, small and basophilic without a halo. The nervous system is affected only under the age of two months. The periventricular matrix and olfactory tracts are particularly affected, and calcium and iron salts are deposited in these areas. Inclusions can be seen in the astrocytes of the subependymal matrix, less commonly in the endothelium of the blood vessels and rarely in the neurons.

IV. *Demyelinating encephalitides*. These



include the encephalitides associated with certain exanthems and vaccination procedures. The pathologic changes in all of them involve the white matter of the cortex, basal ganglia and cord, where initial perivenous loss of myelin is followed by infiltration of microglial cells. When involvement is acute, diapedesis of red cells occurs, giving rise to acute hemorrhagic leukoencephalitis. The meninges are involved first at the septa where the large veins of the cord reach them.

**Etiology.** Many different viruses may be responsible for encephalitis, and in recent years a number of previously unknown ones have been isolated from patients with encephalitis. Some of these diseases are considered in separate chapters. Here the approach is more general and the major groups of viruses are considered with special comments on some of them. The incidence of any one etiologic type of encephalitis will vary with environment. For instance, arthropod-borne encephalitic viruses are almost unknown in the urban centers of the eastern United States, while they are responsible for epidemics and sporadic cases in both rural and urban communities in the Middle and Western States and the insect-ridden areas of the tropics. Subclinical or systemic infections without central nervous system involvement with potentially encephalitogenic viruses appear to be common; reservoirs of encephalitic viruses exist among lower animals.

The encephalitides described here are arbitrarily divided into two groups: (I) those in which a viral etiology is known or strongly suspected; (II) the demyelinating group not directly of viral origin.

**Viral etiology.** **ARBOR (ARTHROPOD-BORNE) VIRUSES.** These viruses are transmitted by mosquitoes, ticks and mites. Although many viruses of this group exist in nature as endemic infections of lower animals, especially birds, relatively few are known to be encephalitogenic for man. The latter include encephalitides due to Eastern and Western equine, Venezuelan, St. Louis, Japanese B., Murray Valley, West Nile, Russian Far Eastern or spring-summer (closely related to, if not identical with, louping ill, a tick-borne disease of sheep), Mengo (apparently identical with the virus of encephalomyocarditis, EMC virus) and dengue.

For a number of these virus infections the animal hosts and the arthropod vectors are known. Birds appear to be the major reservoir for Eastern and Western equine and St. Louis viruses.

A pattern of host-parasite relationship has been demonstrated for certain of these infections; for instance, St. Louis virus may be spread as follows: The virus exists in the chicken mite (*Dermonyssus gallinae*) and can be passed transovarially from one generation to another; bites from infected mites cause a transient viremia in the host bird without clinical illness; this provides a source of virus for other mites and also for accidental infection of the mosquito vector (*Culex tarsalis*), which carries the virus to man.

**NONARTHROPOD-BORNE VIRUSES.** This heterogeneous group is being increased by the identification of new viruses, including the following.

**ENTEROVIRUSES.** There are many viruses present in the human intestine which are associated with no disease or with nonspecific febrile illnesses. However, in three recognized groups certain of their members can affect the central nervous system and produce aseptic meningitis, encephalitis or myelitis with resultant transient or permanent paralysis of muscle groups. These three groups are (a) *poliomyelitis* types I, II, III (see p. 531); (b) *ECHO* (enteric cytopathogenic human orphan), (see p. 529) particularly types 4, 5, 6, 7, 9, 14 and 16; (c) *Coxsackie* (see p. 526), particularly Types 1, 4, 7, 8, 9, 10 of group A and all five of group B.

**MYXOVIRUS GROUP.** (a) *Mumps* (see p. 505). Some involvement of the central nervous system occurs in about 25 per cent of patients with mumps. Most frequently this manifests itself as an aseptic meningitis, but cases of true encephalitis or encephalomyelitis are recognized, and these may be associated rarely with transient or even permanent weakness of muscle groups or nerve deafness.

(b) *Influenza* (see p. 508). Encephalitic symptoms occur in certain patients with influenza, and a neurotropic strain of influenza virus has been isolated in the laboratory. However, the evidence that influenza virus causes encephalitis by direct invasion in man is not firmly established.

**HERPESVIRUS GROUP.** (a) *Herpes simplex* (*Herpesvirus hominis*) (see p. 490). Primary infection by this virus may cause either an aseptic meningitis or a meningo-encephalitis with symptoms of encephalitis. When the central nervous system is involved, there are often no other manifestations, but on occasion there may be such manifestations as stomatitis, conjunctivitis and, especially in the newborn, hepatitis.

(b) *Herpes Zoster* (*Herpesvirus varicellae*) (see p. 497). Pain from involvement of the posterior root ganglion supplying the dermatome presenting the vesicular eruption is characteristic of this infection. Occasionally the virus is responsible for meningoencephalitis with cranial nerve paresis or paralysis of the limbs.

(c) *B. Virus* (*Herpesvirus simii*). This virus causes an enzootic infection in monkeys, the natural history of which is similar to that of herpes simplex infection in man. When man is infected, either by an actual bite or by contamination of cuts by infected saliva or even by infected monkey kidney cells in tissue culture, a highly fatal type of encephalomyelitis occurs, which often takes the form of a Landry's type of ascending myelitis. The incubation period is two to three weeks.

(d) *Subacute Inclusion Encephalitis*. This is suspected but not proved to be of viral origin. The disease has a gradual onset and is progressive for months or years to eventual death. The course is generally afebrile. Mental symptoms occur early and progress to dementia. Apart from these, such manifestations as aphasia, hallucinations, cranial nerve weakness, optic atrophy, "startle attacks," hyperkinesia, muscular rigidity, seizures of various kinds, periodic rhythmic jerking of one or more limbs and periodic loss of muscle tone have been reported. This is chiefly a disease of childhood and early adolescence.

MISCELLANEOUS VIRUSES. (a) *Lymphocytic choriomeningitis* (L.C.M.). The causative virus is enzootic in mice, and man may be incidentally infected. After an incubation period of one to three weeks the patient suffers a grippelike illness for three to seven days to be followed, typically, by development of an aseptic meningitis, although symptoms of encephalomyelitis may predominate. The virus can be isolated from the blood and cerebrospinal fluid. Occasionally only the systemic manifestations occur, and a fatal pneumonitis without central nervous system involvement has been described. Recovery from the meningeal manifestations is the rule, although a progressive fatal arachnoiditis has followed the acute infection. Residual damage of some degree is usual after the encephalomyelitic forms.

(b) *Von Economo's disease* (*Encephalitis lethargica*). This clinical entity was described as occurring in epidemic form for about ten years, beginning in 1917. The etiology was

not identified, although a viral one was strongly suspected. In epidemics the clinical manifestations were of two main types: (1) somnolence and ophthalmoplegia and (2) hyperkinesia. Both types could occur successively in an individual patient. The striking feature of this infection was the insidious occurrence of severe sequels in apparently recovered patients. These might be manifested as parkinsonism; disturbances of sleep rhythm; behavior disorders; and especially typical were the so-called oculogyric crises, in which the child stopped all activity and often lay down, while spasms of the ocular muscles rolled the eyes upward and held them fixed for varying intervals of time.

(c) *Rabies* (see p. 512). This virus is transmitted by the bite of infected animals, including bats, and produces a fatal encephalomyelitis.

(d) *Measles* (see p. 483). It is highly probable that encephalitis occurring at the onset of measles is due to the virus of measles, while the more usual late-occurring encephalitis should be classified as postinfectious.

(e) *Benign Myalgic Encephalitis*, or *Iceland or Akrureyri disease*. This epidemic disease was first noted in Iceland, but has occurred since in various parts of the world. Its etiology is unknown. The clinical picture is characterized by pain and tenderness in the nape of the neck, back and limbs and sometimes paresis of various muscle groups accompanied by low grade fever coming on abruptly or more often insidiously after an incubation period of one week. Relapses with paresis of other muscles may occur after intervals as long as eight weeks. Paresthesia and hypalgesia are common. Deep tendon reflexes may be decreased. There is rarely evidence of nuchal rigidity, and the cerebrospinal fluid is not altered. Improvement may occur in a few days, but residual signs and symptoms of muscle and nerve involvement may persist for as long as six years after the acute episode. Adolescents have been chiefly affected; it is rare under the age of five years.

(f) Certain other diseases of viral or suspected viral origin such as infectious mononucleosis (see p. 518), infectious hepatitis (see p. 704) and some of the adenoviruses (see p. 747) may be responsible for symptoms of meningoencephalitis.

*Demyelinating encephalitides*. POST-INFECTIOUS ENCEPHALITIS. This name is applied to the encephalitic manifestations that



occur as complications of certain systemic infections. They are fairly common in measles (1 per 600 to 1000 cases), less common after German measles (1 per 6000 cases) and smallpox (1 per 2000 cases) and rare after chickenpox. It seems probable that some patients with mumps may have a post-infectious form of encephalitis in addition to or without a preceding viral encephalitis. A similar complication has been described as occurring after upper respiratory tract infections. It is possible that such encephalitides may be shown in the future to be due to an adenovirus or some yet unidentified respiratory virus.

**POSTVACCINAL ENCEPHALITIS.** This occurs as a complication of smallpox vaccination (1 per 4000 to 100,000; see p. 504) and antirabies vaccination (1 per 3000 to 7000; see p. 515).

Extensive demyelination is characteristic of this group of encephalitides, regardless of the primary disease. These findings are generally attributed to an antigen-antibody reaction resulting from development of antibodies against nervous tissue. Some alteration of brain substance to make it antigenic, possibly as the result of initial viral damage, is thought to occur. An identical pathologic picture can be produced in animals by injecting them with brain substance in association with adjuvants.

Encephalitic symptoms may also occur after vaccination against pertussis, influenza and poliomyelitis and have been encountered after yellow fever vaccination in infants under one year of age.

Transient encephalomyelitis, usually associated with optic neuritis, may be the initial evidence of multiple sclerosis which becomes clinically definite in late adolescence or early adult life.

**Epidemiology.** This varies with the infecting agent. An exact etiologic diagnosis is almost impossible to make clinically, but an epidemiologic approach may afford the basis for a well educated guess. For instance, an arthropod-borne viral infection might be suspected in a summer epidemic when suitable vectors were present in the environment, whereas a sporadic case of encephalitis might lead to a diagnosis of lymphocytic choriomeningitis if exposure to mice was elicited. Epidemics of encephalitis due to one of the enteroviruses can be recognized only when the presence of such an agent in the community has been identified in the laboratory.

**Diagnosis.** Etiologic diagnosis is possible only by laboratory methods (see p. 384) either by isolation of the virus from blood or cerebrospinal fluid, from brain, or from nasopharyngeal or rectal swabs, or by demonstrating a rise of antibodies against a known virus.

**Treatment.** Although no specific therapy is available for this group of diseases, the skillful application of supportive and symptomatic measures is of prime importance. These can be summarized as follows:

**Acute phase.** **AIRWAY.** The throat may need to be cleared by suction and at times an airway inserted, or a tracheotomy may be needed. Significant irregularities of respiration are not rare, and artificial respiration may be required to eliminate carbon dioxide (see pp. 736 and 740).

**CONVULSIONS.** These must be controlled by appropriate means (see p. 1117).

**FLUIDS AND NUTRIENTS.** These are given intravenously if necessary, and then by gavage tube until the patient is ready to take foods by mouth. Careful control of electrolyte balance is essential to avoid water intoxication, which can occur easily in disease of the central nervous system (see p. 191).

**GENERAL MEASURES.** These may include administration of oxygen when necessary; reduction of temperature by sponging and aspirin; frequent turning; emptying of the bladder by the use of cholinergic drugs, skilful Credé or, as a last resort, catheterization; emptying of the bowel; and maintenance of adequate sedation.

**SPECIAL MEASURES.** *Broad-spectrum antibiotics* should be given routinely to prevent secondary infection such as aspiration pneumonia. Definite evidence of the 'value of corticosteroids is lacking. However, it seems reasonable to use one of them in pharmacologic doses (6 to 8 mg. per kilogram of body weight per day) for two to three days, with decreasing doses during the next three to four days. Such therapy may prevent edema, by decreasing capillary permeability, and possibly, early gliosis. When there is increased intracranial pressure, *burr holes* for tapping ventricles or *craniotomy* for temporal flaps may be necessary. *Hypothermia* may be effective in lowering the body temperature and may thus decrease cerebral metabolism and oxygen consumption and the body's insensible water loss.

**Convalescent care.** Anticonvulsant therapy may be necessary for several months, and serial electroencephalograms may be

helpful in following the course. Physiotherapy, occupational therapy and corrective surgery should be utilized as necessary. Parents should be warned that transient emotional lability and behavior aberrations are not uncommon and that children appear to recover more quickly when the parents adopt a permissive attitude.

**Prevention.** At present, vaccination is available for poliomyelitis and for rabies; in the latter, vaccination is preferably combined initially with rabies antiserum. Vaccines have not proved successful against the arthropod-borne encephalitides in which they have been tried. More success may be expected from control of the arthropod vector by insecticide sprays and repellents. Avoidance of exposure to known animal reservoirs, e.g., mice in the

case of lymphocytic choriomeningitis, is clearly advisable.

T. F. McNAIR SCOTT

#### REFERENCES

- Farmer, T. W., and Janeway, C. A.: Infections with the Virus of Lymphocytic Choriomeningitis. *Medicine*, 21:1, 1942.
- Fields, W. S., and Blattner, R. J., ed.: *Viral Encephalitis*. Springfield, Ill., Charles C Thomas, 1958.
- Rivers, T. M., and Horsfall, F. L., ed.: *Viral and Rickettsial Infections of Man*. 3rd ed. Philadelphia, J. B. Lippincott Company, 1958.
- Tyler, H. R.: Neurological Complications of Rubella (Measles). *Medicine*, 36:147, 1957.
- Wolf, A.: The Pathology of Some Viral Encephalitides; in Kidd, J. G.: *The Pathogenesis and Pathology of Viral Diseases*. New York, Columbia University Press, 1950, pp. 194-212.

### SUBACUTE SCLEROSING LEUKOENCEPHALITIS

Subacute sclerosing leukoencephalitis (van Bogaert) is a progressive illness occurring almost exclusively in children of school age. Although certain features of the disease suggest either a degenerative or an infectious disease of the central nervous system, both the clinical course and the pathologic findings are sufficiently characteristic to warrant its consideration as an entity of unknown etiology.

The initial manifestations are usually those of psychic and intellectual deterioration, diminution of scholastic ability often being an early symptom. Various types of dyskinesias ranging from myoclonic jerks to convulsive episodes occur subsequently. Cachexia and unexplained periods of fever are common. The cerebrospinal fluid frequently reveals a paralytic type of colloidal gold curve and at times a questionable increase in protein, but otherwise it is normal; there is apparently no pleocytosis. Electroencephalography reveals characteristic rhythmic complexes (K waves)

synchronous with but not the result of myoclonic jerks; they may be absent in isolated tracings. Deterioration is progressive, terminating with decerebrate rigidity and complete dementia; death usually occurs within a matter of months.

Pathologically, the disease consists of a diffuse gliosis, usually with relatively little demyelination, accompanied by a chronic inflammatory reaction; the lesions are usually most severe in the subcortical white matter, but the cortex, basal ganglia, thalamus, hypothalamus and spinal cord may also be involved. Intranuclear and intracytoplasmic inclusion bodies have been identified in a number of instances, but attempts to isolate a virus have been unsuccessful to date.

JAMES B. AREY

#### REFERENCE

- Poser, C. M., and Radermecker, J.: Subacute Sclerosing Leukoencephalitis, van Bogaert Type. *J. Pediat.*, 50:408, 1957.



## RICKETTSIAL DISEASES

The rickettsiae are a group of microorganisms which commonly inhabit the alimentary canal of certain insects and may be associated with disease in man. Stained preparations appear under the ordinary microscope as pleomorphic coccobacilli 0.3 to 0.5 micron in diameter. Most species are retained by bacterial filters, and all require the presence of living cells for multiplication. Biologically, the rickettsiae have some of the characteristics of bacteria and some of viruses and are classified in an intermediate position.

The rickettsial diseases of man, with the exception of Q fever, are febrile illnesses with rashes. They may be separated into four groups on the basis of clinical characteristics, insect vectors, etiologic agent and epidemiology (Table 78).

Epidemic typhus and endemic typhus are almost identical clinically and pathologically. The etiologic agents are so similar antigenically that cross reactions occur in Proteus or rickettsial agglutination tests. The two forms of the disease may be distinguished by specific complement fixation tests and by the

inability of epidemic typhus to produce a scrotal reaction in guinea pigs. Brill's disease is a recrudescence of epidemic typhus.

There are many related strains of rickettsiae which cause spotted fever of variable severity in different parts of the world. The list includes boutonneuse fever of the Mediterranean regions, São Paulo, Tobia and pinta fevers of South America, Kenya or Nigeria fever of Africa, and many others. Rickettsial-pox is included in the spotted fever group because of antigenic relationships of *Rickettsia akari* to the etiologic agent of Rocky Mountain spotted fever.

Tsutsugamushi fever, or scrub typhus, was known in certain areas of Japan for many years, but not until the beginning of World War II was it learned that the disease was present also among the populations of India, Australia, the Dutch East Indies, and Malaya. Effective vaccines are not available, and scrub typhus continues to be a real hazard to those who enter endemic areas.

Q fever differs clinically, histologically and epidemiologically from the other diseases

Table 78. Rickettsial Diseases of Man  
(Summary of Pertinent Information)

Group	Disease	Etiologic Agent	Arthropod Vector	Animal Host	<i>Proteus</i> Agglutination*	Geographic Distribution
Typhus.....	Epidemic typhus	<i>R. prowazeki</i>	Body louse	None	OX19	Worldwide; rarely U.S.A.
	Brill's disease	<i>R. prowazeki</i>	None	None	OX19	Eastern coastal cities of U.S.A.; Israel
	Murine typhus	<i>R. mooseri</i>	Rat flea, louse	Rat	OX19	Worldwide; southern states of U.S.A.
Spotted fever...	Rocky Mountain spotted fever	<i>R. rickettsii</i>	Tick	Rodents mammals	Variable OX2 or OX19	North and South America; related diseases worldwide
	Rickettsial-pox	<i>R. akari</i>	Mite	House mice	None	Reported from Eastern U.S.A.
Tsutsugamushi fever.....	Scrub typhus	<i>R. orientalis</i> (tsutsugamushi)	Mite	Rodents	OXK	Far East
Q fever.....	Q fever	<i>R. burneti</i> ( <i>Coxiella burnetii</i> )	? Rarely ticks	Ticks, cattle, sheep, goats	None	Worldwide; western U.S.A.

\* Specific serologic procedures using rickettsial antigens in complement fixation, agglutination or neutralization tests are more reliable.

listed and is classified with them only because it is caused by a rickettsia.

The pathology, methods for making a laboratory diagnosis, and manner of treatment of each of the rickettsial diseases in man are so similar that it seems appropriate to discuss these topics as a whole before describing the individual diseases.

**Pathology.** The pathologic lesion of the arthropod-borne rickettsial diseases is sufficiently distinctive to be diagnostic in patients with a history of an exanthem. The main changes involve the small blood vessels, chiefly of the skin, subcutaneous tissue and central nervous system. The endothelial cells swell, and occlude the small blood vessels, and thrombosis results. The occluded vessels are surrounded by cuffs of mononuclear cells, plasma cells and macrophages. Rickettsiae localize in the endothelium of capillaries and extend via the intima into larger vessels. Rocky Mountain spotted fever may be distinguished histologically from other rickettsial diseases by the presence of rickettsiae in the smooth muscle cells of the media. This produces more severe destruction of blood vessels and may explain the occurrence of necrosis of skin in sites such as the ear lobes, fingers, toes and scrotum.

The symptomatology of vector-transmitted rickettsial diseases correlates with the degree of involvement and the location of affected vessels. For example, the fall in blood pressure, an outstanding clinical feature of rickettsial disease, is generally conceded to be the result of changes in the peripheral vessels. Perivascular reactions in the lung may result in atelectasis and pneumonia. Vascular changes in the brain may produce central nervous system symptoms.

**Q fever,** which is not accompanied by a rash and does not require an insect vector, differs pathologically from the other rickettsial diseases. The major, and usually the only, lesions occur in the lungs, where there is a patchy interstitial pneumonitis with copious exudate composed of fibrin and mononuclear cells. Alveolar walls, alveolar ducts and terminal bronchioles are infiltrated by large mononuclear cells.

**Diagnosis.** The diagnosis of a rickettsial infection in man usually requires laboratory confirmation which is most readily established by demonstration of acquired specific antibodies. In unusual cases when serologic tests are unobtainable or equivocal it may be necessary to identify the etiologic agent.

**Serologic diagnosis.** During studies of the

etiology of typhus fever, Felix isolated a strain of *Proteus vulgaris* from the urine of a patient. This strain (OX19) was not the etiologic agent of typhus, but by coincidence had sufficient antigenic similarity to *Rickettsia prowazeki* so that serum from patients convalescent from typhus fever contained high titers of OX19 agglutinin. Additional strains of *Proteus* related to the etiologic agents of tsutsugamushi (OXK) and Rocky Mountain spotted fever (OX2) were also discovered. The use of these easily prepared antigens in agglutination tests with patients' serums is referred to as the Weil-Felix reaction.

In epidemic typhus fever the agglutination to OX19 usually reaches a titer greater than 1:160 during the second week of illness; the OX2 and OXK titers remain low. The agglutinin pattern observed with murine typhus is similar to that of epidemic typhus, and the two infections cannot be distinguished by this method. The *Proteus* agglutination test is of little value in the diagnosis of Rocky Mountain spotted fever, owing to the variations in the degree and types of response; classically, the patient should develop a high titer of OX2 agglutinins and little, if any, antibody against OX19 and OXK. *Proteus* OXK agglutinin titers are high after Tsutsugamushi disease. Convalescent serum from patients with Q fever or rickettsialpox does not agglutinate to significant titer the *Proteus* strains used in the Weil-Felix reaction. *Proteus* titers do not persist and are usually below a significant level within three months following the illness.

Specific serologic procedures using rickettsial antigens in complement fixation, agglutination or neutralization tests are much more reliable than the Weil-Felix reaction and should be used to confirm the diagnosis of rickettsial infections. Two samples of serum, one obtained during the first week of illness and the other two or three weeks later, should be available to determine whether a significant increase in titer has occurred during the course of the illness.

**Culturing of rickettsiae.** Rickettsiae may be propagated by inoculating susceptible experimental animals or the developing chick embryo. These techniques are seldom required to diagnose rickettsial infections, but may be used, for example, to study the effectiveness of various antibiotics or to detect the presence of rickettsiae in milk, dust or insects.

The guinea pig responds to intraperitoneal inoculation of rickettsiae-containing material



with a sharp elevation of body temperature that persists for several days. The febrile animal may appear ill, but does not have a rash and only infrequently succumbs. Microscopic examination of Macchiavello-stained impression smears made from the spleen reveals many typical rickettsiae. Specific identification of newly isolated strains of rickettsiae may be performed by cross-immunity tests in animals or by serologic techniques.

Rickettsiae grow well in the yolk sac of the developing chick embryo, and, when large amounts of infectious material are required, the egg is the usual source. Chemical and physical methods may be used to prepare purified antigens or vaccines.

The culturing of rickettsiae in the laboratory is extremely hazardous and has been the source of infection for many investigators. This is a task for a special laboratory with proper facilities and immunized personnel. Serologic procedures, using killed antigen and heat-inactivated serums, involve little risk to the laboratory worker.

**Treatment.** Treatment of rickettsial infections is much more effective since the discovery of the broad-spectrum antibiotics. Mortality rates have fallen markedly, the morbidity rate has decreased, and complications have become infrequent. These drugs, however, are not immediately or invariably effective in influencing the course of the disease, and clinical relapses are not uncommon. Rickettsiae have been isolated from the blood of patients who have received presumably adequate doses of an antibiotic. These difficulties are related to the fact that chloramphenicol and the tetracyclines suppress, but do not destroy, the rickettsiae. Final eradication of the microorganism depends upon the immune processes of the host. Intermittent administration of an antibiotic—five days of treatment, five days without drug and then another five days of treatment—has been suggested as the most effective method.

The recommended dose of the tetracyclines or chloramphenicol to children is 50 to 100 mg. per kilogram per day orally in four divided doses. The maximum or adult daily dose is 4 gm. When the intravenous route is used, 30 to 40 mg. per kilogram per day of either drug should be administered in three equal doses.

Early diagnosis and the proper use of antimicrobial agents are all that is necessary in the management of most rickettsial infections. Vigorous supportive therapy, parenteral fluids,

transfusions, sedations and/or oxygen are necessary for the severely ill patient.

Cortisone has been used with an antibiotic in a few instances when the response to the antibiotic alone was not satisfactory. Although the results have been described as excellent, sufficient information is not available to evaluate this therapy critically, and corticoids are not recommended for the average case.

## TYPHUS FEVER

(EPIDEMIC TYPHUS, LOUSE-BORNE TYPHUS)

**History.** Typhus fever has been associated with misery among mankind since man donned clothing. Typhus was probably responsible for the plague of Athens 430 B.C.; it existed during the Middle Ages and was associated with each of the serious famines in England prior to the discovery of America. Typhus was spread through Europe by louse-infected soldiers and was often the most important factor in determining the outcome of battles or the survival of nations.

In more recent years typhus has been an Old World disease with major outbreaks during time of war. In October, 1943, the disease broke out in Naples as the Allied occupation troops arrived. Typhus was encountered in Nazi concentration camps and was spread through Europe by the escaping inmates. Epidemics have occurred among immigrants in coastal cities in America, but typhus has not been common in the United States during recent years. The existence of endemic areas within a few hours of travel distance, however, makes epidemics of typhus in this country a possibility.

**Etiology and Transmission.** Man is the sole reservoir of *Rickettsia prowazeki*, the etiologic agent of epidemic typhus. The body or head louse may become infected by feeding upon the blood of a person with rickettsemia. The ingested organisms multiply within the cells lining the alimentary tract of the insect and are eliminated in the feces.

Contaminated feces may be introduced into a susceptible human host through abrasions or perforations in the skin, or by way of the conjunctival sac or upper respiratory tract. Inhalation of dried, infected louse excreta present in the clothing, bedding or furniture of a typhus patient is probably an important source of typhus infection.

The infected louse dies soon after con-

tracting typhus and seldom has more than a week to spread disease. The louse cannot fly or jump, but may crawl short distances to another human being, especially if his original host becomes uncomfortably hot or cold.

**Clinical Manifestations.** Typhus fever was a much milder disease in children than in adults even before the availability of chemotherapeutic agents. In the 1943 epidemic in Naples, for example, the mortality rate among children was 1.5 per cent compared to 22 per cent in adults.

The clinical manifestations of typhus in children may include fever, transient rash and only few constitutional symptoms, which often make recognition of the disease difficult.

The incubation period is usually less than fourteen days and is followed by an abrupt onset with severe frontal headache, weakness, malaise, generalized aches and pains, chills, and fever of 104° F. or more. Four to seven days later the rash appears.

Faint, rose-colored spots of irregular outline 2 to 4 mm. in size which fade with pressure appear first over the chest and spread gradually over the abdomen, back and extremities. In twenty-four to forty-eight hours the lesions become dark red and no longer fade with pressure. The lesions may spread to include the palms and soles, but the face and scalp usually remain free. Petechial lesions occur in severe cases. The rash remains for a variable period of time; it may be present for only a few hours or persist after the temperature has returned to normal. In general, the more profuse the rash, the more severe is the disease.

The appearance of the rash marks the beginning of the critical period. The temperature remains high and unrelenting, and periods of stupor are interrupted by bouts of violent delirium. The blood pressure is low, and renal output decreased. Oral intake is low and requires parenteral supplementation. In the absence of complications such as pneumonia, severe central nervous system involvement or renal insufficiency, which are frequently fatal, the patient begins to improve during the third week. The temperature gradually falls, the central nervous system symptoms disappear, and the headache ceases. Recovery from typhus is complete, and even in patients with evidence of diffuse involvement sequelae are rare.

**Laboratory Data.** Leukopenia with a relative lymphocytosis early in the disease is usually followed by a leukocytosis during the second and third weeks; a normocytic anemia

is common. Urinary findings vary with the degree of renal involvement; albuminuria and microscopic hematuria are frequent.

**Differential Diagnosis.** Meningococcemia, typhoid, measles or smallpox may be confused with typhus, but the history, clinical course and laboratory data usually permit a proper diagnosis.

**Control Measures.** The immediate destruction of vectors with an insecticide with persisting effect such as DDT is an important measure in the control of an epidemic. Dust containing excreta from infected lice is also capable of transmitting typhus, and care must be taken to prevent its inhalation. This usually requires washing the patient's clothing, bedding and other possessions with hot water and a disinfectant after they have been dusted with DDT. Vaccination of persons likely to come in contact with typhus is recommended. The preferred vaccine is a killed preparation of a rickettsia grown in the yolk sac of the chick embryo. Insufficient data are available concerning differences in sensitivity to broad-spectrum antibiotics by strains of rickettsiae, but, if resistant forms do not occur, the administration of an antibiotic may be adequate prophylaxis for brief exposures to typhus.

**Treatment.** See page 555.

## MURINE TYPHUS

**Etiology and Transmission.** Unlike epidemic typhus, which is not seen among children in the United States, endemic or murine typhus is fairly common, particularly in Texas and the southeastern states, and has been seen in most regions of this country. It usually occurs in the summer and fall in contrast to typhus, which is characteristically a disease of winter and spring.

Endemic or murine typhus is a disease of rats caused by *Rickettsia mooseri*. It is usually transmitted from rat to rat by the rat louse or flea. In both the rat and the insect vectors murine typhus is a mild disease with no apparent effect on their life span. The eggs laid by infected fleas or lice do not transmit *R. mooseri* to the next generation. Man usually acquires murine typhus when bitten by an infected rat flea, but can also be infected by inhaling or possibly ingesting infected excreta of fleas.

**Clinical Manifestations.** Murine typhus is a mild, seldom fatal illness that can be distinguished from epidemic typhus only by special laboratory procedures.



The incubation period is usually about eight days. Prodromal symptoms such as headache, arthralgia and backache are followed by a gradually increasing temperature which may reach 106° F. in children and last nine to fourteen days. On the first to the eighth day of fever, most often by the fifth day, the rash appears. As in typhus, the eruption begins on the trunk and spreads to the periphery, rarely involving the face, palms or soles. Initially the skin lesion is a dull red macule with ill-defined margins which becomes slightly papular as it matures. It never becomes purpuric and persists for a much shorter period than the rash of epidemic typhus. Twenty per cent or more of children may have no rash or such a transient one that it is not noted. Central nervous system symptoms are uncommon, as is peripheral vascular collapse or other complications.

**Control Measures.** Control of murine typhus requires elimination of the rat reservoir or the insect vector, or both. Immunization of personnel in contact with possibly infected rats is recommended. The vaccine is different from that used for epidemic typhus, although most persons who have recovered from one form of typhus are also immune to the other.

**Treatment.** See page 555.

## BRILL'S DISEASE

Brill's disease is an unusual phenomenon in which a patient with a history of typhus suffers a recrudescence of his illness. It has been observed among immigrants from eastern Europe in the coastal cities of the United States and more recently in Israel. The strains of rickettsiae isolated from such patients are indistinguishable from those of epidemic typhus. It is presumed that organisms have persisted in the tissues of the host for years, and then, for reasons not understood, they increase in number and produce clinical symptoms. A patient with Brill's disease can infect lice and is a potential point of origin for a typhus epidemic when the vector is present. Brill's disease is not a problem in children.

## SCRUB TYPHUS

(TSUTSUGAMUSHI FEVER, MITE TYPHUS)

Scrub typhus, or tsutsugamushi fever, has been recognized in Japan and Formosa for centuries, but not until World War II was

it realized that this disease could be found in localities stretching from India to the Philippines, including Burma, Malaya, New Guinea, the Solomon Islands and Queensland. The incidence of scrub typhus among United States Army personnel in bases north of Australia during 1942 and 1943 was about ten per 1000 troops per year with a case fatality rate of 3 to 10 per cent.

**Etiology and Transmission.** *Rickettsia tsutsugamushi*, also known as *R. orientalis*, is the causal agent of scrub typhus. The vectors which carry the agent are the larval forms of the "chigger" or trombiculid mites. The larvae feed on rats or other rodents and when not feeding are present on low-lying vegetation from where they can attack man. *Rickettsia tsutsugamushi* has been isolated from many species of rodents, and it seems likely that both mites and rodents can serve as reservoirs of rickettsia.

Scrub typhus is mainly a disease of persons whose occupations bring them into contact with infected mites.

**Clinical Manifestations.** The symptomatology of scrub typhus, although showing several distinctive features, is remarkably similar to that of other rickettsial infections. The disease may vary in severity, but characteristically has an abrupt onset twelve to eighteen days following the bite by the infected mite. The initial symptoms are fever and headache, sometimes accompanied by anorexia and vomiting.

Some form of skin lesion is usually present at the site of the mite bite, which begins as an asymptomatic, pink papule, increases in size and becomes either an eschar, consisting of a central, black scab 4 to 8 mm. in diameter surrounded by a dull, red areola, or, in moist areas (axilla, perineum), a pinched-out shallow ulcer. By the end of the first week of illness a maculopapular rash develops on the chest and abdomen and gradually spreads to involve the entire body, except usually the hands and face. Diffuse, tender adenopathy, more marked in the region of the primary lesion, is a common part of the clinical syndrome.

Laboratory confirmation may be obtained by isolation in mice of the causative agent. The Weil-Felix reaction for *Proteus* OXK may become positive by the third week of the illness, but is not invariable, especially in patients treated with antibiotics.

In severe cases signs of pulmonary or cardiac involvement may develop during the second week of illness, and death results.

In mild or treated cases improvement begins by the end of the second week, fever decreases, the rash fades, and the eschar heals. The mortality rate, when antibiotics are used, is less than 5 per cent.

**Control Measures.** The difficulties encountered in attempting to eliminate the widely prevalent mite vector of scrub typhus have led to investigations of control by vaccines. Unfortunately, the vaccines tested have not proved entirely satisfactory, owing to the many antigenically different strains of *R. tsutsugamushi* which are pathogenic for man. It is hoped that an effective polyvalent vaccine can be prepared. Until such a time, protective clothing and early treatment with broad-spectrum antibiotics are the most useful aids to prevent death from scrub typhus.

## ROCKY MOUNTAIN SPOTTED FEVER

**History.** Rocky Mountain spotted fever is an exanthem of man first recognized in the Rocky Mountain region of the United States by Maxey in 1899. Ricketts inoculated monkeys and guinea pigs with infected human blood and was able to transmit the infection and demonstrate the causative agent. He later showed that the disease is spread by the wood tick and discovered infected ticks in the Bitter Root valley of Montana. The name "Rocky Mountain spotted fever" gives a false impression of geographic limitation to a disease that has been observed throughout the United States. The attack rate in Virginia, Delaware and Maryland, for example, is as high as or higher than that in Nevada, Idaho and Montana.

**Etiology and Transmission.** The etiologic agent of Rocky Mountain spotted fever, *Rickettsia rickettsii*, is maintained in nature

by many hosts, including the ground squirrel, jack rabbit, chipmunk, wood rat, meadow mouse and weasel; the animal hosts do not become ill. Transmission among animals and from animal to man is most commonly achieved through the wood tick, *Dermacentor andersoni*, or the dog tick, *Dermacentor variabilis*.

Shepherders, hunters, woodsmen or others whose occupation or recreation brings them into the isolated tick-infested woods of Montana or Idaho are most likely to be bitten by an infected wood tick. In the eastern United States, however, more infections occur in children and women who are probably bitten by infected dog ticks encountered during outings in the woods or while handling the family dog.

Infected female ticks may pass rickettsiae through eggs to the progeny and thus maintain a reservoir for a long time without infecting man.

**Clinical Manifestations.** The incubation period in children varies from one to eight days. The disease usually begins with such nonspecific symptoms as headache, fever, anorexia and restlessness. There is a history of tick bite in approximately half the reported cases, but local reaction at the site of the tick bite is uncommon. The discrete, pale, rose-red macules or maculopapules appear one to five days after the onset of illness. The rash characteristically begins peripherally on the ankles, wrists or lower legs and then spreads, often rapidly, to involve the entire body, including the scalp, palms and soles. Early, the rash fades with pressure, but after one or two days it becomes more purple and no longer disappears with pressure. The clinical illness is similar to that of typhus. Bizarre central nervous system symptoms, peripheral circulatory collapse,



FIG. 166. Patient with Rocky Mountain spotted fever. Note the pronounced edema with closure of the eyes. (Courtesy of Dr. Weston Kelsey, Winston-Salem.)





FIG. 167. Eleventh day of rash in severe Rocky Mountain spotted fever. Note the hemorrhagic character of the diffuse rash. (Courtesy of Dr. Weston Kelsey, Winston-Salem.)

electrolyte disturbances and pneumonia are the most common complications. Fatality rates among unvaccinated children before the availability of antibiotics varied from 10 to 40 per cent. It is generally accepted that rickettsial strains of high and low virulence exist throughout the United States. Recovery in uncomplicated cases occurs in the third week, initiated by a fall in temperature and gradual subsidence of symptoms.

The clinical laboratory findings are not specific.

**Control Measures.** The reservoirs and vectors of spotted fever are so numerous and widespread that removal of the source of infection is not feasible. Protection from tick bite is best accomplished by the use of proper wearing apparel plus tick repellents or, optimally, the avoidance during the tick season of areas known to be infested.

Ticks rarely transmit infection until they have fed on the person for several hours; thus careful examination of children who have been playing in the woods and prompt removal of ticks may prevent disease. This is best accomplished by the use of gloves or forceps which will protect the operator from becoming infected by the crushed insect. The use of a hot match head or a coating of petrolatum to provoke the tick to remove his mouth parts is often recommended.

Vaccines are available and should be used

by those whose pursuits require unusual exposure to virulent strains of rickettsiae.

**Treatment.** See page 555.

## FIÈVRE BOUTONNEUSE

Fièvre boutonneuse is a relatively benign rickettsial disease, limited almost exclusively to Europeans in the countries surrounding the Mediterranean. The natives in this area are apparently infected early in life and develop long-lasting immunity. *Rickettsia conorii*, the causal agent, is transmitted by the dog tick, *Rhipicephalus sanguineus*. As in rickettsialpox or scrub typhus, a local lesion known as *tâche noire*, or primary eschar, develops, and this is followed by a diffuse, maculopapular rash which later becomes petechial. Severe systemic manifestations are uncommon. The diagnosis is usually made on the basis of the clinical symptoms in an exposed person with a primary skin lesion. Agglutinins to both OX19 and OX2 occur during the second week of the disease and may be used to confirm the diagnosis if the more specific complement fixation test is not available. Treatment with broad-spectrum antibiotics is followed by rapid clinical improvement.

## RICKETTSIALPOX

**History.** In 1946 an epidemic of an unusual febrile disease with varicelliform rash occurred in a New York housing development. The disease was recognized as a new entity caused by a previously unknown rickettsia, *Rickettsia akari*, and transmitted by the mouse mite, *Allodermamyssus sanguineus*. The illness, named rickettsialpox, has continued endemic in New York, and isolated cases have been reported from Boston, Philadelphia and Cleveland. The mite vector has been found in many cities of the United States, and more widespread distribution of rickettsialpox may be anticipated.

**Clinical Manifestations.** Rickettsialpox is a mild illness characterized by an initial skin lesion followed by fever, chills, headache and a papulovesicular rash.

The initial lesion, presumed to be the site of the mite bite, has been observed in more than 90 per cent of cases. It may be located anywhere on the body, beginning as a non-tender, nonitching, firm, red papule, 0.5 to 2.0 cm. in diameter. A deeply entrenched vesicle develops in the center of the papule and ruptures after several days, leaving a

crusted, pigmented lesion or eschar which may persist three weeks or longer. Adjacent lymph nodes become enlarged and tender, but do not suppurate.

The initial lesion is followed in two to seven days by fever, headache, chills and sweats. Temperature varies between 102° and 105° F., but the patient remains oriented and does not appear severely ill.

Within twenty-four to seventy-two hours after the onset of fever scattered erythematous maculopapules appear over the body, showing no preference for trunk, head or extremity. The lesions enlarge, become more papular and develop vesicles on the summit of each papule. The secondary lesions (rash) resemble the initial lesion except that they are smaller in size and heal without leaving scars in four to seven days.

The duration seldom exceeds seven to ten days. Complications, sequelae and fatalities are rare.

Except for leukopenia with relative lymphocytosis early in the disease, studies of blood, urine or stool of patients with rickettsialpox show no characteristic changes.

**Differential Diagnosis.** The rash of rickettsialpox may be confused with that of chickenpox. In varicella, however, the vesicles are superficial, thin, dewdrop lesions which appear in successive crops beginning on the chest. These differ from the deeply seated, randomly distributed firm vesicles of the rickettsial disease. The initial lesion, the presence of fever before the rash and a history of chills may also help in the differentiation. Other diseases to be considered include infectious mononucleosis, meningococcemia, Rocky Mountain spotted fever and typhus.

**Control Measures.** Preventive measures should include the eradication of rodent reservoirs as well as the mite vector. *Rickettsia akari* grows well in the yolk sac of the developing chick embryo, and a vaccine could be prepared if there were substantial need.

**Treatment.** See page 555.

## Q FEVER

**History.** Q fever, a febrile disease without rash and often associated with an interstitial pneumonia, was originally observed among Australian abattoir workers in 1935. Initially the disease was infrequently diagnosed in this country except among laboratory workers. During World War II epidemics of "pneumonia of unknown etiology" and "Balkan

grippe" occurring among military personnel in the Mediterranean theatre were shown to be Q fever. Since that time the disease has been reported from all parts of the world.

**Etiology and Transmission.** Q fever occurs naturally in cattle, sheep, goats and many wild animals. The causative agent of Q fever, termed either *Rickettsia burneti* or *Coxiella burnetii*, has been found in many species of ticks, in which it may pass from the adult through ova to progeny.

Experimentally, Q fever has been transmitted by insect vectors through the skin and by inhalation. Careful studies of outbreaks of the disease in human beings have failed to incriminate insect vectors, although this mode of transmission may be important among animals. Person-to-person spread, if it occurs, is rare. Q fever epidemics observed in Italy during the war remained localized and involved only the inhabitants of specific quarters, a fact which led to the idea that Q fever was a "place infection." Recent studies suggest that excreta from infected animals or insects may be a source of infection. In the endemic areas of California, human infections are related to contact with animals which show evidence of *R. burneti* infection. In northern California sheep are the probable source of infection; in southern California, the dairy cow. The main route of infection appears to be inhalation of contaminated material from domestic animals or by direct exposure or by contact with wool, hides, hay or other contaminated materials.

Milk may be another source of infection for man. In a study of sporadic cases of Q fever in England, Marmion isolated *R. burneti* from ten of the twenty (raw) milk sources used by the patients; *R. burneti* may survive pasteurization temperatures.

**Clinical Manifestations.** Q fever may be a mild disease diagnosed only in retrospect by serologic survey, but, as commonly recognized, it is a disease of moderate severity with a duration in children of two to three weeks. The onset of illness is characteristically sudden, but in some instances symptoms may increase slowly in intensity. Malaise, fever, chilliness and generalized weakness appear early, but the most prominent symptom is severe frontal headache, often associated with pain upon movement of the eyes. There is no rash. Complaints referable to the respiratory tract are mild and infrequent. Cough may occur late in the first week of illness with production of small amounts of blood-streaked sputum, and



chest pain may be associated with pneumonitis or infrequently with pleural effusion.

Pneumonitis is common; rales may be audible, but the diagnosis of pulmonary involvement is usually established roentgenographically. Pulmonary consolidation is usually patchy and in the peripheries of the lower lobes; hilar involvement is rare. Resolution is slow and may require three to six weeks.

During the acute phase the temperature may reach 104° to 105° F., but may be remitting with wide daily swings. After five to fifteen days the temperature gradually returns to normal, and most symptoms disappear. After severe illness convalescence may be prolonged for several weeks. Complications are rare. The mortality rate is less than 1 per cent.

Routine hematologic data are not significant. Falsely positive serologic tests for syphilis may exist during the illness.

**Control Measures.** Complete control of Q fever is not possible because of ignorance of the exact mode of spread. Recognition of the disease in livestock should alert communities to the risk of infection. Stockyard workers and others exposed to infected material might receive the formalinized vaccine, which at present is not generally available. Milk from infected herds must be pasteurized at temperatures sufficient to destroy the rickettsiae. Person-to-person spread of Q fever is not a problem, and special isolation measures are not necessary.

**Treatment.** See page 555.

ELI GOLD  
FREDERICK C. ROBBINS

## REFERENCES

- Bell, E. J., and Philip, C. B.: Human Rickettsioses. *Ann. Rev. Microbiol.*, 6:91, 1952.
- Commission on Acute Respiratory Diseases: Epidemics of Q Fever among Troops Returning from Italy in the Spring of 1945. *Am. J. Hyg.*, 44:72, 1946.
- Cooke, J. V.: Rocky Mountain Spotted Fever in Children. *Yale J. Biol. & Med.*, 16:495, 1944.
- Greenberg, M., and others: Rickettsialpox—Newly Recognized Rickettsial Disease; Clinical Observations. *J.A.M.A.*, 133:901, 1947.
- Holmes, W. H.: *Bacillary and Rickettsial Infections*. New York, Macmillan Company, 1940.
- Huebner, R. J., and others: Rickettsialpox—Newly Recognized Rickettsial Diseases. *Pub. Health Rep.*, 61:1605, 1946.
- Kelsey, W. M., and Harrell, G. T.: Management of Tick Typhus (Rocky Mountain Spotted Fever) in Children. *J.A.M.A.*, 137:1356, 1948.
- LaBocchetta, A. C., and others: Rickettsial Pox; 4 Apparent Cases in Pennsylvania. *Am. J. Med.*, 13:413, 1952.
- Lennette, E. H., and Clark, W. H.: Observations on Epidemiology of Q Fever in Northern California. *J.A.M.A.*, 145:306, 1951.
- Ley, H. L., Jr., and Smadel, J. E.: Antibiotic Therapy of Rickettsial Diseases. *Antibiotics & Chemother.*, 4:792, 1954.
- Marmion, B. P.: Q Fever—Natural History. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 48:197, 1954.
- Murray, E. S., and Snyder, J. C.: Brill's Disease. I. Clinical and Laboratory Diagnosis. *J.A.M.A.*, 142:1059, 1950.
- Ong, H. A., and Raffetto, J. E.: Rocky Mountain Spotted Fever; Analysis of 18 Cases in Children. *J. Pediat.*, 17:647, 1940.
- Ormsbee, R. A., and others: The Comparative Effectiveness of Aureomycin, Terramycin, Chloramphenicol, Erythromycin and Thiocymetin in Suppressing Experimental Rickettsial Infections in Chick Embryos. *J. Infect. Dis.*, 96:162, 1955.
- Rivers, T. M., Ed.: *Viral and Rickettsial Infections of Man*. 2nd ed. Philadelphia, J. B. Lippincott Company, 1952.
- Robbins, F. C., and others: Q Fever in Mediterranean Area. *Am. J. Hyg.*, 44:64, 1946.
- Smadel, J. E.: Symposium on Viral and Rickettsial Diseases. *Bact. Rev.*, 14:197, 1950.
- Symposium on the Rickettsial Diseases of Man. Dec., 1946, Boston. *Am. Assoc. for Advancement of Science*, 1948.
- Wolbach, S. B.: Rickettsiae and Rickettsial Diseases of Man: A Survey. *Arch. Path.*, 50:612, 1950.

# MYCOTIC INFECTIONS

## ACTINOMYCOSIS

**Definition and Etiology.** Actinomycosis is a chronic granulomatous infection characterized by the formation, in various parts of the body, of abscesses which tend to break down and form multiple draining sinuses. The disease is more frequent in adults than in children, but must be considered in the differential diagnosis of chronic infections of the lung and of draining sinuses in the jaw, neck or thoracic or abdominal region.

The causative agent, the anaerobic *Actinomyces (bovis) israeli*, appears in the lesion as small hyaline-like to yellow "sulfur granules." On microscopic examination the crushed granule is seen to be a mass of entangled branched mycelial filaments of approximately the same width as bacteria. The filaments in the periphery of the granule may be clubbed. The organisms must be cultured anaerobically, preferably in thioglycolate broth or brain-heart infusion agar. They can often be recovered from the mouth, from tonsils and from pyorrheal pus of patients without actinomycosis, suggesting the possibility of an endogenous source of infection. The disease is not contagious.

**Pathology.** The lesions are those of a chronic granulomatous infection with a great tendency to suppuration with abscess formation, fibrosis, the formation of scars and multiple draining sinuses. The presence of typical "sulfur granules" is characteristic but not pathognomonic.

**Clinical Forms.** *Cervicofacial actinomycosis* (57 per cent of cases). The fungus enters through a carious tooth or the mucous membrane of the mouth or pharynx and produces a gradually enlarging hard or "woody" swelling in the jaw or neck. The tense overlying skin is often reddish or purple. The swelling later softens and drains to the outside through multiple sinuses, but can penetrate deeper to involve the bone and meninges. "Sulfur granules" may be found in the discharging pus. Pain is minimal, and the general health is not greatly affected.

*Abdominal actinomycosis* (22 per cent of cases). Infection may follow an appendectomy and may appear several months later as a hard, irregular mass in the ileocecal region. This mass tends to soften and drain to the outside. Frequently, however, the

infection extends through the diaphragm, after involving the liver and other abdominal organs, to produce thoracic lesions. With a severe infection there are chills, fever, night sweats and loss of weight.

*Thoracic actinomycosis* (15 per cent of cases). The clinical pattern is that of a chronic pulmonary infection with cough, sputum, fever, dyspnea, hemoptysis and loss of weight. Roentgenograms generally reveal bilateral involvement, usually in the lower lobe. The infiltration is often smooth and massive. Extension to the pleura causes accumulation of pleural fluid and involvement of the ribs and subcutaneous tissues with multiple sinus formation.

**Diagnosis.** The diagnosis requires finding the organisms in the pus or biopsy material from the sinus walls. A drop of pus is crushed under a coverglass and examined under the low power of the microscope for the typical "sulfur granules." The disease closely simulates tuberculosis, but other diseases which must be considered are osteomyelitis, amebiasis, hepatic abscess, chronic appendicitis, pulmonary abscess and other fungus infections.

**Prognosis.** This depends upon the extent of the infection; widespread infection may be fatal.

**Prevention and Treatment.** Removal of chronically infected tonsils and treatment of pyorrhea may eliminate possible sources of infection. A general supportive regimen similar to that used in the treatment of tuberculosis should be supplemented by penicillin therapy alone or in combination with sulfadiazine. Potassium iodide is useful in chronic actinomycosis and should be given with the more specific drugs for three to six months after the patient is apparently well. Surgical excision and drainage may be necessary. The broad-spectrum antibiotics or stilbamidine are no more effective than penicillin combined with a sulfonamide; they can be used, alternating with penicillin if the patient fails to respond to the initial therapy, but failure to respond generally means inadequate surgical drainage.

## NORTH AMERICAN BLASTOMYCOSIS

**Definition and Etiology.** North American blastomycosis is an infection with *Blasto-*



*myces dermatitidis* characterized by chronic granulomatous lesions and micro-abscess formation in any part of the body, but with a predilection for lungs, skin and bone. It is practically confined to the North American continent and especially to the Southeast and Mississippi Valley states. Recent evidence suggests that the usual portal of entry is the lungs and that both skin and bone lesions are metastatic.

The source of the infection is unknown. *Blastomyces* have been found in domestic animals (dog and horse) but not living free in nature (soil and wood). In tissues and in pus the fungus appears as a thick-walled, double-contoured, single-budding organism averaging 8 to 12 microns in diameter. On Sabouraud's medium at room temperature it grows slowly as a mold composed of branching filaments and small spores. The budding yeastlike forms are obtained on blood agar incubated at 37° C. Small forms of the organism must be distinguished by cultural means from *Histoplasma* and *Monilia*. The disease is not spread from man to man.

**Pathology.** The organism incites an inflammatory reaction which in the acute phase and in the advancing portions of the lesion is characterized by the formation of minute (micro-) abscesses, in which a search should be made for the organisms. In the older portions of the lesion the reaction is essentially chronic and granulomatous, resembling tuberculosis. Necrosis and fibrosis are present to a variable degree.

**Clinical Forms.** Evidence is accumulating that the disease, like coccidioidomycosis and histoplasmosis, may exist more frequently as a mild primary infection than as the more severe form usually recognized at present. In a well documented epidemic seven of ten patients were children, and the majority of these had only mild pulmonary lesions and few systemic manifestations; one patient cleared spontaneously without therapy.

**Pulmonary blastomycosis.** The usual history is of an acute upper respiratory infection which persists. Cough, chest pain, weakness and loss of weight may occur. The roentgenogram may show a variety of lesions; infiltrations resembling virus pneumonia, diffuse miliary lesions, nodular or homogeneous areas of consolidation and abscesses of various size. With progression, the symptoms increase in severity and the patient loses weight, has irregular bouts of fever, has bloody, purulent sputum and becomes cachec-

tic. Spread of this infection may be either local or hematogenous.

**Cutaneous blastomycosis.** Cutaneous blastomycosis may result by direct inoculation of the organism into the skin or by dissemination to the subcutaneous tissue from a pulmonary lesion which may be unrecognized. The initial lesion is a small papule, usually on an exposed area of the body, which undergoes ulceration and crusting. The infection spreads by peripheral extension with a tendency to heal in the center. The periphery of the lesion tends to be serpiginous with a raised, ulcerated granulomatous border in which there are many micro-abscesses. The pus expressed from the micro-abscesses usually shows the budding organisms. The lesions may be single or multiple, but rarely are there any systemic symptoms unless there is involvement of other organs.

**Disseminate blastomycosis.** The usual sequence is extension from a primary lesion in the lungs to many organs in the body, in particular to the bones, skin, subcutaneous tissues and internal organs. Skeletal involvement results in localized or diffuse osteomyelitis with destruction of bone and the formation of cutaneous sinuses from which pus exudes. The subcutaneous nodules and abscesses, which may be painful, have a tendency to break through the skin and then assume the characteristics of the cutaneous lesions. Systemic symptoms may be relatively mild in the predominantly osteomyelitic form, but severe in the widely disseminated group.

**Diagnosis.** The pulmonary lesions may resemble those of tuberculosis, neoplasms, pneumonia, abscess, sarcoidosis and other fungus diseases. Diagnosis may be made by finding and culturing the organism's in sputum or, in children, in the gastric washings. Pus from draining sinuses should be mixed with a drop of 10 per cent potassium hydroxide and examined for the characteristic refractile, thick, double-contoured, walled organisms. The cutaneous lesions can be mistaken for syphilis, tuberculosis, pyoderma, cat-scratch disease, carcinoma, bromide rashes, granulomas, and other fungus infections.

Infection results in a positive delayed skin reaction to blastomycin or *blastomyces* vaccine. However, a negative skin reaction does not exclude the diagnosis, and a positive reaction may be obtained in persons without clinical manifestations. Severe and disseminate lesions tend to produce complement-fixing antibodies in the blood.

**Prognosis.** The localized, mild pulmonary lesions have a good prognosis, as do the localized cutaneous lesions. Widespread pulmonary and disseminate lesions have a poor prognosis and are usually fatal without extensive treatment. A negative skin test with a positive complement fixation test indicates a poor prognosis and the probability of relapse after therapy. A positive skin test with a negative complement fixation test is a good prognostic sign.

**Treatment.** Hydroxystilbamidine diisethionate is the drug of choice. The initial dose for adults is 50 to 100 mg. given intravenously in 100 ml. of 5 per cent glucose. It is followed by daily intravenous doses of 225 mg. in 300 cc. of 5 per cent glucose for thirty days, or in several series of ten to fourteen days each with a rest period between each series. Proportionately smaller amounts are given to children; weakness, nausea and circulatory collapse may result from too rapid administration. Hydroxystilbamidine is stored in the tissues and continues to exert its effect for months after the course has been completed. When the stilbamidines are not effective, or there is a relapse after several courses, Amphotericin B may be tried. In addition, iodides may be used, but the patient should first be desensitized to blastomycetes vaccine if the skin test is strongly positive. Operation, performed under a mistaken diagnosis of neoplasm, has occasionally been curative in localized pulmonary lesions, but may precipitate dissemination. Appropriate antimicrobial agents should be used for secondary infection occurring in the skin, lungs or bones.

## CRYPTOCOCCOSIS

(TORULOSIS)

**Definition and Etiology.** Cryptococcosis is a subacute or chronic infection caused by *Cryptococcus neoformans* (*Torula histolytica*), a fungus which can invade the lungs, skin, joints and subcutaneous tissues, but has a predilection for the central nervous system. The disease is worldwide in distribution and occurs at all ages. The organism has been found on various fruits, in soil, pigeon excreta and in cow's milk. It probably enters the body through the respiratory tract, but may also enter through the skin.

**Pathology.** The fungus is relatively inert, and the early lesion is a cystlike cavity containing gelatinous material with little or no

cellular reaction. Older lesions may become granulomatous, but cryptococcosis usually remains a nonsuppurative disease. The earliest pulmonary lesion is probably a subpleural nodule which may go on to spontaneous healing. In the brain and meninges there is a chronic inflammatory reaction with giant cells, macrophages and lymphocytes, but relatively few neutrophils.

**Clinical Manifestations.** Symptoms of central nervous system cryptococcosis are those of meningitis or brain abscess, with headache, dizziness and stiffness of the neck. Signs of increased intracranial pressure appear after weeks or months; the cerebrospinal fluid pressure is increased, and the cell count may be high. Coma ensues, and death results from respiratory failure.

The clinical picture of pulmonary cryptococcosis is not diagnostic. There is low grade fever, mild cough, and infiltrative lesions of variable size in the lungs, frequently bilateral. Although pulmonary involvement in itself may cause death, the chief danger is dissemination to the central nervous system.

Infection of the skin usually occurs on the face, beginning as an acneiform, firm, nodular, painless eruption which may enlarge, become necrotic and ulcerate. The lesions resemble carcinoma, sarcoid, tuberculosis and other fungus infections.

Of particular interest is the generalized disseminate form which has been found in the *newborn*. The symptoms date from birth and include central nervous system manifestations, jaundice, hepatomegaly, splenomegaly, chorioretinitis and intracranial calcifications. Hydrocephalus and cerebral degeneration may occur. The manifestations resemble those of congenital toxoplasmosis and cytomegalic inclusion disease.

Infection with cryptococcosis and dissemination of the disease probably depend largely on host factors. There is a great susceptibility in patients with malignant lymphoma, Hodgkin's disease and leukemia; one third of all cryptococcosis occurs in conjunction with these diseases.

**Diagnosis.** Diagnosis is established by finding encapsulated budding yeast cells in the cerebrospinal fluid and in lesions (biopsy) by direct examination and culture. The fungus appears as a thin-walled budding yeast surrounded by a large gelatinous capsule. Growth on Sabouraud's medium is creamy white, mucoid and glistening. Smears from the culture show budding yeast cells,



but the capsule is demonstrated best in a fresh India ink preparation. Fungus cells in cerebrospinal fluid may easily be mistaken for lymphocytes unless the India ink preparation is used to demonstrate the capsule.

In differential diagnosis, tuberculosis and infections by other fungi must be considered.

**Prognosis and Prevention.** The prognosis is serious in all forms of the disease, and meningitis is usually fatal. Early treatment of pulmonary, cutaneous and subcutaneous infections is advisable to obviate the danger of central nervous system involvement. The disease is not communicable from man to man.

**Treatment.** Treatment of localized lesions consists in surgical excision and drainage. Iodides may be helpful. More recently, promising results even in the treatment of cryptococcosis meningitis have been reported from the use of Amphotericin B; other antibiotics are valueless. Sulfonamides have a slight effect.

## MUCORMYCOSIS

**Definition and Etiology.** Mucormycosis is a bizarre, usually acutely fatal disease characterized by a necrotizing and inflammatory process in which broad, nonseptate, hyphal strands can be seen in histologic sections. The causative organisms belong to the family *Mucoraceae*, and two species of the genus *Rhizopus* have been isolated from clinical cases. These organisms are generally saprophytes of widespread distribution (bread molds) and achieve pathogenic invasiveness only in persons whose resistance has been lowered by diabetes or some debilitating illness. The organisms grow well on Sabouraud's medium at room temperature as a true fungus with characteristic asexual and sexual spores.

**Pathology.** When pathogenic and invasive rather than saprophytic, the organism causes an intense inflammatory reaction with a polymorphonuclear response and extensive necrosis. Of particular interest is the tendency of the organism to invade blood vessels and cause thrombosis. The hyphae penetrate and grow in the walls of both arteries and veins, breaking out in some sections through the adventitia and in other parts rupturing the intima. Thrombosis occurs, and the organisms can be seen together with many leukocytes and fibrin strands in the clot. The resulting infarction accounts for much of the necrosis. In addition there may be a

striking invasion of nerves and perineural lymphatics. Involvement of the cranial cavity ("cerebral mucormycosis") may cause leptomeningitis, infarctions due to vascular thromboses, direct nerve involvement by invasion and acute necrotizing encephalitis.

**Clinical Forms.** The disease usually develops in association with severe and prolonged metabolic disturbance through uncontrolled diabetes, uremia, chronic diarrhea, adrenal hormone therapy, prolonged chemotherapy, malignancies and other cachectic states.

**Pulmonary form.** Pulmonary mucormycosis occurs by direct or hematogenous invasion of the lungs resulting in the pathologic processes described above. The clinical picture is that of an extremely acute, severe, lobular pneumonia or infarction. The patient complains of chest pain and has bloody sputum, friction rub, fever and leukocytosis.

**Cerebral mucormycosis.** In this type the organism probably enters the nasal cavity or the sinuses. Necrosis and acute inflammation extend to the orbit, palate, meninges and brain. Symptoms and signs of orbital cellulitis, sinusitis, cavernous sinus thrombosis, nerve involvement or meningoencephalitis result. Of the known cases all except two have been fatal.

**Other forms.** The organism may invade the digestive tract, the heart and other organs, where the same pathologic sequence is observed. Symptoms are those of inflammation and infarction of the involved organs.

**Diagnosis.** The appearance of manifestations of acute inflammation, infarction or necrosis in the lungs, gastrointestinal tract, orbits and the intracranial cavity in a patient debilitated by a chronic disease should suggest the possibility of mucormycosis. Diagnosis depends upon recognition of the fungus in specimens of tissue or of body fluids.

**Prevention and Treatment.** Both prevention and treatment are best accomplished by proper care of the underlying predisposing debilitating illness. The two known recoveries were in diabetic patients whose diabetes was brought under control and the mucormycosis was treated by desensitization with a vaccine made from the fungus, administration of large doses of iodides and antimicrobial treatment of secondary bacterial infections.

## NOCARDIOSIS

**Definition and Etiology.** Nocardiosis is

a noncontagious, subacute or chronic suppurative disease primarily of the lungs, but with a tendency to hematogenous dissemination. The causative organisms belong to the same family as does *Actinomyces*. They are gram-positive with branching filaments, but, in contrast to *Actinomyces*, may be partially or strongly acid-fast, can be grown aerobically on simple media at room temperature and are found living free in nature (soil). Of the nine recognized species, *N. asteroides* is the commonest cause of systemic infection.

**Pathology.** The basic histologic lesion is a focal area of necrosis surrounded by a variable cellular infiltrate. These abscesses are characteristically not encapsulated, but may show secondary fibrosis, or they may caseate and cavitate. Pulmonary infection (probably produced by inhalation of contaminated dust) begins as an acute pneumonitis which may become chronic and persist for a long time. The lesions may extend locally and spread hematogenously to the subcutaneous tissues and to other organs, especially the brain. Demonstration of the organisms in tissues requires the gram or acid-fast technique, since they are not stained by the routine hematoxylin-eosin method. Differentiation from tuberculosis may be extremely difficult because of the histology, the acid-fastness of the organisms and their ready fragmentation into bacillary forms.

**Clinical Forms.** Aside from the localized primary cutaneous and subcutaneous infections which are uncommon in the United States, the clinical picture of nocardiosis is that of a chronic suppurative pulmonary disease which spreads locally and metastasizes to other organs. Twelve per cent of these cases have occurred in children—as early as four weeks of age. Common manifestations are cough, fever, anorexia, weight loss, malaise, night sweats, fatigue, dyspnea, chest pain and leukocytosis up to 50,000 per cubic millimeter. Local extension may result in empyema. A characteristic sequence is pulmonary disease followed shortly by pustular eruption of the skin. There is a pronounced tendency to chronicity with remissions and exacerbations over many years. Secondary intracranial involvement results in cerebral abscess and/or meningitis. When the organisms, particularly *Nocardia madurae*, gain entrance through abrasions in the feet, they produce a burrowing infection of the subcutaneous tissues and bone, *mycetoma pedis*.

**Diagnosis.** Roentgenograms of the lungs usually reveal small infiltrative lesions or

large lobular areas of consolidation, with the lower lobes of the lungs involved most often. Suppuration and cavitation may occur. The important features are chronicity with gradual progression, multiple lesions, failure to show resolution with antibiotic therapy and the diagnosis not established by routine methods.

Differentiation must be made from actinomycosis by cultural means and by examination of the pus (sulfur granules are seldom present in *N. asteroides* infections). This is important, since therapy is different in the two conditions. Owing to the clinical resemblance to tuberculosis and the acid-fastness of the organisms, the differentiation is extremely difficult; it has been estimated that nocardiosis accounts for 1 to 5 per cent of patients in tuberculosis hospitals. When the lesion metastasizes to other organs, the resemblance to staphylococcal pyemia is striking. The chronic pulmonary disease has been also mistaken for cystic fibrosis of the pancreas.

**Prognosis and Treatment.** The over-all mortality is probably over 50 per cent. However, lesions respond well to symptomatic care and sulfonamide therapy in their early stage. Surgical excision may be necessary. The organisms are partially susceptible to the broad-spectrum antibiotics, but resistant to penicillin, in contrast to actinomycosis, in which the organisms are more sensitive to penicillin and other antibiotics than to sulfonamides.

## SPOROTRICHOSIS

**Etiology.** Sporotrichosis is caused by *Sporotrichum schenckii*, a fungus which most frequently infects the skin and subcutaneous tissues, producing a series of nodules and ulcerations. The fungus also may infect the mucous membranes, lungs and other organs. It is one of the most common "deep mycoses" and is the least serious, since it responds well to therapy. The organism has been isolated from soil, plants and infected timber. It is probably inoculated by direct contact into abrasions in the skin.

**Pathology.** Section of a nodule usually shows granulation tissue with epithelioid cells and giant cells surrounding a necrotic area, a lesion similar to that produced by tuberculosis or other fungus infections.

**Clinical Manifestations.** The lesion begins usually in the skin or in the subcutaneous tissue as a small, hard nodule not attached to the skin. This nodule later adheres to



the overlying skin, which becomes darker in color and finally ulcerates, discharging a small amount of purulent material. This primary "chancre" may persist for months and is followed usually by a succession of freely movable nodules, which form a chain along the course of the lymphatic drainage. These nodules may subsequently become attached to the skin and ulcerate. The patient is afebrile, and the general health is not affected. Sporotrichotic infections of the mucous membranes, lungs, bones and other organs occur, but are rare except for bone and joint infections, which comprise 17 per cent of total infections.

**Diagnosis.** The disease may resemble tuberculosis, syphilis or infections by other fungi. The local lesions suggest tularemia, but the general symptoms are not those of an acute bacterial infection. Diagnosis depends upon culturing the fungus from the chancre or subcutaneous nodule.

The fungi occur in the lesions as intracellular, small "cigar-shaped" bodies, 3 to 4 microns in length, and are demonstrated with difficulty. Direct smears cannot be depended upon as a diagnostic procedure. On Sabouraud's medium the fungus grows as a white or black mold identified as clusters of small, delicate, pear-shaped spores borne on short branches of narrow mycelial filaments.

**Prognosis.** Though the disease may persist for many months, the prognosis is good under adequate therapy.

**Treatment.** Oral administration of potassium iodide in increasing amounts up to tolerance is almost specific. The medication should be continued for at least a month after healing has occurred. Abscesses may be aspirated, but incision and curettage should be avoided. For patients who are sensitive to iodides or have systemic lesions, hydroxystilbamidine diisethionate and possibly Amphotericin B may be helpful.

JEROME S. HARRIS

## REFERENCES

### General

- Conant, N. F., Smith, D. T., Baker, R. D., Callaway, J. L., and Martin, D. S.: *Manual of Clinical Mycology*. 2nd ed. Philadelphia, W. B. Saunders Company, 1954.
- Keeney, E. L.: *Practical Medical Mycology*. Springfield, Ill., Charles C Thomas, 1955.
- Smith, D. T., Ed.: *Symposium on Fungus Infections*. *J. Chronic Dis.*, 5:371, 1957.
- Vilson, J. W.: *Systemic Fungous Infections*. *Disease-a-Month*, Dec., 1956.

### Blastomycosis

- Smith, J. G., Jr., Harris, J. S., Conant, N. F., and Smith, D. T.: An Epidemic of North American Blastomycosis. *J.A.M.A.*, 158:641, 1955.

### Cryptococcosis

- Littman, M. L., and Zimmerman, L. E.: *Cryptococcosis*. New York, Grune & Stratton, Inc., 1956.
- Neuhauser, E. B. D., and Tucker, A.: The Roentgen Changes Produced by Diffuse Torulosis in the Newborn. *Am. J. Roentgenol.*, 59:805, 1948.

### Mucormycosis

- Baker, R. D.: Mucormycosis—A New Disease? *J.A.M.A.*, 163:805, 1957.
- Harris, J. S.: Mucormycosis. *Pediatrics*, 16:857, 1955.

### Nocardiosis

- Ballenger, C. N., Jr., and Goldring, D.: Nocardiosis in Childhood. *J. Pediat.*, 50:145, 1957.
- Gunderson, G. A., and Nice, C. M., Jr.: Nocardiosis. *Radiology*, 68:31, 1957.

### Sporotrichosis

- Mikhelsen, W. M., Brandt, R. L., and Harrell, E. R.: Sporotrichosis. *Ann. Int. Med.*, 47:435, 1957.

## HISTOPLASMOSIS

Histoplasmosis is an acute, subacute or chronic infectious disease caused by the fungus *Histoplasma capsulatum*. Histoplasmosis, once thought to be invariably fatal, is now recognized as a relatively common benign (often clinically inapparent) or only moderately severe disease and less frequently as an overwhelming one. At least 30 per cent of the observed cases of histoplasmosis have occurred in children.

**Etiology.** *Histoplasma capsulatum* has two distinct growth phases. When cultivated on artificial media at room temperature, it produces a white, cottony, aerial, mycelial growth and a brownish-yellow subsurface growth. In tissues and when first cultivated on enriched media at 37° C., it grows in a yeast cell phase, having a relatively thick, translucent capsule. It can be identified in the mycelial culture by the characteristic tuberculate chlamydospores. The fungus has been isolated from dogs, mice, rats and horses, and from soil, principally adjacent to chicken houses and pigeon lofts, but also in damp places, along streams and in caves. There is no evidence that the disease is transmitted from man to man or from animal to man.

**Pathogenesis and Pathology.** The fungus apparently enters the body through the skin or through the mucous membrane of

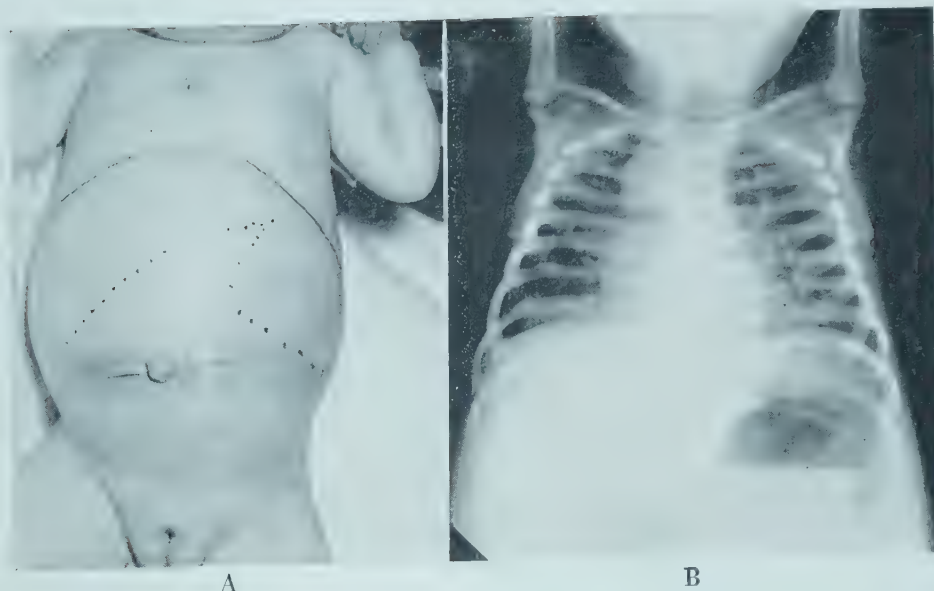


FIG. 168. Histoplasmosis in infancy. A, An infant, aged 5½ months, with pyrexia, anemia, hepatosplenomegaly and leukopenia. Note site of sternal puncture; yeast cells of *H. capsulatum* were found in smears and cultures of the sternal marrow. B, Chest roentgenogram shows diffuse pneumonitis and a mediastinal mass. Diagnosis confirmed by autopsy. (Hild: *Am. J. Dis. Child.*, Vol. 63.)

the mouth, nasopharynx, respiratory tract or intestinal mucosa, producing an ulcerative lesion. The disease may manifest itself as a generalized process involving the reticuloendothelial system in the bone marrow, lung, liver, spleen and lymph nodes. The individual lesions are tubercle-like granulomas, occasionally with central necrosis; calcium is often deposited in the healing lesion.

**Clinical Manifestations. Severe form.** The progressive form of the disease, which is more likely to occur in infants and young children or in debilitated adults, is generally recognized only after it has reached a moderately advanced stage, when the clinical pattern may be suggestive of leukemia. The temperature is irregularly elevated from 101° to 103° F. The signs and symptoms vary considerably; there may be a mild gastrointestinal disturbance often with diarrhea, weight loss, malaise, irritability, pallor, indefinite joint and muscle pains or abdominal enlargement. Pneumonitis is common. In most cases there is enlargement of the spleen and liver. The roentgenogram of the chest may reveal scattered parenchymal lesions and/or enlarged mediastinal nodes, which on occasion are responsible for localized obstructive emphysema. Purpura, ecchymoses and melena may be present in the terminal stages. In children peripheral lymphadenopathy of a marked degree is uncommon. Meningitis with cerebrospinal fluid changes similar to

those of tuberculous meningitis has been observed.

**Mild and moderately severe forms.** In the decade of 1930 it became evident that a large number of persons living in the central and southern states bordering the Mississippi River and in the states of the Western Appalachian slope had what appeared to be calcified tuberculous lesions in the tracheobronchial lymph nodes and in the lungs, but with a negative reaction to tuberculin. Subsequently it was discovered that most of these persons had a positive skin reaction to histoplasmin. It now seems apparent that they were infected with *H. capsulatum* and in most instances were not aware of the time of the acute stage.

Thus it appears that histoplasmosis, like tuberculosis and coccidioidomycosis, may be a widespread infection, with common benign and rare severe forms, which sensitizes the human host to its antigen and whose lesions in the benign form heal by calcification, and which, like coccidioidomycosis, has a distinct geographic distribution. Noncalcified single and multiple focal lesions have been demonstrated in the lungs with associated involvement of the hilar lymph nodes which subsequently calcify. In neither stage are these lesions distinguishable from tuberculous lesions (Figs. 169, 170). When children with such lesions have positive skin reactions to histoplasmin and negative ones to tuberculin,



it is assumed that they have active (noncalcified) or healed (calcified) histoplasmosis. There is no evidence that persons who have such calcifications have any impairment of health or any increased likelihood to development of the severe, progressive form of the disease.

In a disease in which severe fatal forms and asymptomatic benign ones are recognized it would seem reasonable that there would be intermediate forms. *Histoplasma capsulatum* has been isolated from children with splenomegaly, ulcerations of the skin or mucous membranes and/or pulmonary infiltrations, who have recovered. These children have skin sensitivity to histoplasmin and complement-fixing antibodies.

**Laboratory Diagnosis.** Changes in the blood usually consist in a progressive hypochromic anemia and a leukopenia with a relative lymphocytosis. There may be a pancytopenia, suggestive of an aleukemic phase of leukemia; the platelets, however, are usually not reduced until late in the course of the disease. On occasion the parasites can be demonstrated in the white blood cells.

The yeast phase of the fungus as it occurs in the cells of the body appears as a small (1 to 5 microns), encapsulated oval body in the large mononuclear cells. The cellular elements of the bone marrow are otherwise normal. Thick-drop preparations or smears of the peripheral blood and bone marrow should be stained with Wright's or Giemsa's

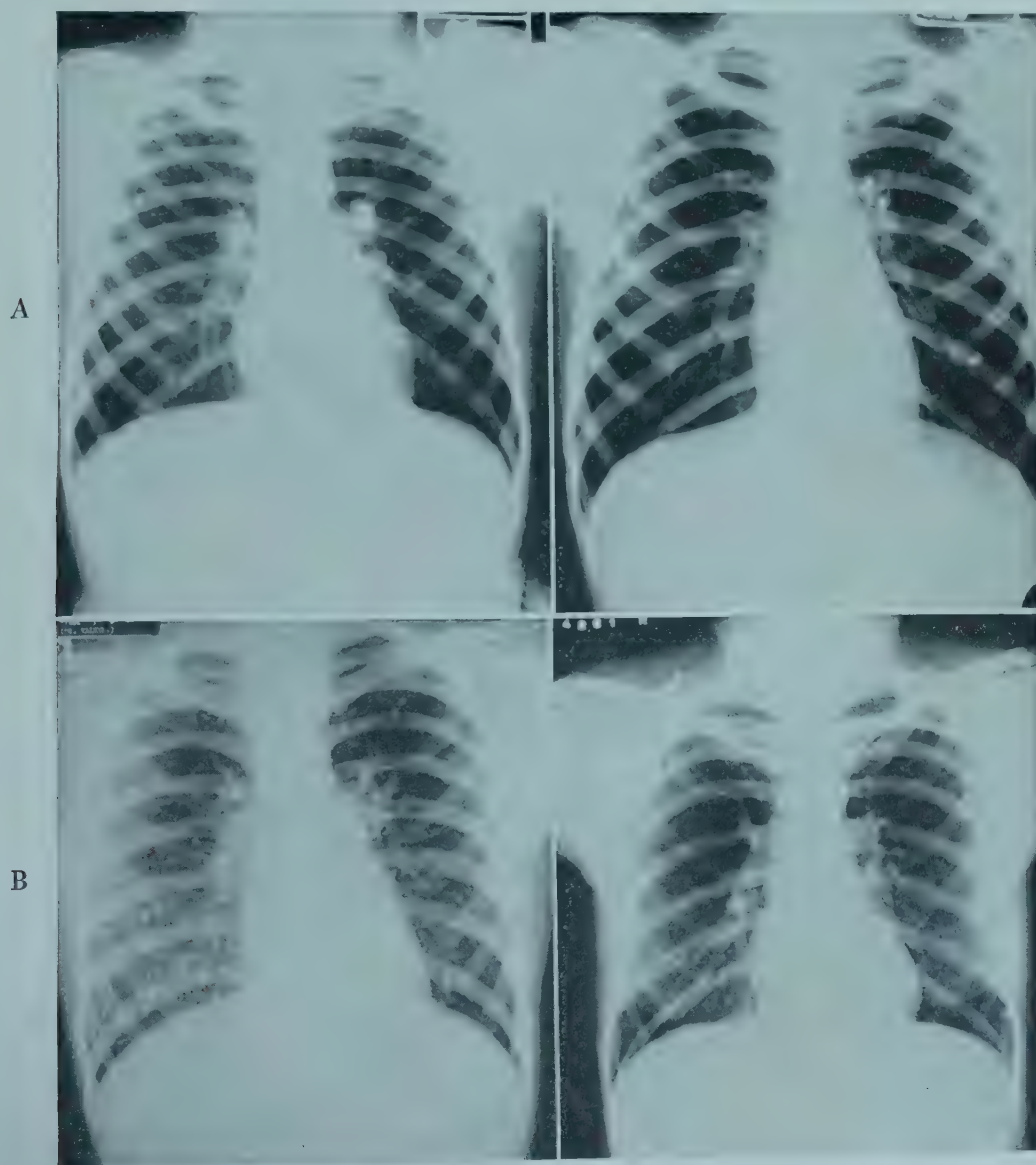


FIG. 169. Examples of pulmonary and mediastinal calcifications in histoplasmin-positive and tuberculin-negative patients. A, Single pulmonary and mediastinal calcified masses strikingly similar to so-called healed pulmonary tuberculous complex. B, Multiple parenchymal calcifications suggestive of healed miliary tuberculosis.



FIG. 170. Roentgenogram of chest, showing fibrosis, calcification and cavity formation in the left upper lobe. Note similarity to chronic tuberculosis in apical area. The histoplasmin reaction was strongly positive; none to tuberculin. *Histoplasma capsulatum* was cultured from sputum. The patient regained his weight and was reported well one year after this roentgenogram was taken. (Johnson and Batson: Dis. of Chest, Vol. 14.)

stain. Biopsy material from lymph nodes or from the liver or spleen, as well as sputum or material swabbed from an ulcerative lesion, can also be smeared and stained by one of these methods.

**Technique of culture.** The technique to be followed varies somewhat with the material. Biopsy specimens are ground to a thin paste, using a minimal amount of sterile saline solution. Swabs from infected areas are placed in test tubes containing 1 to 2 ml. of sterile saline solution. Blood is mixed with heparin, rather than citrate, as an anticoagulant and is centrifuged at sufficiently high speed to allow separation of the white cells, which are pipetted off and placed in a test tube containing 1 to 2 ml. of sterile saline solution. After one hour, and again after twenty-four to forty-eight hours of incubation, the material is streaked heavily on duplicate screw cap bottles (25 by 50 mm.) containing slants of peptone or meat extract agar to which has been added plasma or blood serum to a concentration of 5 per cent and 50 units per milliliter of penicillin and 0.4 mg. per milliliter of streptomycin in the media. The use of bottles instead of Petri dishes or plates has decreased air contamination by fungi and permits small amounts of material to be studied. The bottles must be sealed; one bottle is incubated at 37° C., the other at room temperature. The cultures should be examined at intervals of three to four days and should not be considered negative until after an observation period of four weeks. Positive cultures which have been kept at 37° C. will frequently have colonies of yeast cells rather than of

mycelium. At room temperature *H. capsulatum* grows only in the mycelial phase, producing the characteristic tuberculate chlamydospores. The older the mycelial culture, the more likely are chlamydospores apt to be present. Thus in young cultures they may not be found, and the culture may be considered negative.

**Histoplasmin test.** The histoplasmin skin test resembles the tuberculin test. The testing material, a filtrate of a broth culture of *H. capsulatum*, is injected intracutaneously. The reaction is read at forty-eight hours; a positive reaction consists of an area of erythema with induration of at least 0.5 mm. in diameter. A positive reaction is evidence of sensitization to *H. capsulatum*, but does not indicate whether the infection is active. Conversion from a negative to a positive reaction within a few weeks or a positive reaction in infants is suggestive of an active infection. Persons with progressive disseminated histoplasmosis frequently fail to react to histoplasmin.

Serologic tests are useful to establish the presence of progressive infection.

**Differential Diagnosis.** Histoplasmosis may simulate a number of other clinical conditions. The presence of progressive anemia, leukopenia and hepatosplenomegaly requires differentiation from leukemia, the lipid storage diseases, Banti's syndrome, malaria and



brucellosis. Both extrathoracic and intrathoracic tuberculosis must be considered, and when there are persistent gastrointestinal signs, tuberculous peritonitis or enteritis must be included in the differential diagnosis. Ulceration of the skin or mucous membranes must be differentiated from actinomycosis, leishmaniasis and toxoplasmosis; irrespective of lymph node enlargement, Hodgkin's disease and other malignant lymphomas must be ruled out. Other systemic mycotic diseases and coccidioidomycosis in particular must be included in the differential diagnosis of the pulmonary infection.

**Treatment.** No chemotherapeutic or antibiotic agent has been found which satisfactorily inhibits the growth of *H. capsulatum* without injuring the tissue of the host. The usual antibiotics are completely without effect, and some of them may facilitate growth of the fungus. In the author's experience sulfonamides (triple sulfonamides) have seemed to offer the most benefit in doses sufficient to obtain blood levels of 15 to 20 mg. per 100 ml. Amphotericin B is being used, and there are some reports suggesting favorable effects. The drug is toxic, however, and should be used only on an experimental basis.

AMOS CHRISTIE

## REFERENCE

Schwarz, J., and Baum, G. L.: The History of Histoplasmosis, 1906 to 1956. New England J. Med., 256:253, 1957.

## COCCIDIOIDOMYCOSIS

(SAN JOAQUIN FEVER, VALLEY FEVER, DESERT RHEUMATISM, COCCIDIOIDAL GRANULOMA)

**Etiology.** Coccidioidomycosis is an infection caused by the fungus *Coccidioides immitis*. The minute spores of its so-called saprophytic phase are inhaled or, rarely, enter through an abrasion. They round up into spherules which develop endospores within doubly refractile walls, the characteristic sporangium of the so-called parasitic phase. These spherules do not spread from person to person or from animal to man; so the infection is not contagious. The mycelial form frequently occurs in pulmonary cavities, but no cases of contagion have been discovered. However, as they occur in nature and on surface cultures, the arthrospores (chlamydospores) of the "saprophytic phase" are highly infectious. Within the arid endemic areas of

California's San Joaquin Valley, in scattered regions in southern California, in central and southern Arizona and even in western and southern Texas, from three quarters to nine tenths of the population have been infected along with cattle, sheep, dogs and wild rodents. Infection is quickly acquired and apparently confers a permanent immunity. Therefore, where the population is stable, it is a childhood infection.

**Clinical Forms.** The human infection must be considered under two broad headings: (1) a benign, self-limited primary infection; and (2) a rare, disseminating, generally fatal disease.

**Primary coccidioidomycosis.** The incubation period varies from one to three weeks, with an average of ten to sixteen days. In 60 per cent of infected persons there are no clinical manifestations. Symptoms are influenzal in type, and the onset may be insidious, or abrupt with malaise, chills and fever. Night sweats and anorexia are common, and on occasion there is a persistent dry cough with which there may be a painful throat. There may be headache, backache, chest pain, which may vary from a mere sense of constriction to excruciating pleurisy with labored respirations, arthritis, phlyctenular conjunctivitis and skin rashes.

There may be a generalized, fine, macular erythema within the first day or two somewhat similar to the rash of measles or scarlet fever. The most frequent dermatologic manifestation, however, is erythema nodosum with or without erythema multiforme. These lesions develop in approximately 5 per cent of infected persons at the time sensitivity to coccidioidin is maximal, three to twenty-one days after onset of symptoms, although skin lesions may occur in persons otherwise asymptomatic.

Physical examination of the chest rarely discloses positive findings, even though roentgenography reveals extensive consolidation. Infrequently dullness, a friction rub or fine rales may be detected. Pleural effusions occur at times and may be so massive as to embarrass respiration. Like tuberculous pleural effusions, they may develop without preceding respiratory symptoms. Infrequently a cavity may develop in an area of pulmonary consolidation. There are usually no symptoms related to it, and the diagnosis is made from the roentgenogram. Occasionally, however, there is hemoptysis which, although it may recur and be alarming, is seldom so severe as to impair health. Dissemination of infectious

material from these cavities resulting in lesions in other areas is extremely rare. The infection appears to be focalized as well in persons with cavities as in those without them. Pulmonary residuals sometimes persist, but are not harmful. They pose problems of differentiation from tuberculosis.

**Disseminated or progressive coccidioidomycosis (coccidioidal granuloma).** Certain persons seem to lack ability to focalize the coccidioidal infection. Dissemination, which is rare and occurs mainly in males, especially in those of the dark-skinned races, usually follows the initial illness within six months, often without any interlude. The closest analogy is to progressive primary tuberculosis. Meningitis is the most serious of the disseminated lesions, clinically being similar to tuberculous meningitis. In white persons it is not unusual for meningitis to be the only extrapulmonary lesion. Papillomatous skin lesions and cold abscesses, both subcutaneous and osseous, occur most frequently in the dark-skinned races. The tendency to abscess formation is relatively more frequent in coccidioidal granulomas than in tuberculous lesions. Miliary dissemination and peritonitis are clinically and, except by demonstration of the etiologic agent, pathologically indistinguishable from tuberculosis. The case fatality rate of the disseminated infection is at least 50 per cent, and of meningitis practically 100 per cent.

**Diagnosis.** Diagnosis of the disseminated infection may be established by biopsy or at autopsy. If histologic examination demonstrates the characteristic double-contoured spherules with endospores and without budding, the diagnosis is certain. In both primary and disseminated infections recovery of the fungus by culture and animal inoculation is also diagnostic. Coverglass examination is not sufficient, since the diphasic character of the fungus should be demonstrated. Sputum is generally scanty in the primary infection, so that gastric lavage may be advisable, especially in children. The fungus will not withstand the concentration procedures used for tubercle bacilli. The material should be cultured or, after treatment with penicillin and streptomycin or 0.05 per cent copper sulfate, injected intratesticularly into a guinea pig. Any suspicious white fluffy fungus should be injected into a mouse or guinea pig to demonstrate diagnostic spherules. All cultures must be moist, and care must be exercised in handling them, since infections are frequently contracted in the laboratory.

**Coccidioidin test.** The test is specific except for occasional cross reactions in histoplasmosis and blastomycosis. Like the tuberculin test, a positive reaction does not distinguish between a recent or old infection unless preceded within a reasonably short time by a negative test. Obviously, its usefulness is restricted in residents of an endemic area. The coccidioidin is administered intradermally as 0.1 ml. of a 1:100 or 1:1000 dilution. The reaction generally reaches its peak at thirty-six hours and should be read at twenty-four and forty-eight hours. The criterion for a positive test is an area of induration more than 5 mm. in diameter. Patients with erythema nodosum suspected of being coccidioidal should have the weaker solution, since they are likely to be hypersensitive. Patients with disseminated infections are much less sensitive, a 1:10 dilution often being required to elicit a reaction. There is no danger of disseminating or activating a coccidioidal infection by a strong coccidioidin reaction, although there may be a systemic reaction as well as a local one. Coccidioidin does not evoke humoral antibodies, so that the skin test may precede serologic tests and provides information necessary for their interpretation.

**Blood and cerebrospinal fluid.** Serum precipitins and complement fixation appear after coccidioidin sensitivity has become demonstrable and persist during periods of anergy associated with overwhelming disseminated lesions. In general, the more severe the infection, the higher the titer of complement fixation. Humoral antibodies are generally not demonstrable in asymptomatic infections. The sedimentation rate is rapid in both primary and disseminated infections and is helpful in evaluating the clinical status. Eosinophilia is a common finding. The cerebrospinal fluid findings, other than a frequently encountered paretic type of colloidal gold curve, are similar to those of tuberculous meningitis.

**Roentgenography.** During the primary infection, roentgenograms of the chest may reveal no pulmonary changes, and those that occur are not diagnostic. Hilar adenopathy occurs frequently, and there may be single or multiple sharply circumscribed or soft feathery small pulmonary densities or larger consolidated areas. Pulmonary cavities, when present, tend to be thin-walled. There may be pleural effusions of variable extent. The osseous lesions of the disseminated infection are usually multiple with a predilection for



cancellous bone; the lesions often show considerable proliferation and are generally indistinguishable from those of tuberculosis.

**Treatment.** No drugs are known to be beneficial except for symptomatic relief. Salicylates, with or without iodides, may be given, especially when there is erythema nodosum. If a cavity develops and does not close after a month or two of bed rest, the patient may, unless the activity produces serious symptoms, be permitted up, provided he is kept from competitive sports and strenuous exertion. Most cavities disappear, even those which have existed for a year or so. If they increase in size, are repeatedly secondarily infected, or produce severe hemoptysis, surgical removal is recommended.

During the acute infection, in order to reduce the danger of dissemination, rest is advisable until the child is symptom-free and the sedimentation rate approaches normal. When dissemination occurs, little can be done to influence the course. Vaccines have been advocated, but their value has not been

established. Occasionally excisions, amputations and fusion operations have been beneficial in the treatment of osseous lesions. Treatment, in general, consists in the supportive measures used for tuberculosis.

CHARLES E. SMITH

#### REFERENCES

- Faber, H. K., Smith, C. E., and Dickson, E. C.: Acute Coccidioidomycosis with Erythema Nodosum in Children. *J. Pediat.*, 15:163, 1939.
- Jamison, H. W.: Roentgen Study of Chronic Pulmonary Coccidioidomycosis. *Am. J. Roentgenol.*, 55:396, 1946.
- Schwarz, J., and Muth, J.: Coccidioidomycosis: A Review. *Am. J. M. Sc.*, 221:89, 1956.
- Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G.: Varieties of Coccidioidal Infection in Relation to Epidemiology and Control of the Diseases. *Am. J. Pub. Health*, 36:1394, 1946.
- Smith, C. E.: Coccidioidomycosis. *Pediat. Clin. North America*, 2:109, 1955.
- Smith, C. E., Saito, M. T., and Simons, S. A.: Pattern of 39,500 Serologic Tests in Coccidioidomycosis. *J.A.M.A.*, 160:546, 1956.

# PARASITIC DISEASES

## HELMINTHIC AND ARTHROPOD DISEASES

Helminths and arthropods are Metazoa, i.e., many-celled animals, and both belong to the invertebrates. The helminths, or parasitic worms, comprise three large groups, the Nematoda (roundworms), the Platyhelminthes (flatworms) and the Hirudinea (leeches). The arthropods constitute the largest group in the animal kingdom and include centipedes, scorpions, spiders, ticks, mites and insects.

Table 79. Epidemiology of the More Important Helminthic Infections Encountered in Pediatric Practice

<i>Peroral Exposure</i>	<i>Transmission Source</i>	<i>Helminth and Stage Involved</i>	<i>Disease</i>
1. From raw or inadequately processed foods	a. Fruits and vegetables	Ascaris and Trichocephalus (fully embryonated eggs)	Ascariasis, trichocephaliasis
	Water cress	Fasciola (encysted metacercariae)	fascioliasis
	Water nuts	Fasciolopsis (encysted metacercariae)	Fasciolopsiasis
	b. Meat		
	Pork	Trichinella (encapsulated larvae)	Trichinosis
		Taenia solium (encapsulated cysticerci)	Teniasis
	Beef	Taenia saginata (encapsulated cysticerci)	Teniasis
	Bear meat	Trichinella (encapsulated larvae)	Trichinosis
	c. Fish	Diphyllobothrium latum (sparganum larvae)	Diphyllobothriasis
		Clonorchis, Opisthorchis, Metagonimus, Heterophyes (encapsulated metacercariae)	Clonorchiasis, etc.
	d. Crabs and crayfish	Paragonimus (encapsulated metacercariae)	Paragonimiasis
2. From fresh water	Cyclops and Diaptomus	Dracunculus (infective larvae); Sparganum (procercoid larvae)	Dracontiasis, sparganosis
3. From person-to-person contact	Anus→fingers→mouth or anus→clothing→fingers→mouth	Enterobius and Hymenolepis nana (fully embryonated eggs)	Oxyuriasis, hymenolepiasis
4. From contaminated soil	Dirty toys or candy; eating earth	Ascaris and Trichocephalus (fully embryonated eggs)	Ascariasis, trichocephaliasis
5. From contact with domestic mammals	a. Dog feces	Echinococcus (eggs)	Hydatid disease
		Toxocara canis (fully embryonated eggs)	Visceral larva migrans
	b. Cat feces	Toxocara cati (fully embryonated eggs)	Intestinal toxocariasis
	c. Dog and cat fleas	Dipylidium caninum (infective-stage larvae in fleas)	Dipylidiasis
	d. Rodent fleas	Hymenolepis diminuta (infective-stage larvae in fleas)	Hymenolepiasis
<i>Percutaneous Exposure</i>	<i>Transmission Source</i>	<i>Helminth and Stage Involved</i>	<i>Disease</i>
1. From infested ground		Hookworms and Strongyloides (filariform larvae)	Hookworm disease, strongyloidiasis
2. From infested fresh water	Mollusca-intermediate hosts in water	Schistosoma species (cercarial larvae)	Schistosomiasis; schistosome dermatitis
3. From blood-sucking insects	Mosquitoes, coffee flies, mango flies, etc.	Filaria worms (filariform larvae)	Filariasis



Owing to the greater opportunities for exposure, diseases produced by most animal parasites occur more frequently in children than in any other age group. Furthermore, children are more likely to manifest acute evidences of these diseases, because in the early years of life there is no immunity or tolerance to many of the parasites. Later, as humoral and cellular resistance develops, the

body tends to become more accustomed to the invader and may even develop a relatively solid immunity. Thus the morbidity and the mortality of animal parasite diseases are higher in childhood than in later life, and as a general rule evoke more conspicuous and severe symptoms in the first decade of life.

For information on the comparative epidemiology of these diseases see Table 79.

### *Infections Produced by Roundworms (Nematoda)*

All the important roundworm infections are produced by species belonging to the phylum Nematoda, which includes the true roundworms. These are elongated, cylindroid, unsegmented animals covered with a tough, relatively impermeable cuticle secreted by the underlying tissue layer, the hypodermis. They have a complete digestive tract, consisting of a mouth which is frequently provided with lips, teeth or other organs designed for penetration and attachment, a muscular esophagus, a midgut in which digestion of food takes place, and a hindgut, or rectum. The nervous system is primitive and is elaborated only at the oral end. A conspicuous body cavity contains the organs of excretion and reproduction. The sexes are usually separate. The female reproductive opening (vulva) is mid-ventral in position, near the equatorial plane or anterior to this level. The male reproductive system joins the rectum to form a cloaca, which opens externally at or near the posterior end of the body.

The most important roundworm infections (nematodiasis) are ascariasis, oxyuriasis, trichocephaliasis, the hookworm infections, strongyloidiasis, trichinosis, the filariases and dracontiasis.

#### **ASCARIASIS**

**Etiology.** Ascariasis is produced by the giant roundworm, *Ascaris lumbricoides*, which normally lives in the lumen of the small intestine. The mature female worm is about the size of a pencil, and the male is about one fifth smaller. Both sexes have three fleshy lips surrounding the triangular mouth, and both taper to a sharp posterior end, although the male is curved ventrally at the posterior extremity. The female lays approximately 200,000 eggs each day. These are infertile if males are lacking, and some are infertile if the female is just beginning to

oviposit. The fertile eggs are passed in the patient's feces in the one-celled stage. They are broadly ovoidal, measure 35 to 50 microns in cross section by 45 to 75 microns in greatest diameter, are provided with a thin, resistant inner shell, a thick hyaline middle shell and a mammillated outer covering which is usually bile-stained. Within the shell covering is a densely granular spherical egg cell (Fig. 171).

**Epidemiology.** Ascariasis is widely distributed through the warm climates of the world and extends into the temperate zones as far north and south as latitude 40 degrees. The fertile eggs are able to survive practically all external conditions except heat. When the egg is deposited on the ground, in cracks between stones or on the floor of the house, it proceeds to embryonate and in warm weather within nine days or more contains a motile first-stage larva. A week later, during which the larva moults once, the egg is infective. It does not hatch on the soil, but only after being swallowed. In favorable environments, as in the Gulf Coast area of the United States, the embryonated eggs may remain viable during the infective stage for several months or even years (Headlee, 1936). The worms are harbored principally by young children, who are more frequently exposed to infection and are the primary source of supply for "seeding" the soil with eggs. This is due to promiscuous defecation by small children who find it more convenient to deposit their excreta where they are playing than to use toilets. The eggs develop in the top soil, and children take some of them into the mouth on contaminated fingers, candy or play objects, or as a result of eating dirt. Where these unsanitary conditions prevail 60 to 100 per cent of children from one to ten years of age are infected with *Ascaris*. Older children and adults are parasitized to a less degree and can usually trace their in-



FIG. 171. A, Fertilized egg of *Ascaris lumbricoides*.  $\times 550$ . B, Unfertilized egg of *Ascaris lumbricoides*.  $\times 550$ . C, Egg of *Diphylllobothrium latum*.  $\times 550$ . D, Egg of *Hymenolepis nana*.  $\times 550$ . E, Egg of *Schistosoma mansoni* from feces. F, Egg of *Schistosoma haematobium* from urine.  $\times 550$ . G, Advanced stage of schistosomiasis japonica in a 13-year-old Chinese boy, with ascites resulting from hepatic cirrhosis, splenomegaly, fever, anemia and dysentery. (After E. G. Nauck: *Lehrbuch der Tropenkrankheiten*. Courtesy of Georg Thieme Verlag, Stuttgart.)

fections to sources provided by the younger groups.

Ascariasis is encountered occasionally among children in the northern United States, but the southern Appalachians and their extension into the Ozarks and the Gulf Coast states constitute the regions of high endemicity in the United States. Hard clay soils are most favorable for the development of *Ascaris* eggs, in contrast to moist sandy humus for those of hookworms.

Hogs are infected with an *Ascaris* morphologically indistinguishable from that in man, but hog *Ascaris* is rarely if ever in-

fective for human beings under natural conditions.

**Pathology.** When infective-stage *Ascaris* eggs are swallowed and reach the duodenum, they hatch, and the escaping larvae enter the intestinal wall. The larvae penetrate into the mesenteric lymphatics or venules, commonly migrating through the liver, and are carried to the lungs through the right side of the heart. From the pulmonary capillaries the larvae invade the air sacs, causing the discharge of a minute pool of blood at each site of escape. An acute cellular infiltration typically occurs in the immediate vicinity,



temporarily blocking the passage of the larvae up the respiratory tree (Fig. 172). If the number of larvae migrating through the lungs is appreciable, an atypical pneumonia results.

After a second larval moult in the lungs the third-stage larvae reach the epiglottis, are swallowed and become established in the small intestine. Between the sixtieth and seventy-fifth days after the eggs have been swallowed, mature worms mate, and the females begin their egg-laying. If the worms become irritated by their environment, as, for example, owing to digestive disturbances or fever, they may pass down the bowel and be spontaneously evacuated; or they may enter the stomach to be vomited or escape through the nares. They may block the appendiceal lumen, perforate the intestinal wall, block the common bile duct, migrate into the parenchyma of the liver or reach the pleural cavity. Extensive destruction of the hepatic parenchyma may occur as a result of their movements, their toxic metabolites and those of their eggs.

**Clinical Manifestations.** During their temporary stay in the lungs the young worms may cause an atypical pneumonia. The sensitization produced by these migrating larvae is responsible for the manifestations of *Ascaris* allergy frequently observed, including asthma, urticaria and eosinophilia.

Intestinal infection with *Ascaris* may be apparently symptomless, or there may be such manifestations as nausea and vomiting,

anorexia, loss of weight, insomnia, slight rise in temperature, nervousness and irritability, or physical and mental languor. The most common complaint of infected children is intestinal colic. Some patients are highly intoxicated by the by-products of the worms and may have a rapid rise in temperature. Acute symptoms accompany ectopic excursions of the worms. A mass of writhing worms knotted together frequently produces acute intestinal obstruction, at times resulting in perforation of the wall, in intussusception or in paralytic ileus.

**Diagnosis.** The diagnosis is commonly made by the recovery of fertile or infertile eggs in microscopic fecal films (Fig. 172). Direct unconcentrated films usually provide this evidence after the mature females have begun to oviposit. If only male worms occur (in less than 5 per cent of infections), clinical diagnosis may be confirmed by the therapeutic test. From time to time adult or immature worms passed in the stool or vomited or discharged from the nostril require diagnosis. Occasionally, during barium studies of the gastrointestinal tract for other purposes, *Ascaris* are demonstrated.

**Prognosis.** Except when large numbers of *Ascaris* larvae in the lungs initiate lobular pneumonia or when adult worms produce intestinal obstruction or perforation, the prognosis is good to excellent, provided a specific anthelmintic is administered.

**Prevention.** In highly endemic areas re-

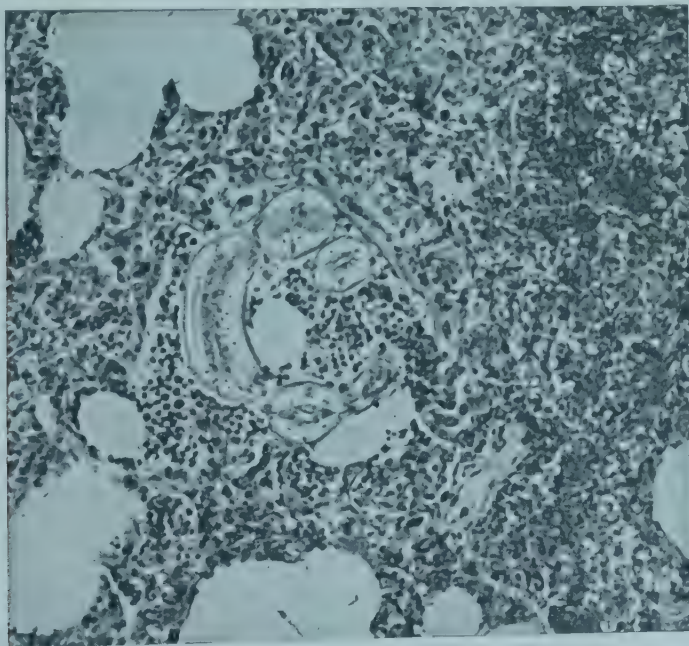


FIG. 172. Larva of *Ascaris lumbricoides* in migration through the lung, in center of small pool of blood, with leukocytic infiltration.  $\times$  ca. 200. (After Mackie, Hunter and Worth: A Manual of Tropical Medicine.)

exposure is the rule, and reinfection takes place about every three months. Thus both the physician and the public health officer are concerned with problems of control. Children as well as adults must have comfortable, clean toilets and must be taught to use them habitually. If soil in a courtyard is heavily seeded with *Ascaris* eggs, the top 2 inches of soil should be turned under. Finally, all infected persons should receive specific medication.

**Treatment.** The older drugs used for removal of *Ascaris* from the intestine are either not sufficiently effective (e.g., thymol) or are dangerous in full therapeutic doses (e.g., oil of chenopodium). Until recently the drug of choice was hexyresorcinol crystoids, a safe, highly efficient ascaricide. The patient is prepared the night before treatment with saline purgation, preferably with Glauber's salt (sodium sulfate),  $\frac{1}{2}$  ounce or 15 gm. (adult dose) in a glass of water, or a fractional amount for small children. On the morning of treatment, Crystoids Anthelmintic (in 0.1- or 0.2-gm. hard gelatin pills) are administered on an empty stomach. The pills must be swallowed without being opened, to prevent a superficial, temporary, painless erosion of the buccal mucosa. For small children the pills may be placed in the back of the mouth with a finger or in a teaspoonful of jelly and washed down with a half-glass of water. The dose is 0.1 gm. per year of developmental age up to 1 gm., in a single dose per day. Food is prohibited for four to five hours. A post-treatment saline purge is recommended to evacuate dead and dying worms and prevent further systemic intoxication. Though this drug is about 90 per cent effective in removing *Ascaris* from the intestine, it does not kill migrating larvae.

In ascariasis complicated with hookworm infection, Crystoids Anthelmintic may be safely administered and are about 75 to 85 per cent efficient against hookworms. Hookworm infection should not be treated with tetrachloroethylene if *Ascaris* is present, without an accompanying ascaricide. This combination of infections may be treated with tetrachloroethylene and oil of chenopodium in the proportion of 9 to 1 in gelatin capsules or on a teaspoon with sugar. The patient is prepared with saline purgation the night before and given 0.2 cc. of the mixture for each year of developmental age up to fifteen years, after which the full dose of 3 cc. is prescribed. Post-treatment purgation is advised, and no food is allowed until after a

copious defecation. *Piperazine citrate* (diethylene diamine) is an almost ideal drug for this infection. In a pleasant-tasting, fruit-flavored syrup (Antepar) the preparation contains the citrate equivalent of 100 mg. of piperazine hexahydrate per milliliter. This drug requires no pretreatment or post-treatment purgation and no fasting, and in recommended doses produces no side effects. A highly satisfactory dosage schedule is as follows: for children weighing 15 to 30 pounds, 2.5 ml. twice daily; 30 to 60 pounds, 5 ml. twice daily; and over 60 pounds, 10 ml. twice daily; for four to seven days.

## TOXOCARIASIS AND VISCERAL LARVA MIGRANS

See also Löffler's Syndrome, page 801, and Tropical Eosinophilia, page 602.

**Etiology.** Intestinal toxocariasis is produced by *Toxocara cati*, the cat ascarid, and *Toxocara canis*, the dog ascarid. There are possibly eighteen authentic records of intestinal infection with *T. cati* in children and only one questionable record of *T. canis*. By contrast, extraintestinal infection (visceral larva migrans) seems to be characteristic of *T. canis*. The life cycle of these worms in their normal hosts parallels that of human *Ascaris*, including a required migration through the lungs.

**Epidemiology.** Eggs of *Toxocara* embryonate on the ground. When they get into the mouths of children and reach the duodenum, they hatch, and the escaping larvae penetrate into the intestinal wall. Cumulative reports indicate that extraintestinal infection with the larval stage of *T. canis* (visceral larva migrans) is relatively common in children in the United States, especially in the deep South.

**Pathology.** Clinical investigations supplemented by experimental studies have shown that *T. canis* undertakes a migration through the viscera, but fails to develop. Usually it becomes trapped in a granulomatous tissue reaction, most frequently in the liver, at times in the lungs and eyeballs (Fig. 173), and rarely in the brain and other soft tissues. If thousands of infective-stage eggs are ingested, there may be a large number of granulomas, one surrounding each larva which has hatched and has attempted pulmonary migration. Once trapped, the larva may soon die and become fibrosed or calcified, or it may survive for months, but it does not proceed with normal growth in the



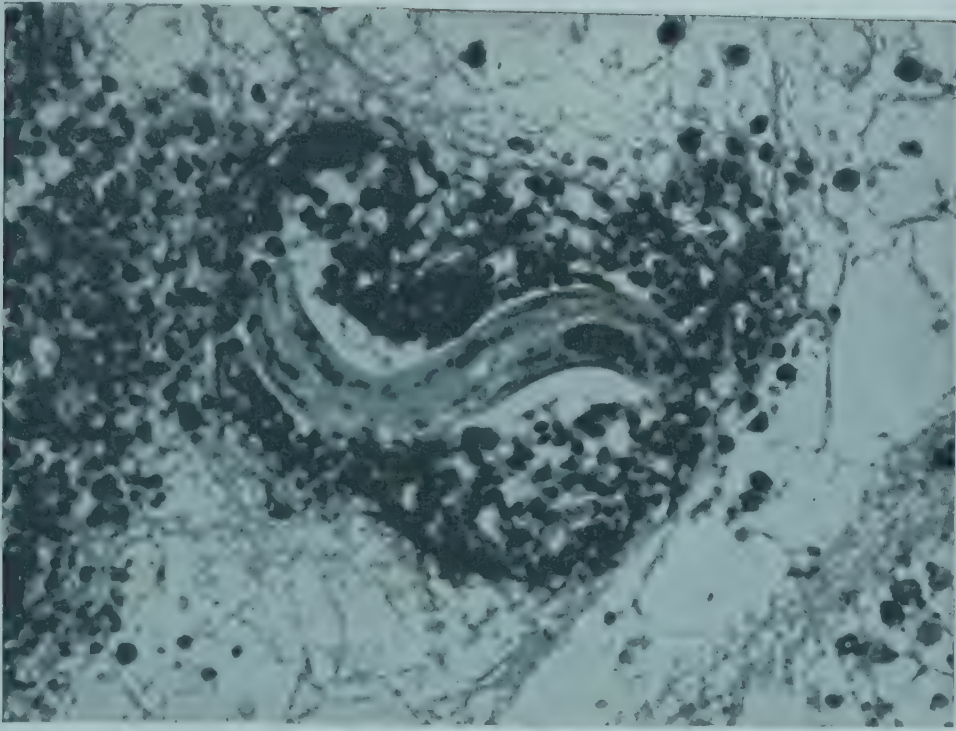


FIG. 173. Visceral larva migrans. Second-stage larva of dog ascarid, *T. canis*, in center of granuloma in vitreous chamber of human eye.  $\times 220$ . (After Wilder; courtesy of Armed Forces Inst. of Path., and Tr. Am. Acad. Ophth. & Otolaryng.)

human body and probably never completes its migration back to the intestinal tract to develop into an adult worm.

**Clinical Manifestations.** The evidence may be solely a persistent eosinophilia, or there may be hepatomegaly, multiple pulmonary infiltrations, fever, cough, hyperglobulinemia or symptoms referable to the brain or eye.

**Diagnosis.** Diagnosis is made by demonstration of the larvae in granulomatous areas of the liver (biopsy), from enucleated eyes or at autopsy.

**Prognosis.** In limited invasions visceral larva migrans is a relatively benign disease, except when the larvae are trapped while migrating ectopically through the brain or eyeball; in extensive infections the prognosis is grave.

**Prevention.** Periodic deworming of household dogs is indicated.

**Treatment.** No specific therapy is known.

## OXYURIASIS

(ENTEROBIASIS)

**Etiology.** Oxyuriasis is produced by the pinworm *Enterobius vermicularis* (seatworm, Oxyuris of older textbooks). The adult worms are small (males, 2 to 5 mm. in length, and curved ventrally at the posterior end; females,

8 to 13 mm. in length, robust in the middle and drawn out into a long sharp point posteriorly). The worms live attached by their lips to the mucous coat of the cecum and appendix. Gravid worms become detached, migrate down the bowel and characteristically crawl out the anus onto the perianal and perineal skin, where each female deposits several thousand eggs in a sinuous track. Eggs are laid within the bowel in only about 5 per cent of infections, and these are usually infertile or immature. The eggs laid outside the anus are elongated, ovoidal, flattened on one side, with a thick, slightly opalescent shell, and measure 50 to 60 by 20 to 30 microns. They contain a coiled larva at the time of oviposition (Fig. 174). At most they require only a few hours after deposition to become infective.

**Epidemiology.** This infection is cosmopolitan in distribution. Children are particularly susceptible, and those in large families and dormitory groups are more heavily parasitized than the population at large. They are exposed to infection by scratching the itching skin around the anus, where the eggs are lodged, or from soiled night garments or undergarments, bed linen or contaminated objects in the room, and in this way getting the eggs onto the tips of their fingers and then into their mouths; from breathing air-



FIG. 174. Fully embryonated egg of *Enterobius vermicularis* obtained by perianal swabbing.  $\times 800$ . (From Cram: Introduction to Nematology. Bureau of Plant Industry, Washington, D.C.)

borne eggs; and occasionally as a result of reinfection, in which eggs hatch on the perianal skin and the larvae migrate inside the anus and up to the cecal area, where they mature. Fertile eggs remain infective in the average environment for at least nine days.

**Pathology.** When viable eggs are swallowed and pass down the digestive tract, they hatch at the duodenal level, and the escaping larvae migrate directly to the cecum, become attached and develop into adults in about forty-five days or less. They usually produce no appreciable damage at the site of attachment, although they may cause hemorrhage from the appendiceal wall or provide an opening for pathogenic bacteria which may provoke a submucous abscess. Gravid worms, crawling out the anus, usually at night, frequently cause a severe pruritus, and the inevitable scratching results in scarification and secondary infection of the skin. In the female patient the gravid worms may enter the genital tract, cause a salpingitis, become encapsulated in the tubules or enter the peritoneal cavity and provoke encapsulation.

**Clinical Manifestations.** The appendiceal lesions occasionally produce symptoms of acute or subacute appendicitis, with indications for excision of the organ. Pruritus ani is frequently complicated by bacterial invasion of the skin and the production of weeping, eczematous areas. Children, especially young girls, may have irritability, loss of appetite and weight, and insomnia, resulting in chronic emotional disturbances. Vaginitis has been ascribed to direct invasion by the worms. Eosinophilia may be produced, but is not present in all cases.

**Diagnosis.** Oxyuriasis is rarely diagnosed by fecal examination. The eggs (Fig. 174) can usually be recovered in one to several swabbings of the perianal and perineal skin, preferably in the morning before dressing, bathing or defecation.

A simple and probably the most efficient anal swabbing technique consists in the use of a 2-inch length of adhesive-cellulose tape, placed sticky side out on the end of a 3-by-1-inch clean microscope slide held in place with the thumb and index finger. As the tape is brought in contact with the anal sphincter and the perianal folds, it collects *Enterobius* eggs among the flecks of mucus and cellular debris. After swabbing, the tape is placed flat, sticky side down, on the slide. It may be examined microscopically at any convenient time by allowing a drop or two of toluene to filter between the slide and the tape.

**Prognosis.** This is usually good. When the adult worms all spontaneously migrate out of the bowel or are removed by enema or catharsis, the infection may be permanently eliminated, unless auto- or heteroreinfection occurs.

**Prevention.** Scrupulous personal and group hygiene is advised, but in itself will not eradicate oxyuriasis. Accurate diagnosis and treatment of all infected persons in a household, repeated several times if necessary, constitute an integral part of the control program.

**Treatment.** Gentian violet medicinal is specific for the treatment of oxyuriasis. The 0.012-gm. and 0.03-gm. four-hour enteric-coated Seal-Ins or Enseal tablets are recommended, in order to permit the drug to be carried to the lower ileum or cecum before it is released. No pretreatment or post-treatment purgation is needed. The tablets are administered orally, three times a day for seven to ten days, discontinued for one week and then repeated. The individual dose is one small tablet (0.012 gm.) for children four to six years; two small tablets for those six to eight years; and one large tablet (0.03 gm.) for those eight to twelve years. The first period of treatment usually kills all the mature and maturing worms. The second period of treatment after a week's intermission is designed to take care of larvae hatched from eggs which might have been swallowed during the period of treatment. The drug is best tolerated when given with meals. Gastrointestinal irritation sometimes results from a defect in the enteric coating of the tablets. If they crack when placed under running



water, they should be discarded. Oxytetracycline (Terramycin) has as high a cure rate as gentian violet, provided all infected persons in a group are treated simultaneously and complete the full course of treatment. Brown (1952) used the following dosage schedules: age two to five years, 100 mg. four times daily for two days, then 50 mg. four times daily for two days, then 50 mg. daily for fourteen days; age six to ten years, 250 mg. four times daily for two days, then 250 mg. twice daily for two days, then 250 mg. daily for fourteen days; age eleven years and up, 500 mg. four times daily for two days, then 250 mg. twice daily for two days, then 250 mg. daily for fourteen days. Probably the most effective and harmless drug for oxyuriasis is *piperazine citrate* in a pleasant-tasting, fruit-flavored syrup (Antepar). It is prescribed in the following daily schedule: up to 15 pounds weight,  $\frac{1}{2}$  teaspoonful; 16 to 30 pounds, one teaspoonful; 31 to 60 pounds, 2 teaspoonfuls; and over 60 pounds, 4 teaspoonfuls of the syrup (each teaspoonful contains the equivalent of 500 mg. of piperazine hexahydrate). Completely successful results have been reported with a regimen of seven days' treatment, seven days' rest, seven days' treatment, seven days' rest and a final seven days' treatment. This preparation is easy to administer and, in the prescribed doses, produces no side effects.

All infected persons in a family or dormitory *must* be treated simultaneously. Even if *Enterobius* is completely eradicated from a household, periodic reinfection may be anticipated from outside contacts.

## TRICHOCEPHALIASIS

### (TRICHURIASIS)

**Etiology.** This infection is produced by the whipworm, *Trichocephalus trichiurus* (*Trichuris trichiura*), whose body is composed of two portions, a capillary anterior three fifths and a fleshy posterior two fifths. The males measure 30 to 45 mm. in length and are coiled at the posterior end. The females measure 35 to 50 mm. in length and have a club-shaped posterior end. These worms live with their anterior ends attached to the mucous coat of the cecum and appendix and, in heavy infections, in the adjacent parts of the ileum and ascending colon, and even in the sigmoid colon and rectum. The females daily lay a few thousand barrel-shaped eggs, which have mucus-like polar

plugs and are commonly bile-stained (Fig. 175).

**Epidemiology.** Whipworm infection is widely distributed in warm, moist climates. It is most common in children over five years of age, but may be prevalent in younger patients. The eggs passed in feces and deposited on moist, shaded soil require ten to fourteen days to develop to the infective stage, at which time each contains a coiled larva. When ripe eggs get into the mouth and are swallowed, they hatch at the level of the duodenum, and the escaping larvae slowly migrate to the cecum or appendix, become attached, and in about three months develop into adult worms.

**Pathology.** At each site of attachment there is a microscopic focus of inflammation. Toxic by-products at times provoke allergic manifestations, but usually the infection is well tolerated unless the worm burden is heavy (i.e., several hundred), as it frequently is in the tropics or the moist subtropics. In heavy infections the worms colonize the intestinal mucosa from the posterior level of the ileum almost to the anal sphincter.

**Clinical Manifestations.** Many persons, especially in the southern United States, harbor a few worms without apparent symptoms, but a small proportion experience loss of appetite, loss of weight, insomnia, physical and mental apathy or nervous symptoms. Heavily infected patients typically have a secondary anemia, with pallor, shrunken skin, dull eyes, dry hair and, at times, edema of the abdomen and lower extremities. In addition to the erythropenia there may be a neutropenia with monocytosis and a moderate eosinophilia. Children may fail to de-

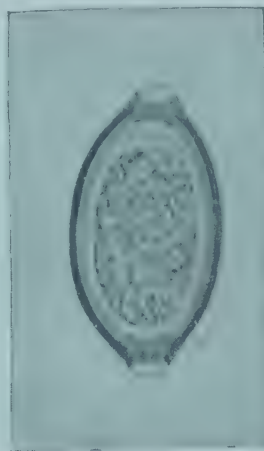


FIG. 175. Egg of *Trichocephalus trichiurus*, as seen in freshly passed feces.  $\times 666$ . (After Faust, in Brennemann's Practice of Pediatrics. Courtesy of W. F. Prior Co.)



FIG. 176. Prolapse of rectum in a Louisiana child, due to heavy infection with *Trichocephalus trichiurus*, showing many worms attached to the rectal mucosa. Symptoms were relieved after hexylresorcinol enemas. (Photo, courtesy of Dr. J. C. Swartzwelder.)

velop physically or sexually. In heavy infections there is profound irritation of the bowel wall, resulting in a bloody, mucous diarrhea, at times with an associated prolapse of the rectum (Fig. 176).

**Diagnosis.** Diagnosis is made on the recovery of the characteristic eggs (Fig. 175) in direct or concentrated fecal films.

**Prognosis.** Prognosis is good in most patients, especially if a majority of the worms are removed by the use of anthelmintics.

**Prevention.** This consists in the habitual use of comfortable sanitary toilet facilities and the sanitary disposal of sewage. Children must be encouraged not to take contaminated objects and dirt into their mouths.

**Treatment.** In Latin America the fresh sap of the bastard fig tree (*Ficus glabrata*), referred to as *leche de higuérón*, is specific in its action on these worms. It is administered periodically in the amount of 2 ounces (60 cc.) to children or adults and is well tolerated. No purgation is required before or after its administration. This drug, either in its crude or refined state (ficin), is not available in the United States.

Tetrachloroethylene with oil of chenopodium, in the proportion of 9 to 1, is moderately efficient and safe. Purgation with Glauber's salt (sodium sulfate) (adult dose,  $\frac{1}{2}$  ounce or 15 gm.) on the night before treatment is followed in the morning with a high retention enema of physiologic saline

solution to wash out viscous feces adherent to the worms. Then the anthelmintic mixture is administered orally on an empty stomach in the amount of 0.2 cc. per year of apparent age up to fifteen years, when the adult dosage of 3 cc. is prescribed. Two hours later purgation with Glauber's salt is repeated. No food is allowed until copious stools have been passed. Treatments at weekly intervals may be necessary in order to reduce the infection below clinical level.

When whipworms are attached to the wall of the lower colon and rectum, a high retention enema of the following emulsion is recommended: 1 gm. of hexylresorcinol Crystoids for each 300 cc. of a 10 per cent mucilage of acacia, to which 30 gm. of fine kaolin are added to reduce colonic cramps. Several successive enemas may be required to remove all the worms. This enema should be preceded by a cleansing one, preferably a tepid physiologic saline solution.

The clinical introduction of the cyanine dye *dithiazanine* for treatment of intestinal roundworm infections has provided for the first time an eminently satisfactory drug against *Trichocephalus* infection. When administered in coated tablets by mouth (adult dose: 200 mg., three times a day) for five or more days, depending on the severity of the infection, this anthelmintic is highly effective for removal of these worms without producing side effects. Since it is also valuable



for treatment of ascariasis, it is particularly suitable for use in combined *Trichocephalus* and *Ascaris* infections.

## HOOKWORM INFECTION

**Etiology.** These diseases are produced by certain species of hookworms which parasitize man: *Necator americanus*, the so-called American hookworm; *Ancylostoma duodenale*, the so-called Old World hookworm; and *Ancylostoma braziliense*. The first two are exclusively parasites of man; *A. braziliense* is normally a parasite of dogs and cats. These worms are 7.5 to 13 mm. long and 0.3 to 0.4 mm. in greatest breadth. The males are slightly smaller than the females. The mouth of *Necator* is provided with a pair of upper and a pair of lower cutting plates; that of *Ancylostoma*, with two or three pairs of upper teeth. The females have a bluntly pointed caudal extremity and a vulvar opening midventral in position near the equatorial plane. The caudal extremity of the male is drawn out into an umbrella-like expansion, the copulatory bursa. These worms are attached by their mouth capsule to the mucosa of the small bowel, typically at the level of the duodenum, jejunum and adjacent portion of the ileum.

After insemination each female hookworm lays several thousand eggs a day. These eggs (Fig. 177) are broadly ovoidal, thin-shelled and hyaline and measure 60 to 76 by 36 to 40 microns. They are usually in an early stage of development when evacuated, but in constipated stools may be more advanced in their development (Fig. 177, right).

**Epidemiology.** *Necator americanus* is the tropical hookworm of the Eastern Hemi-

sphere; it is the only widely distributed hookworm in the Americas, including the southern United States. *Ancylostoma duodenale* is the hookworm of the Mediterranean basin and similar latitudes in Asia and is the more common species on the Pacific coast of South America. *Ancylostoma braziliense* has a spotted distribution in warm climates. Intestinal infection with this species appears to be limited almost exclusively to canine and feline hosts.

When eggs of *Necator* and *A. duodenale* are evacuated from the human bowel and deposited on a moist, sandy humus soil in a shaded site in warm climates, they embryonate rapidly and hatch in twenty-four to forty-eight hours. The escaping larvae feed ravenously on bacteria and organic debris, grow, moult, feed again and, between the fifth and tenth days, transform into infective-stage larvae. Human exposure occurs when these third-stage larvae come in contact with the skin, as when persons walk barefooted on or handle infected soil. Infants and small children are seldom exposed to infection except in hyperendemic areas. Older children and young adults, especially males, are most frequently parasitized and in highly endemic areas are subject to repeated infection. Thus man initiates the extrinsic phase of the life cycle by discharging hookworm eggs on the soil and, in turn, picks up the infection by direct contact with the soil.

The human, canine and feline strains of *A. braziliense* are physiologically distinct. Man acquires intestinal infection from the human strain, and cutaneous larva migrans (creeping eruption) from canine or feline strains.

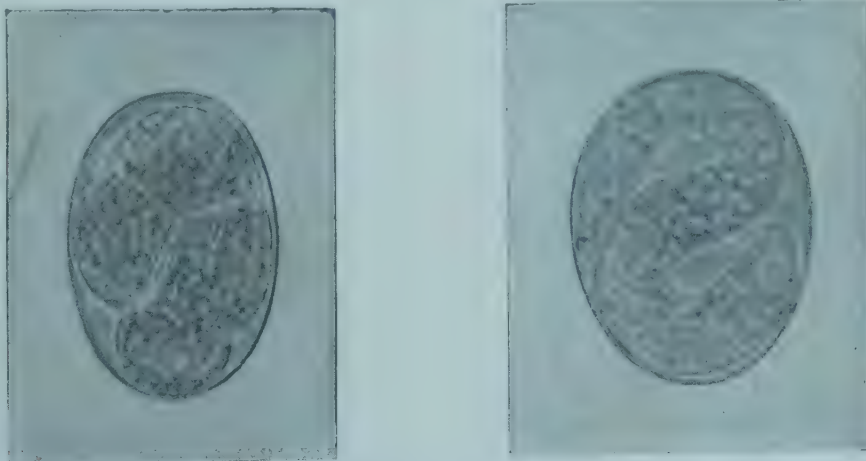


FIG. 177. Eggs of human hookworm, *Necator americanus*, as seen in freshly passed feces. Left, 4-cell stage; right, maturing embryo.  $\times 666$ . (After Faust, in Brennemann's Practice of Pediatrics. Courtesy of W. F. Prior Co.)



FIG. 178. Cutaneous larva migrans of the left foot, showing the serpiginous tunnel produced in the deeper layers of the skin by infective-stage larva of a hookworm (probably *Ancylostoma braziliense* of the dog or cat). On the left, the older part of the tunnel, with evidence of pyogenic inflammation; on the right, the inner part of the tunnel, with the larva in the most advanced position. (Courtesy of Dr. Alex J. Steigman and P. Hess.)

**Pathology.** The infective-stage larvae of the human strains invade the human skin through hair follicles or under particles of desquamating epidermis. They migrate to the cutaneous blood vessels, enter the venules, are carried to the lungs through the right side of the heart and lodge in the pulmonary capillaries, where a third larval moult occurs. From the capillaries they penetrate the alveoli, migrate up the respiratory tract, pass over the epiglottis and are swallowed. On arrival in the small bowel they develop a temporary mouth capsule, become attached to a villus and begin to digest the tissues and suck blood. They then develop a permanent mouth capsule under the earlier one, which is now shed, become sexually mature and copulate. In five to ten weeks after invasion of the skin the females begin to lay eggs.

Temporary trauma and tissue reaction develop at the sites where the larvae invade the skin and again after escape of the larvae from the pulmonary capillaries into the air sacs, but these are not serious unless the cutaneous lesions become secondarily infected or the number of invading larvae is large. After attachment to the villi in the small bowel, the adolescent worms secrete lytic juices which digest the epithelium and the walls of the villous blood capillaries. This partially predigested food of blood and epithelial cells is now sucked into the intes-

tine of the worm, in part used as nourishment, but to a greater extent passed through the worm's body as a source of oxygen, since hookworms are primarily aerobic in their metabolism. Once this blood pumping is well under way, each worm may deprive the victim's body of as much as 0.67 ml. each day. The blood loss can be readily compensated if the number of worms is small, but frequently, when the number is more than fifty or the nutritional balance of the host is already precarious, decompensation occurs, with a resultant microcytic hypochromic anemia. This is the essential factor in hookworm disease.

**Clinical Manifestations.** As the intestinal infection develops, either rapidly as a result of a heavy single inoculation or cumulatively as a result of repeated exposure, digestion becomes disturbed and the stools are usually unformed, contain undigested food, and frequently are tarry with decomposed blood. Absorption of by-products of the worms results in systemic toxemia, but the more profound manifestations are the result of continued loss of blood. The skin becomes harsh and has an ashen pallor, or may have an icteric tinge. The eyes are dull, and the hair is lusterless. Owing to the anemia, there is a decreased oxygen-carrying capacity. The heart works at increased speed in an attempt to oxygenate the tissues and becomes more or less permanently dilated. Mental apathy is pronounced. These conditions are more marked in children than in adults, and physical growth and sexual development are delayed.

In creeping eruption, *cutaneous larva migrans*, resulting from infection with canine or feline strains of *A. braziliense*, less commonly the cosmopolitan dog hookworm *A. caninum* and rarely the human hookworms *N. americanus* and *A. duodenale*, the larvae penetrate to the deeper layers of the skin, but, being unable to enter the peripheral blood vessels, continue to migrate for months (*larva migrans*) through serpiginous tunnels in the skin. This produces an inflamed appearance of the somewhat elevated channels, which usually become infected as a result of scratching the pruritic lesions (Fig. 178).

At the end of the incubation period of human intestinal hookworm infection there is usually a moderate neutrophilic and eosinophilic leukocytosis. Later there is a neutropenia with monocytosis; there is also hypoproteinemia. In chronic infections the



hypochromic anemia may be replaced by a hyperchromic macrocytic anemia. There is frequently a pre-existing state of malnutrition with a conspicuous hypoproteinemia, which is accentuated by the hookworm disease.

**Diagnosis.** Diagnosis is based on identification of eggs (Fig. 177) in the stool.

**Prognosis.** Prognosis is usually good with specific treatment, provided reinfection is controlled, the hemoglobin content is returned to normal and an adequate, balanced diet is provided.

**Prevention.** This consists in (1) detection and thorough treatment of all infected persons to reduce soil contamination; (2) provision for, and use of, sanitary toilets; and (3) the habitual use of shoes in hookworm areas. Children on vacation in areas where hookworm infection exists should be warned about the danger of going barefooted.

**Treatment.** Several efficient anthelmintics are available, although not all are eminently safe. Before specific medication is undertaken it is desirable to provide the patient a well balanced, nutritious diet, reinforced with iron (ferrous sulfate). One or more blood transfusions may be desirable. After a week or ten days specific treatment may be safely undertaken. Liver therapy is indicated only if there is a macrocytic type of anemia.

Thymol, oil of chenopodium in full therapeutic doses and carbon tetrachloride are too toxic for general use. *Tetrachloroethylene* is well tolerated and has an efficiency of 90 per cent or more for worm removal, provided it is fresh and is kept in a cool place. It is preceded the night before by purgation with Glauber's salt (sodium sulfate) (adult dose,  $\frac{1}{2}$  ounce or 15 gm. in a half-glass of water). The following morning, on an empty stomach, the drug is given in gelatin capsules or on a spoon with sugar, in the amount of 0.2 cc. for each year of developmental age up to fifteen years, after which the adult dosage of 3 cc. is prescribed. Two hours later purgation with Glauber's salt may be repeated. No food or carbonated drink should be allowed until a bowel movement has been obtained. Treatment may be safely repeated in one week. When small children are in a poor physical state or when hookworm infection is complicated with ascariasis, hexylresorcinol crystoids (Crystoids Anthelmintic) should first be administered (see p. 578). This drug will remove about 90 per cent of the ascarids and 75 per cent of the hookworms. After two or three doses

at weekly intervals the number of hookworms will usually be reduced below the level of clinical significance. In the event of an associated whipworm infection it is advisable to give tetrachloroethylene and oil of chenopodium combined in the proportion of 9:1 (see p. 582).

Creeping eruption of hookworm origin may be brought under control by freezing the infected area, especially the growing end, with ethyl chloride spray.

## STRONGYLOIDIASIS

**Etiology.** This infection is produced by the threadworm, *Strongyloides stercoralis*. The delicate, threadlike parasitic females, which are barely visible to the naked eye,

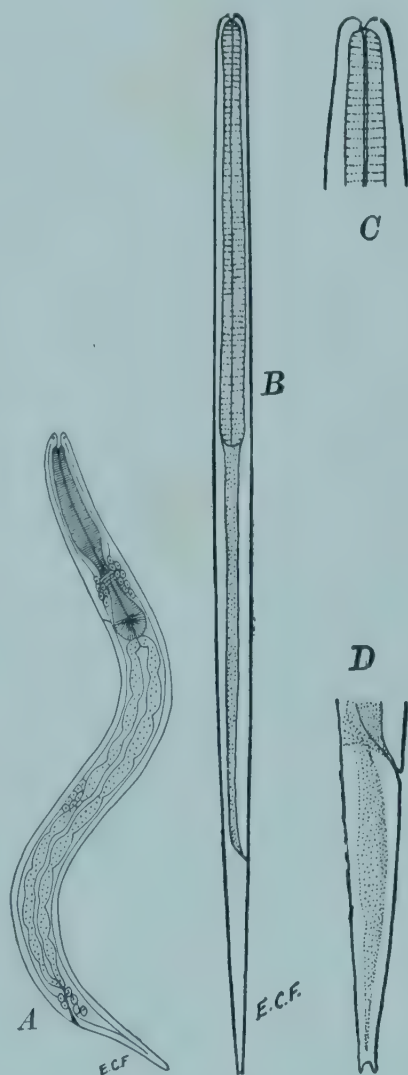


FIG. 179. *Strongyloides stercoralis*. A, Rhabditoid larva,  $\times 310$ ; B, filariform larva,  $\times 120$ ; C, D, anterior and posterior ends of filariform larva,  $\times 640$ . (Craig and Faust: Clinical Parasitology. Lea & Febiger.)

live primarily in the depths of the mucous coat of the intestine, from the pyloric wall of the stomach to the rectum, but for the most part at the duodenal level, where they lay eggs in the tissues. As the eggs filter out to the intestinal lumen, they mature and hatch, setting free the active larvae, which escape into the lumen of the bowel, feed and usually moult once in transit, and are evacuated in the feces. On deposition on the soil in a warm, moist, shaded site, the larvae grow and undergo one additional moult on or before their fifth day in the soil, becoming transformed into the third (infective) stage; or they may undergo one or more free-living cycles before they reach the infective stage.

**Epidemiology.** Strongyloidiasis is relatively common in warm, moist climates, but is occasionally seen as far north as Canada. Exposure results from direct contact of the skin with infected soil, especially where there is a high ground-water level, as in the bayou regions of the Gulf coast of the United States and in tropical rainfall areas.

**Pathology.** The sites and methods of entry of *Strongyloides* into the skin and its migration to the intestine by way of the lungs are essentially the same as in hookworm infection (see p. 584). Occasionally, as these worms escape from the pulmonary capillaries, there is considerable cellular infiltration into the alveoli and bronchioles, but this does not destroy the worms, which continue to grow in the smaller respiratory passages and may even enter the bronchial or tracheal epithelium, where foci of infection are sometimes established. Nevertheless the majority of young worms reach the intestine; the females burrow into the mucosa and, about twenty-six days after exposure, begin to deposit eggs. The continued burrowing of the worms, together with the filtration of their eggs, and the hatching and escape of the larvae contribute to the trauma and frequently to the sloughing of portions of the mucosa. There is, otherwise, a general irritation of the involved mucosa with secretion of excess mucus and impaired absorption of food.

**Clinical Manifestations.** There is only a temporary prickling pain at the sites of entry of the infective-stage larvae into the skin. If the number of larvae migrating through the lungs is appreciable or if some become established in the bronchial epithelium, there may be symptoms of an atypical pneumonia. Owing to the changes in involved levels of the bowel, normal tone and function are lost. There is usually dull or sharp

pain in the epigastric region. There may be a debilitating, unchecked mucous diarrhea or diarrhea alternating with constipation. Dehydration and poor digestion may produce severe emaciation. During the chronic phase the larvae may transform to the infective stage in transit down the bowel and produce internal autoinfection; or they may be responsible for perianal invasion. Cutaneous larva migrans due to perianal autoinfection has been observed in Southeast Asia. Patients with chronic infection are more likely to be constipated than to have diarrhea and frequently have neurotoxic manifestations.

The blood picture at the end of the incubation period is that of a leukocytosis with an eosinophilia of 25 per cent or more. In the chronic stage there is characteristically a neutropenia with a moderate eosinophilia and a monocytosis.

**Diagnosis.** This is based on the detection and identification of larvae in the stool (Fig. 179, A, B) or in material aspirated from the duodenum. A high eosinophilic count suggests the possibility of this infection.

**Prognosis.** The prognosis is fair to good in the recently acquired infection, provided persistent specific treatment is carried out. Absence of eosinophilia is a poor prognostic sign, indicating low resistance.

**Prevention.** This requires sanitary disposal of human feces, treatment of infected persons and care not to expose the skin to polluted soil.

**Treatment.** For years the standard therapy has been oral administration with meals of gentian violet medicinal in enteric-coated Seal-In tablets in 0.012- or 0.03- gm. ( $\frac{1}{8}$  or  $\frac{1}{2}$  grain) sizes. The dosage schedule is 0.01 gm. daily for each year of developmental age, for sixteen days. Vomiting once or twice is not a contraindication to continued treatment. If the infection is not eradicated after two courses of oral therapy, 25 cc. of a 1 per cent solution of the drug may be deposited directly in the duodenum by intubation. If there is proof of pulmonary or other extraintestinal strongyloidiasis, it may be necessary to consider intravenous gentian violet therapy, giving a triply filtered 0.5 per cent solution in an amount not in excess of 20 cc. every other day for two weeks. This method of treatment is not advised except in emergencies. Larvae may be passed for several weeks after treatment, but eventually cease to appear with successful termination of the infection. Frequently patients are refractory to treatment.



In such instances it will be well to determine whether there is a likelihood of internal or perianal autoinfection which is maintaining the infection.

**Dithiazanine**, 3-ethyl-2[5-(3-ethyl-2-benzothiazolinyldene)-1,3-pentadienyl]benzothiazolium iodide, is much more effective than gentian violet in the treatment of strongyloidiasis, especially in chronic infections. It has the added advantages of ease of administration and essentially no side effects. In the adult dose of 200 mg. orally in coated tablets three times daily for five or more days, this agent eradicates *Strongyloides* in up to 89 per cent of instances.

## TRICHINOSIS

**Etiology.** This infection is produced by *Trichinella spiralis*. The adult worms are microscopic and live in the mucous coat of the small bowel, especially at the duodenal level. The females produce living young (larvae) which gain access to the mesenteric venules and lymphatics, migrate through the blood stream and filter out in skeletal muscle, where they become encapsulated in about twenty-one days.

**Epidemiology.** Trichinosis is common among pork-eating populations of the North Temperate Zone, in southern South America and in South Africa. Hogs (occasionally bears) are the source of infection, to which man is exposed by the consumption of infected meat in a raw or inadequately processed state. For this reason young children are less commonly infected than older children and adults. Epidemic outbreaks of trichinosis continue to occur in the United States, frequently as a result of eating pork products from a single heavily infected hog, slaughtered on a farm.

**Pathology.** When meat containing viable trichina cysts is eaten, the cysts become separated in the stomach. In the duodenum the larvae break out of the cyst, burrow into the mucosa, mature in about five days, and mate. The females larviposit for about six weeks. There is inflammation as the excysted larvae enter the intestinal wall and mature. Inflammation continues as the larval progeny migrate through the blood stream and become lodged in the muscular tissues.

**Clinical Manifestations.** Symptoms of acute food poisoning begin within a few hours after ingestion of heavily infected meat and last four or five days, paralleling the entry of the excysted larvae into the

bowel wall and their development into mature worms. During the period of larval migration there are typically intense muscular pains, stiffness and tenderness in the diaphragm, lower extremities and muscles of the throat, causing difficulties in breathing, walking, swallowing and talking. An increasingly toxic condition results in edema, especially around the eyes. During this stage or after encapsulation of the larvae there may be disturbances of the central nervous system (motor, sensory or of the higher centers), depending on the sites where migrating larvae have set up inflammatory reactions. There may also be clinical and electrocardiographic evidence of myocarditis resulting from inflamed tracts in the heart muscle through which the larval worms have passed, but in which they do not encyst.

Beginning with the invasion of the duodenal mucosa and continuing through the weeks of larval migration, there is an elevation of temperature to 99° to 102° F. (37.2° to 38.8° C.) or even higher.

There is an early leukocytosis with eosinophilia, later a leukopenia with eosinophilia and monocytosis.

When the infection is not heavy, there may be few or no apparent symptoms.

**Diagnosis.** During the incubation period and the early migration of the larvae diagnosis can be made only presumptively on clinical and epidemiologic evidence. After the larvae have become encapsulated (after the twenty-first day) the disease may be detected by biopsy of deltoid, biceps or gastrocnemius muscle strips, or by intradermal tests, using a 1:10,000 antigen and doing an immediate reading at twenty minutes and a final one at twenty-four hours. The positive intradermal test should be supplemented by the precipitin test to determine whether the infection is recent (ppt +) or of long standing (ppt -). Many cases are diagnosed only at necropsy, and then merely as an incidental finding.

**Prognosis.** This varies from grave to excellent, depending on the severity of the infection.

**Prevention.** Thorough cooking, or freezing of all pork for at least twenty-four hours, will prevent human infection. Since this is not always done, the cooking of all garbage fed to hogs is a valuable method of prevention.

**Treatment.** There is no specific therapy. Management includes administration of analgesics, abundance of citrus fruit juices

and an ample fluid intake to maintain a good urinary output. If trichinosis is suspected during the first two or three days after exposure, daily saline purges with Glauber's salt (sodium sulfate) may serve to dislodge the young worms before they become embedded in the intestinal mucosa and the females start larvipositing.

## FILARIASIS

**Etiology.** Filariasis is produced by one of several filaria worms, the more important of which are *Wuchereria bancrofti*, *W. malayi*, *Onchocerca volvulus* and *Loa loa*. The adult worms are threadlike objects characteristically coiled up in certain body tissues. *Wuchereria bancrofti* and *W. malayi* inhabit lymphatic vessels and lymphoid tissues; *Onchocerca* adults are immured in fibrous subcutaneous nodules; *Loa loa* migrate through subcutaneous tissues. These worms all produce microscopic snakelike embryos called microfilariae, which eventually migrate through the superficial blood vessels or skin.

**Epidemiology.** *Wuchereria bancrofti* is widely distributed through the tropics in both hemispheres; *W. malayi* occurs in India, the Far East and the Southwest Pacific. *Onchocerca* is found in tropical Africa, in a small area where Guatemala and Mexico are contiguous and in eastern Venezuela. The loa worm is found in tropical Africa.

Microfilariae are picked up by bloodsucking flies and develop to the infective-stage larvae in their thoracic muscles. *Wuchereria bancrofti* and *W. malayi* utilize mosquitoes; *Onchocerca*, species of *Simulium*; *Loa loa*, the mango fly *Chrysops*. After incubation in the appropriate insect host the larvae migrate to the tip of the fly's proboscis and enter the skin of the exposed person in or near the puncture wound made by the fly. In endemic areas children are more commonly infected than older persons.

**Pathology.** The developmental period in Bancroft's filariasis is about a year, but is not definitely known. Indirect evidence indicates that the larvae, on entering the skin, invade lymphatic vessels and may make long migrations through the lymphatic system before they reach the sites where they mature and mate, and the females begin to parturite. During this period, if they lodge for any time in a lymph node and thus block lymph flow, they may produce an acute lymphangitis and associated lymphad-

enitis. At the end of the incubation period the microfilariae discharged by the female appear in the tissues around the parent worms, and within a short time those of *Wuchereria* and *Loa loa* may be found in the blood. Tissue reaction may be temporary during the migration of larvae or adults, but in Bancroft's and Malayan filariasis, there is usually a series of acute episodes of lymphangitis, often with fever, and subsequently fibrosis of the dead or dying parent worms, resulting in more or less permanent blockage of the involved lymphatic vessels. In onchocercosis, fibrosis around the adult worms develops without acute local reaction, but almost invariably with systemic sensitization. In loa infection there is only temporary swelling in the subcutaneous tissues through which the worm is migrating.

**Clinical Manifestations.** In infection with Bancroft's and Malayan filariasis the biologic incubation period may be marked by acute lymphangitis or allergic states. A second period, usually symptomless, begins when microfilariae are first recoverable, one year or more after exposure. Most patients have repeated attacks of lymphangitis, usually with fever. With fibrotic obstruction of lymph flow, elephantiasis gradually develops, and the skin becomes thickened and is deprived of practically all its blood supply. It cracks readily, providing easy entry for secondary pathogens. The subcutaneous tissues are remarkably thickened and consist of a matrix of fibrous tissue in which lymphatic fluid and adipose tissue are locked.

*Onchocerca* adults produce a painless swelling on any site of the body, but particularly at the junction of the long bones and on the temporal and occipital areas of the head. Their microfilariae tend to migrate to the eyeball and optic nerve, causing diminished vision and eventually blindness. *Loa* usually produces only pruritus, but at times there is generalized edema or giant urticaria.

**Diagnosis.** This is suggested by the clinical manifestations, and is confirmed by recovery of the microfilariae in blood at night (*W. bancrofti*, *W. malayi*), in the daytime (*Loa loa*) or in biopsied skin (*Onchocerca*). When parent worms have died and in the biologic incubation period, microfilariae will be absent.

**Prognosis.** The prognosis is variable and depends on the degree of involvement and on the anatomic location of the lesions.



**Prevention.** This is a difficult task and requires control of the breeding of bloodsucking flies which transmit the infection. DDT has provided a moderately effective means of control.

**Treatment.** There is no simple chemotherapy for any filaria infection, although Suramin (naphuride sodium) and Hetrazan (diethylcarbamazine citrate) are efficacious in killing circulating microfilariae and are moderately lethal for adult worms. The individual dose of Hetrazan is 1 mg. per pound of body weight three times daily after meals. Specific treatment of onchocercosis is complicated by the patient's sensitization reaction to the sudden release of metabolites of dying and dead parent worms. In elephantiasis of an extremity a modified Kondeleon operation may be performed, but is only of temporary value. Tight bandaging with turkish towelling forces the lymph into collateral channels, allowing reduction of the lesion and considerable absorption of the elephantoid tissue. In onchocercosis the subcutaneous tumors should be removed as soon as they appear, to lessen the possibility of grave ocular disease. In loiasis the parent

worm is readily removed when it crosses in front of the eye or over the bridge of the nose.

## DRACUNCULOSIS

(DRACONTIASIS)

Dracunculosis is produced by the dragon or Medina worm, *Dracunculus medinensis*, a distant relative of the filaria worms. It is prevalent in India, the Middle East, Africa and, to a less extent, in other areas. The meter-long adult female migrates from the viscera to the skin to deposit living young in fresh water when a small blistered area of the skin produced by the anterior tip of the worm breaks open in contact with the water, as, for example, during bathing or wading. Infection results from drinking or rinsing the mouth with water containing the infected intermediate host, Cyclops. Prevention is not on a practical basis. There is no satisfactory systemic chemotherapy, but an emulsion of phenothiazine, introduced into the skin along the track of the parturient female, causes its death in a few hours and permits its removal by gentle traction.

## Infections Produced by Tapeworms (Cestoda)

Tapeworms are flatworms (Platyhelminthes), invertebrate animals characterized by either a simplified digestive tract or none at all, a protonephridial excretory system, male and female genitalia usually in the same organism (hermaphroditism), no body cavity and, primitively, a ciliated ectodermal covering. Each tapeworm consists of a group of coordinated units as follows: (1) a scolex or "head," provided with suckers and frequently with rostellar hooklets for attachment; (2) a "neck" or region of growth; (3) a series of proglottids or segments, beginning with immature ones arising from the distal part of the neck and becoming increasingly developed and finally gravid in the distal portion of the worm. The entire worm is called a strobila. Each mature proglottid contains a full set of male and female genitalia. The gravid proglottids are storehouses of eggs. Tapeworms have the following stages in their life cycle: egg, embryo, larva, adult.

The important tapeworm infections of man are teniasis (including the larval-stage infection cysticercosis), hymenolepiasis, diphyllbothriasis and hydatid disease. Dog

tapeworm infection occasionally occurs in children who fondle infected dogs or cats. The comparative epidemiologies of these infections are summarized in Table 79 (p. 574).

## TENIASIS

**Etiology.** Teniasis is produced by the beef tapeworm, *Taenia saginata*, and the pork tapeworm, *Taenia solium*. The former has a length of 15 feet or more, contains about 1000 to 2000 proglottids and has a head with four suckers, but no rostellar hooklets. *Taenia solium* seldom attains a length of more than 5 to 8 feet, has less than 1000 proglottids and has an apical ring of rostellar hooklets, as well as four head suckers. The most distal proglottids are gravid and contain fully embryonated eggs which may be passed in feces, but are more commonly excreted in proglottids (Fig. 180) which are detached from the parent worm.

**Epidemiology.** *Taenia saginata* infection is common in beef-eating peoples like the Mohammedans and also occurs frequently in the United States. *Taenia solium* infection

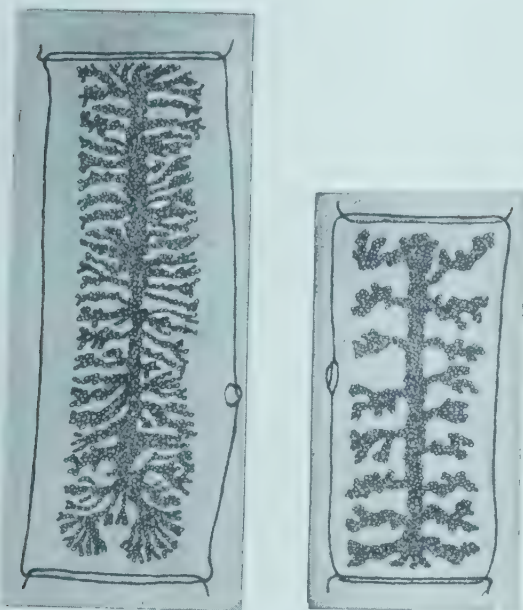


FIG. 180. Gravid proglottids of *Taenia saginata* and *T. solium*, as passed in the feces or as they migrate from the anus, showing differential patterns of uteri. Left, *T. saginata*; right, *T. solium*. (After Faust, in Brennemann's Practice of Pediatrics. Courtesy of W. F. Prior Co.)

occurs most often in eastern and southeastern Europe, is relatively rare in the United States, but is as common as *T. saginata* in Mexico and certain other Latin American countries. Gravid proglottids, discharged in human feces, disintegrate, and the contaminated soil is infective for cattle (*T. saginata*) or hogs (*T. solium*). The larval stage (cysticercus) develops in striated muscle of these animals, and the flesh becomes infective in about three months. Human beings who consume raw or rare beef or pork are liable to infection with the adult worm.

**Pathology.** The larvae are digested out of the meat in the human stomach, become attached in the upper small intestine and, in about three months, develop into mature worms. Although there is slight inflammatory reaction at the site of attachment, the important pathogenic action is toxic, with generalized manifestations. Occasionally obstruction of the bowel may result from a tangled mass of worms or from detached proglottids which become lodged in the lumen of the appendix.

**Clinical Manifestations.** Toward the end of the incubation period there is considerable digestive disturbance, including mucous diarrhea due to the irritative action of the worm's by-products on the intestinal mucosa. There may be false hunger pains, especially at night. When the worm is mature, there

may be no intestinal disturbance, but there may be other manifestations. These include: (1) inconvenience from gravid proglottids which, having migrated from the anus, crawl down the leg; (2) nutritional drain on the patient; (3) appendiceal inflammation from detached proglottids; and (4) neurotoxic manifestations.

Man is also subject to infection with the cysticercus stage of *T. solium* by swallowing eggs in contaminations from his own or another person's intestinal infection. These cysticerci lodge in any tissue, including the brain, the meninges and the eyeball. Involvement of the brain almost invariably ends in a jacksonian type of epilepsy.

The blood picture at first shows a leukocytosis with moderate eosinophilia; later there is a slight neutropenia with monocytosis and, at times, a secondary anemia.

**Diagnosis.** Teniasis can be diagnosed by recovery of typical *Taenia* eggs in the stool, but most patients do not pass eggs in appreciable numbers. Specific diagnosis can be made from a gross examination of gravid proglottids passed in the stool or migrating from the anus. When these are freed of debris and flattened in the fresh condition (not hardened in alcohol or formalin) between two glass slides, it is easy to count the number of main lateral arms of the uterus. In *Taenia saginata* the number is fifteen to twenty-one, in *T. solium*, seven to thirteen (Fig. 180).

**Prognosis.** This is good in intestinal teniasis if the worms are removed. Rarely, acute intestinal or appendiceal obstruction is a hazard. In cysticercosis cerebral lesions create a grave prognosis.

**Prevention.** Teniasis may be prevented by eating only previously frozen or well cooked beef and pork. More fundamental is the sanitary disposal of human feces.

**Treatment.** Oleoresin of male fern (*Aspidium filix-mas*), formerly the drug of choice, and carbon tetrachloride, which is equally satisfactory, are relatively toxic and require hospitalization of the patient. *Quinacrine* (Atabrine) is superior to either in effectiveness and ease of administration and is less toxic.

For treatment with Atabrine the patient should be on a light, nonconstipating diet for the preceding forty-eight hours and should have complete evacuation of the bowels the night before the drug is administered, if necessary by saline purgation with Glauber's salt (sodium sulfate) (adult dose,  $\frac{1}{2}$  ounce



or 15 gm. in a half-glass of water). In the morning on an empty stomach the adult patient takes by mouth five 0.1-gm. tablets of Atabrine with an equal amount of sodium bicarbonate. For children the dose must be reduced in proportion to developmental, not chronologic, age. Two hours later a saline purge is administered. The worm is characteristically passed intact, deeply yellow-orange stained and contracted, but alive. Nausea and possibly vomiting may be anticipated. To reduce these side effects no food or carbonated drinks should be permitted until after a good bowel movement.

## HYMENOLEPIASIS

**Etiology.** Hymenolepiasis is produced by the dwarf tapeworm, *Hymenolepis nana*, and the rat tapeworm, *H. diminuta*. The former is a small worm, only 1 to 2 cm. in length. Its head is provided with four suckers and a crown of rostellar hooklets. *Hymenolepis diminuta* is appreciably larger (20 to 60 cm. in length) and has suckers but no hooklets on the head. The most distal gravid proglottids disintegrate as they become fully ripe, setting the characteristic eggs (Figs. 171, D; 181) free in the small bowel to be evacuated in the feces.

**Epidemiology.** The dwarf tapeworm, *Hymenolepis nana*, is cosmopolitan in distribution, except in cold climates. It is most commonly a parasite of children. Although this species is found in rats and mice, the strains are distinct and are not readily infective for human beings. Human infection with *Hymenolepis diminuta* results primarily from contact with infected rat or mouse fleas. *Hymenolepis nana* infections are common in children in the southern United States, in many countries of Latin America, India and in the Mediterranean area. *Hymenolepis diminuta* infections have been recorded from several countries and from the United States.



FIG. 181. Egg of *Hymenolepis diminuta*,  $\times 500$ . (Craig and Faust: Clinical Parasitology. Lea & Febiger.)

Eggs of *H. nana* passed in human feces are directly infective for man. They hatch soon after ingestion. On reaching the duodenum the escaping embryos bore into the villi, transform into larvae, return to the intestinal lumen, become attached, and grow into adults within a few weeks. Eggs of *H. diminuta* must undergo a period of larval development in certain insects, usually rat fleas. Ingestion of these intermediate hosts is the source of infection for human beings.

**Pathology.** Except in heavy infections, the damage produced is largely toxic. There is suggestive evidence that in continued heavy infections with *H. nana* internal autoinfection occurs repeatedly.

**Clinical Manifestations.** There may or may not be clinical evidence of infection. A single *H. nana* in a child may at times evoke severe manifestations, with irritability, insomnia, loss of appetite and weight, and rarely convulsions. On the other hand, a moderate number in another child may evoke only mild symptoms. There is usually a moderate eosinophilia.

**Diagnosis.** This is made by demonstration of eggs (Fig. 181) in the feces.

**Prognosis.** This is almost always good, provided specific medication is instituted promptly. In heavy infections with *H. nana* the prognosis may be poor, owing to repeated internal autoinfection.

**Prevention.** Dwarf tapeworm infection can be controlled only by the most careful personal and group hygiene and by treatment of all infected persons. Rat tapeworm infection may be eliminated as a human infection by campaigns against rats and mice and by use of DDT in rat runs or in nests to kill rodent fleas.

**Treatment.** See under Teniasis. Hexylresorcinol (Cryptoids Anthelmintic) as administered in ascariasis (p. 578) is moderately efficient and should be tried first in small children because of its low toxicity.

## DIPHYLLOBOTHRIASIS

**Etiology.** Diphyllobothriasis is produced by the fish tapeworm, *Diphyllobothrium latum*, which measures 5 to 30 feet in length and has possibly as many as 3000 proglottids. The head is spatulate and is provided with a pair of longitudinal sucking grooves. The proglottids never become strictly gravid, but discharge immature eggs.

**Epidemiology.** Fish tapeworm infection is prevalent in the lake districts of Minnesota

and northern Michigan, adjacent territory in Canada and in the lake districts of Chile and Argentina, northern, eastern and south-eastern Europe, Russia, Palestine, Syria, Siberia, Japan and Australia. Elsewhere it is rarely endemic, but iced fish shipped from endemic areas are responsible for many cases in other regions. Gefüllte fish may be a source of infection if it is eaten before it has been cooked. The immature eggs passed in feces are broadly ovoidal and operculate (Fig. 171, C). When discharged into cold fresh water, they must incubate for about two weeks, whereupon the shell opens to release a ciliated embryo. This swimming organism is eaten by little water fleas of the genera *Diaptomus* and *Cyclops*, in the bodies of which the embryos transform into proceroid (first-stage) larvae. Fresh-water fish consume the infected water fleas and acquire infection in their flesh, the plerocercoid or sparganum (second-stage) larvae. Larger fish in turn consume the smaller ones and acquire the infection in their muscular tissues. Man, dogs or bears eat the fish in a raw or inadequately processed condition and become infected.

**Pathology.** Fish tapeworm infection frequently produces a toxic state, possibly due to absorption of unsaturated fatty acids, particularly if the worms are attached to the duodenal mucosa, where they prevent absorption of vitamin B<sub>12</sub>.

**Clinical Manifestations.** In addition to the toxic condition, fish tapeworm may be associated with a primary anemia. It is believed that the tapeworm, when attached to the duodenal or jejunal mucosa, precipitates an anemic state in persons having an unstable equilibrium with respect to the antianemic intrinsic factor. There is usually a leukocytosis with eosinophilia, followed in the chronic period by a leukopenia with a monocytosis. At times there is a macrocytic or normocytic hyperchromic anemia.

**Diagnosis.** This is made on recovery of the eggs (Fig. 171, C) in the patient's feces.

**Prognosis.** This is good with specific treatment.

**Prevention.** Thorough cooking of all fresh-water fish would prevent infection. Prohibition of catching fish during the summer months when the fish are heavily parasitized would also reduce the hazard. Basic control consists in sanitary disposal of human excreta, since the reservoir hosts (dogs and bears) probably contribute little to human infection.

**Treatment.** See under Teniasis (p. 590).

## HYDATID DISEASE

(ECHINOCOCCOSIS)

**Etiology.** Hydatid disease is produced by the larval stage (hydatid cyst) of *Echinococcus granulosus* and *E. multilocularis*, minute worms which live as adults in the small intestine of the dog and its wild relatives.

**Epidemiology.** This disease is widely distributed wherever sheep, cattle and hogs are associated with dogs. It is particularly common in man in Australia, New Zealand, Palestine, Syria, Argentina, Uruguay, southern Brazil and Chile. Occasionally autochthonous cases occur in the United States. *Echinococcus multilocularis* is common in the highlands of Central Europe, where foxes replace dogs and wood mice replace sheep, cattle and hogs in the natural evolution of the infection (see below). This cycle also occurs in northern Alaska, Siberia and Japan.

The eggs of *E. granulosus* passed in an infected dog's feces initiate the infection in practically any mammal, except a rodent, which ingests the eggs. These hatch in the duodenum; the escaping embryos bore into the intestinal wall, gain access to mesenteric venules or lymphatics and are carried to various parts of the body where they are filtered out. Dogs become infected from eating the carcasses of animals which have died of the disease. Man's association with infected sheep and cattle dogs and parasitized pet dogs provides the means for exposure to the disease.

**Pathology.** Unless the young larvae lodge in some vital location in the human body, they will develop to a considerable size before their presence is discovered. Thus infection acquired in childhood may not be detected until middle life. Although the little hydatid cyst provokes an acute inflammatory reaction at the site of implantation, it proceeds to vacuolate, to develop its germinative layer with many viable heads (scolices) and to accumulate hydatid fluid within the cavity. The cysts grow slowly, but in several years may reach the size of an orange or grapefruit. They are usually spherical and filled with fluid. The outer layer is essentially a non-cellular laminated structure which is friable; the entire cyst is surrounded by adventitia. The fluid contains considerable foreign protein and is extremely toxic for the host if there is appreciable seepage or if the cyst bursts. Rupture of a cyst may cause anaphylactic shock or may only set free a large num-



ber of viable scolices which become implanted elsewhere and develop secondary cysts. If the cyst reaches the shafts of long bones, it may proceed to grow as a syncytium (osseous hydatid). The most common sites of hydatid cysts in man are, in descending order, the liver, lungs, brain, peritoneal cavity and bone, but no tissues are exempt. The hydatid of *E. multilocularis* is alveolar, without limiting membrane or adventitia, almost invariably develops in the liver, and is essentially malignant in its growth.

**Clinical Manifestations.** If the larva of *E. granulosus* lodges on a heart valve or in the brain or eye, the lesion causes grave symptoms relatively early in the infection. If it develops in the lungs, the first evidence may be a violent paroxysm of coughing with discharge of the contents of a ruptured cyst. If a unilocular cyst is hepatic in location, twenty or more years may pass before the weight of the cystic mass causes sufficient inconvenience to bring the patient to a physician. However, a blow on the abdomen may rupture the cyst and cause death from anaphylactic shock. The hydatid of *E. multilocularis* produces symptoms of hepatic disease. Eosinophilia is proportionate to the leakage from the cyst.

**Diagnosis.** This is difficult before operation. Eosinophilia is suggestive, but depends on leakage from the cyst. Hydatid thrill is suggestive, but difficult to elicit. Serologic tests are the most reliable. These include complement fixation, precipitin and intradermal tests with antigen prepared from sterile hydatid fluid, which is usually obtained from infected sheep.

**Prognosis.** The prognosis of a unilocular hydatid is fair if the cyst is in an operable site. Recurrence from the spilling of scolices from the parent cyst at the time of operation is common. Osseous hydatid disease is serious, and surgical intervention is rarely helpful. In alveolar hydatid disease the prognosis is always grave because the lesion is uncircumscribed.

**Prevention.** Control in endemic areas involves the deep burying of dead sheep and cattle. Periodic deworming of dogs with arecoline hydrochloride in endemic areas greatly reduces the amount of exposure to the eggs. Man must be careful to keep dog feces from contaminating his food, drink or cooking utensils. Children should not be allowed to play with dogs which have access to sheep, cattle or pigs in endemic areas.

**Treatment.** No chemotherapy is available for treating the larval stage of the two species of hydatid infections which occur in man. If the cyst is unilocular and in a favorable location for operation, an incision is made down to the outer cyst wall and the hydatid fluid is aspirated, with care not to spill a drop in the operative area. Then the cyst wall is incised and enough 10 per cent formaldehyde is introduced into the cavity to sterilize the germinative layer. If possible, the entire cyst should be enucleated; if this is not feasible, the cyst should be collapsed and closed with sutures separately from closure of the operative wound. In inoperable cases desensitization with hydatid antigen, as in the treatment of bee allergy, offers some promise of relief.

## Infections Produced by Flukes (Trematodes)

Flukes belong to a group of flatworms (Platyhelminthes) which are comparable to a single mature segment (proglottid) of a tapeworm. They have an incomplete digestive tract and are either unisexual or hermaphroditic. The flukes which parasitize man have a complicated life cycle, with a required development and multiplication in certain species of snails. In some flukes there is also a required second intermediate host in which encystation occurs. The most important fluke infections are the schistosomiasis and those due to the intestinal flukes, the liver flukes and the lung flukes (see Table 79, p. 574).

### SCHISTOSOMIASIS

**Etiology.** This group of diseases is produced by the two intestinal blood flukes, *Schistosoma japonicum* and *S. mansoni*, and the vesical blood fluke, *S. haematobium*. These worms are unisexual and small enough to live as mated pairs in the smaller venules draining the intestine and the urinary bladder. The female, held in the ventral sex canal of the male, deposits a series of eggs which completely fill the venule. Oviposition is repeated in adjacent venules into which the worms migrate, so that entire venous radicles may be crowded with eggs. These



FIG. 182. Egg of *Schistosoma japonicum* as seen in freshly passed feces,  $\times 666$ . (After Faust, in Brennemann's Practice of Pediatrics. Courtesy of W. F. Prior Co.)

eggs are partially embryonated when deposited and soon secrete a lytic fluid which oozes through minute pores in the shell. By pressure on, and digestion of, the wall of the venule the eggs escape into the perivascular tissues and then through the mucous coat of the organ into its lumen, together with extravasated blood. Eggs of the intestinal types are passed in the stool; those of the vesical type, typically in the urine, but at times also in the feces (Figs. 171, E, F.; 182).

**Epidemiology.** The blood fluke infections have an extensive distribution and involve millions of people in endemic territory. *Schistosoma japonicum* occurs in the Orient, especially in central, west and south China; in five foci in Japan and on five of the Philippine Islands; *S. mansoni*, in Africa, Arabia, Puerto Rico, the Lesser Antilles, extensive areas of Brazil, Dutch Guiana and two foci in Venezuela; *S. haematobium*, in Africa, the Near East, Iran, Iraq, western India and the southern tip of Portugal. Children are more frequently exposed than adults.

If eggs evacuated in feces or urine soon reach fresh water, they hatch, and the escaping ciliated larvae (miracidia) are enabled to attack and enter the soft tissues of appropriate species of snails. After development and two consecutive stages of multiplication in the snails, the parasite emerges in the fork-tailed larval stage (cercaria) and swims in the water, but eventually dies unless it infects man or certain other mammals.

**Pathology.** When man invades infected water, the blood fluke larvae attach them-

selves to his skin. They enter cutaneous blood vessels, producing slight injury, are carried to the lungs, gradually squeeze through the capillaries, and most are returned to the systemic circulation. Some larvae break out of the pulmonary capillaries with resultant petechial hemorrhage. The larvae which arrive by way of the mesenteric arteries in the portal blood stream feed on whole blood, grow and then migrate back into the mesenteric venules against the incoming portal blood. *Schistosoma japonicum* enters the drainage of the small bowel; *S. mansoni*, that of the large bowel; and *S. haematobium* migrates through the rectal and hemorrhoidal veins into the vesical venous plexus. Here the worms mature and mate, and the females begin to lay eggs. The approximate incubation periods are, for *S. japonicum*, four to five weeks; for *S. mansoni*, six to seven weeks; and for *S. haematobium*, ten to twelve weeks.

During the incubation period, as the larval worms reach capillaries through which they cannot pass and where they perish, or as they rapidly increase in size in successful locations, an increasing amount of toxic metabolites is distributed throughout the patient's body, in particular among the tissues and organs in the immediate vicinity of the worms. Then, as eggs are laid, there is initially extensive traumatic damage as they escape from the blood vessels and filter through the tissues. Later, pseudoabscesses form around eggs which become lodged in the perivascular tissues. These lesions usually are transformed into pseudotubercles.

**Clinical Manifestations.** At each site of invasion of the skin by the cercariae there is a minute lesion with sharp needling pain which lasts only a few hours. As the larval worms pass through the lungs and later lodge elsewhere, there is considerable local and generalized reaction, particularly in the liver, which becomes greatly enlarged and tender, and on the skin as giant urticaria. Toward the end of the incubation period there are late afternoon fever and night sweats. In the intestinal types there is a prodromal toxic diarrhea. Then, with the discharge of eggs, there is an accompanying dysentery (*S. japonicum*, *S. mansoni*) or hematuria (*S. haematobium*). The patient usually becomes acutely ill and, in the intestinal types, bedridden. After a few weeks of rest the dysentery is arrested, but on physical exertion is reactivated. Digestive disturbances are increased as fibrosis of the intestinal wall develops, while papillomas and cicatricial tissue



prevent the normal passage of food or feces. The liver shows signs of periportal cirrhosis, the spleen becomes greatly enlarged, and the thoracic cavity is reduced in capacity as a result of the increase in size of the abdominal viscera. In the vesical type the urinary bladder gradually becomes thickened, fibrosed and infiltrated with phosphatic salts. Renal colic is caused by bladder stones produced by deposition of uric acid crystals on the eggs as nuclei. In the intestinal types, ascites develops in the late chronic stage. In the vesical type there is incontinence of urine. In both varieties of schistosomiasis, sepsis may be anticipated in the chronic stage, and carcinoma of the liver, intestinal wall or urinary bladder may develop as a result of constant irritation.

During the acute stage there is a pronounced eosinophilia. Later there is a neutropenia with a moderate eosinophilia and monocytosis.

**Diagnosis.** This is made by recovery of the typical eggs in the stool (*S. japonicum*, Fig. 182; *S. mansoni*, Fig. 171, E) or in the urine (*S. haematobium*, Fig. 171, F).

**Prognosis.** This is fair to excellent in the acute or early chronic stages with specific therapy, but is poor in long-standing, inadequately treated chronic infections. In highly endemic areas, as in China, the Philippines and parts of Egypt and Brazil, children who are repeatedly subjected to heavy exposure die of the disease before reaching maturity.

**Prevention.** The use of copper sulfate or newer molluscicides such as sodium pentachlorophenate (Santobrite) in "infected water" to kill the snails which are intermediate hosts and prohibition of wading or bathing in suspected water are temporary and relatively inadequate measures. Permanent control can be effected only by sanitary disposal of human excreta. In endemic areas of *S. japonicum* infection the control problem is complicated by many mammalian reservoir hosts which can perpetuate the disease in the absence of human infection.

**Treatment.** Antimony salts are specific. Sodium antimony tartrate and potassium antimony tartrate (0.5 to 2 per cent solutions) are the drugs most likely to be effective in a single course of treatment, but their toxicity should be appreciated. The antimonials are introduced slowly into a vein, with care not to allow a single drop to escape into perivascular tissues and so cause painful necrosis. The patient must be recumbent during the period of administration and for at least a

half hour thereafter. The drug is administered three times a week for four to twelve weeks, beginning with 6 cc. and increasing to a tolerance of 20 cc. of the 0.5 per cent solution in adults with a weight of 50 kg., with proportional reductions for children.

Fuadin (stibophen), another antimony compound, is better tolerated and more easily administered than the antimony tartrates, since it is introduced intramuscularly and is more slowly absorbed, but its efficiency is considerably less, and treatments frequently must be repeated. The drug is administered as a 6 per cent solution three times a week. The first and second injections consist of 1.5 cc. and 3.5 cc., respectively, and are followed by nine ampules of 5 cc. each. These dosages are for adults, but may be given to children nine years of age or older. Fractional doses should be given to younger children.

Miracil D, which is administered orally, has been used with some success for *S. haematobium* infection, but is ineffective for intestinal schistosomiasis.

In advanced chronic cases specific treatment is useless because of the irreparable tissue damage.

**Cercarial (Schistosome) Dermatitis.** The cercariae of human blood flukes do not produce "swimmer's itch." Swimmer's itch, or

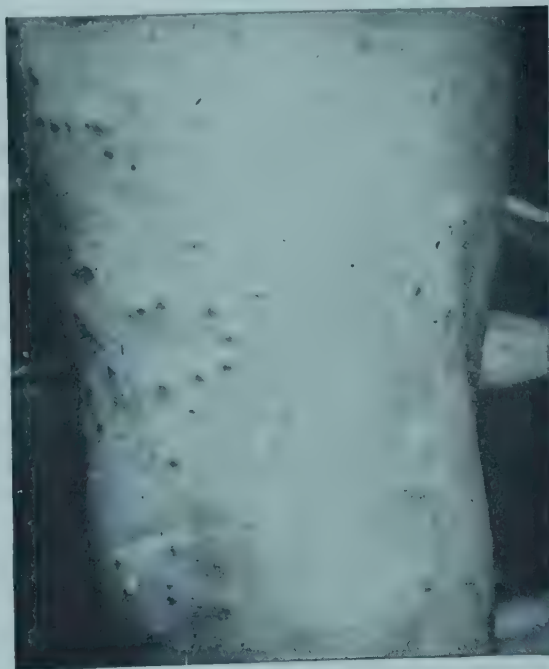


FIG. 183. Papular eruption of leg in cercarial dermatitis (swimmer's itch) acquired in a Michigan lake. (After Dr. D. B. McMullen, Army Med. Graduate School, from Mackie, Hunter and Worth: Manual of Tropical Medicine.)

"cercarial dermatitis," is caused by penetration of cercariae of blood flukes which are not able to complete their development in the human body. These are usually blood flukes of aquatic birds, occasionally of passerine birds or of domestic mammals. "Cercarial dermatitis" is widely distributed through the world, including the lake districts of the northern United States and both fresh- and salt-water areas along the east and west coasts. These cercariae on entry into the epidermis are not able to get into the cutaneous blood vessels, and their presence causes a pruritic dermatitis (Fig. 183). Children are highly susceptible, and are exposed especially during their vacation months.

## INTESTINAL FLUKE INFECTIONS

### (INTESTINAL TREMATODIASIS)

**Etiology.** Several groups of trematodes inhabit the intestine of man. These include *Fasciolopsis buski*, the giant intestinal fluke, which is fleshy and measures 20 to 75 mm. in length by 8 to 20 mm. in breadth; several species of echinostomes, which have a cervical collar of toothlike spines and vary in size from 0.5 to 20 mm. in length by 0.1 to 2.5 mm. in breadth; and the heterophyid species, which superficially resemble small seeds. These worms are most frequently attached to the duodenal and jejunal mucosae. Their eggs are operculate and vary in size from 140 by 85 microns (*F. buski*) to 28 by 16 microns (heterophyid species).

**Epidemiology.** *Fasciolopsis buski* has an extensive distribution in the Far East, southeast Asia and eastern India. It is contracted from the consumption of raw water plants such as the "water chestnut" and "buffalo nut," on which its larval stage is encysted. Echinostome species are found in the Far East, India and occasionally in the Balkans; infection with these species results from eating raw plant and animal tissues. Heterophyid species are present in the Orient, Egypt and the Balkans; they reach the human intestine in raw or inadequately cooked fresh-water and brackish-water fish. Some of these species occur commonly in reservoir hosts.

**Pathology.** The adult worms, especially the larger species, tend to erode the intestinal mucosa at the site of attachment. Moreover, their by-products are absorbed. Heterophyid flukes provide an additional grave hazard. Their minute eggs may get into the mesenteric lymphatics and venules and

be carried to various organs where they cause small pseudotubercle formations.

**Clinical Manifestations.** When the adult worms of the larger species attach themselves to the intestinal mucosa, they provoke intestinal disturbances, including a more or less serious mucous diarrhea. Their by-products, when absorbed, cause edema (especially around the eyes), ascites and even anasarca. These symptoms are frequently noted in children, the age group most commonly infected. When the minute eggs of the heterophyid flukes lodge in the heart muscle, they provoke a myocardial disturbance similar to that of beriberi; in the central nervous system they cause embarrassment to motor and sensory functions.

**Diagnosis.** This is made by recovery of the particular type of egg from the feces.

**Prognosis.** This is good to excellent with specific anthelmintic medication, except in heterophyid infections in which eggs have infiltrated into critical centers.

**Prevention.** There are few data on prevention. Control is particularly difficult, since these parasites exist in many reservoir hosts. Thorough cooking of all foods would provide a safeguard, but this is not feasible in many endemic areas.

**Treatment.** Tetrachloroethylene, as administered in hookworm infection (p. 585), and hexylresorcinol crystoids (Crystoids Anthelmintic), as administered in ascariasis (p. 578), are safe, efficient drugs.

## LIVER FLUKE INFECTIONS

### (HEPATIC TREMATODIASIS)

**Etiology.** The important liver flukes which parasitize man are *Fasciola hepatica*, the sheep liver fluke; *Clonorchis sinensis*, the Chinese liver fluke; and *Opisthorchis felinus*, the cat fluke. *Fasciola hepatica* is a moderately large species which lives in the proximal bile passages and the gallbladder. *Clonorchis* and *Opisthorchis* are delicate, lanceolate species which inhabit the bile ducts. *Fasciola* lays large eggs (140 by 75 microns) practically indistinguishable from those of *F. buski*. Eggs of *Clonorchis* measure 29 by 16 microns, and those of *Opisthorchis* 30 by 11 microns. These eggs are transported in bile and are evacuated in feces.

**Epidemiology.** *Fasciola hepatica* exists wherever sheep are raised and is an important parasite in these and other herbivorous mammals. Human infections are comparatively



few, but there are several hundred authentic records, many from Latin America and southern France, and several from Hawaii. Man frequently acquires *Fasciola* infection from eating raw water cress. Clonorchiasis is common throughout the Orient; opisthorchiasis is prevalent in eastern and southeastern Europe, Russia, including Siberia, and French Indochina. They are acquired by man and other mammals that eat raw fresh-water fish. A related species of *Opisthorchis* (*O. viverrini*) occurs in northern Thailand.

**Pathology.** On consumption of food containing the encysted larvae and their passage into the duodenum, excystation occurs. The larvae of *Fasciola* migrate through the bowel wall, traverse the peritoneal cavity, penetrate Glisson's capsule and burrow through the hepatic parenchyma to the larger bile ducts. They produce extensive damage en route through the liver. The larvae of *Clonorchis* and *Opisthorchis* migrate through the ampulla of Vater to the smaller bile ducts. Man is usually infected with a relatively small number of *Fasciola*, but several hundred to a few thousand of *Clonorchis* and *Opisthorchis* may accumulate over a period of years. Occasionally *Fasciola* larvae en route from the duodenum to the bile ducts via the peritoneal cavity lodge and develop in ectopic foci, as in the abdominal wall.

**Clinical Manifestations.** When the worms are established and mature, they provoke a hyperplasia of the biliary epithelium, followed by fibrotic encapsulation of the duct and eventually by pressure necrosis of the parenchyma, occasionally terminating in periportal cirrhosis. The most frequent symptoms are those of cholecystitis and cholelithiasis.

**Diagnosis.** This is made by recovery of the eggs from feces or by biliary drainage. The latter method is more reliable in view of the close resemblance of all these eggs to those of intestinal trematodes.

**Prognosis.** This is fairly good in less heavily infected cases in which liver function is usually not seriously impaired.

**Prevention.** The only practical prophylactic measure is thorough cooking of salad greens and fresh-water fish.

**Treatment.** Emetine hydrochloride (6 per cent solution), administered in the amount of 0.036 gm. ( $\frac{3}{5}$  grain) intramuscularly daily for nine to twelve days, is fairly satisfactory for removing *Fasciola*, and in this dosage is relatively safe. Gentian violet medicinal, as recommended in strongyloidiasis (p. 586), is lethal for *Clonorchis* in early

infections before fibrosis of the bile ducts occurs, but is of little value in old infections.

## LUNG FLUKE INFECTION

(PULMONARY TREMATODIASIS)

**Etiology.** The only fluke which produces pulmonary infection in man is *Paragonimus westermani*. This is a fleshy little worm somewhat resembling the kernel of a hazelnut. The eggs are broadly ovoidal, dark golden brown, have a relatively flat operculum, and measure about 90 by 55 microns.

**Epidemiology.** *Paragonimus westermani* is widely distributed through the Orient and the Southwest Pacific islands, and has been found in isolated regions of Colombia, Ecuador and Peru. Man, cats and dogs are exposed to infection when they eat raw or inadequately pickled crab and crayfish meat in infected areas. On arrival in the duodenum the larvae excyst and migrate through the intestinal wall, traverse the peritoneal cavity, bore through the diaphragm and reach the lungs by way of the pleural cavity. They migrate to sites near bronchioles and provoke tissue encapsulation. In addition, there are numerous instances of these worms in nonpulmonary tissue, particularly the brain, abdomen, groin and neck.

**Pathology.** In the lungs the worms become partly walled off, but invariably have an opening into an adjacent bronchiole. Frequently blood vessels extend into the lesion. The eggs escape into the bronchiole and are coughed up, at times with blood.

**Clinical Manifestations.** In pulmonary infections there is excessive bronchial secretion which may have a rusty brown color, owing to the presence of eggs. Hemoptysis may occur. In the abdomen the worms typically provoke abscess formation; in the groin, a small hard tumor; in the brain they produce lesions responsible for a jacksonian type of epilepsy, a condition common in infected children in Japan.

**Diagnosis.** Pulmonary infection requires differentiation from tuberculosis and other pulmonary diseases. The diagnosis is established by identifying the eggs in the sputum or, when swallowed, in the feces. Though this worm may be suspected as the cause of symptoms in other areas of the body, specific diagnosis depends on operation or on post-mortem examination.

**Prognosis.** This is fair to good in pulmonary infection, fair in abdominal or groin involvement, and grave in cerebral infection.

**Prevention.** No effective control has been developed, but thorough cooking of crabs and crayfish would safeguard human beings.

**Treatment.** There is no satisfactory treatment, but emetine hydrochloride, given as in liver fluke infections, may help.

## *Arthropods as Causative Agents and Transmitters of Disease*

The role of arthropods (i.e., insects and their allies) in the production of disease is three-fold: (1) Certain arthropods elaborate venoms which they introduce into the human body; (2) certain arthropods are tissue invaders; (3) many arthropods are mechanical transmitters of pathogenic microorganisms, and more are obligatory incubators and transmitters of disease-producing microorganisms.

### VENENATING ARTHROPODS

This group of arthropods includes centipedes, scorpions, spiders, ticks, mites and several species of insects.

**Centipedes.** These animals have a pair of hollow jaws which serve as fangs to introduce into the skin toxic substances elaborated in their heads. The venom is relatively weak and at most, even in an infant, will produce an inflammatory reaction at the puncture site and mild lymphangitis. It may be treated with local compresses of magnesium sulfate.

**Scorpions.** Many species of scorpions, including the dangerous ones in the southwestern United States, Latin America, North Africa, southern Europe, and India, have potent venom. This is elaborated in the swollen caudal segment and is introduced through the sharp, hollow caudal extremity into the skin of a person who accidentally steps on the animal or unconsciously brushes it with the arm.

The venom of some species produces only local tissue reaction, while that of other species is primarily neurotoxic in its action. Such venom contains several fractions, including hemolysins, endotheliolysins and neurotoxins. In addition to an intense, aching pain, radiating from the site of the injury, and lymphadenitis, there is typically an ascending motor paralysis, with convulsions resembling those observed in strychnine poisoning, rapid weak pulse, extreme thirst, and dysuria; at times there is evidence of an acute pancreatitis. Deaths from scorpion stings occur particularly in children under four years of age. In most countries where the more dangerous species are common, standardized species-specific or group-specific

antivenin is available for intramuscular administration.

Supportive treatment consists in parenteral administration of glucose and amino acid solutions. Shock should be treated with parenteral solutions, including blood plasma. Morphine is not indicated. Such patients can be controlled effectively by phenobarbital. Relatively large doses of sodium phenobarbital are necessary for irrational patients and those with convulsions. For example, 120 mg. (2 grains) of sodium phenobarbital are injected subcutaneously initially in infants and children up to twelve years of age; subsequent doses of similar amounts are given at intervals of twenty or thirty minutes up to four or five administrations. Epinephrine is given for the temporary relief of hypotension.

The application of residual sprays of DDT in and around homes and outbuildings where scorpions hide will greatly reduce their numbers.

**Spiders.** All spiders produce venoms to stun or kill their prey, but relatively few species have powerful enough fangs or potent enough venom to endanger human beings as does the black widow spider, *Latrodectus mactans*. When her web is accidentally touched by the unprotected human body, this spider attacks. She strikes with her fangs and inserts them deeply into tender skin. There is an immediate sharp pain at the site, with a burning, swollen, inflamed area surrounding the puncture wound. The venom enters the blood stream and produces dizziness, weakness, tremors, abdominal cramps and typically a spastic contraction of the muscles, particularly of the abdomen. There is rapid shallow respiration, tachycardia and high arterial blood pressure. Acute nephritis may develop as a result of the intoxication. Hemoglobinuria has been reported in small children. The double fang markings at the site of inoculation may provide a diagnostic clue, but diagnosis is usually made from the clinical history.

Treatment consists in intramuscular injection of standardized species- or group-specific antivenin if available. Pain can be reduced by the intravenous injection of 10



cc. of a 10 per cent solution of calcium gluconate. Barbiturates may be needed to allay muscle spasm and pain. Neostigmine bromide, U.S.P., may also be used to reduce spasms of smooth muscle. Most of the reported deaths have occurred because the patients were brought to the hospital too late for supportive or antivenin treatment.

Species of the hairy brown genus *Loxosceles*, which are domestic in their habitats, produce *necrotic arachnidism*. *L. laeta* and *L. rufipes* in South America cause topical necrosis and at times systemic hemolysis. In Missouri, Kansas and the southwestern United States the species *L. reclusus* is relatively common in closets, cellars and outbuildings. It is not aggressive, but when crushed or entangled in clothing both the male and the female bite, causing severe local pain, with rapid development of a thick wheal which transforms into a violaceous sloughing ulcer, leaving a deep granulating base. Healing takes place slowly. Within twenty-four to thirty-six hours after the bite systemic reactions consisting of restlessness, fever and at times a scarlatiniform rash are observed. Experimentally, the venom has been found to contain a powerful necrotoxin.

Ten per cent DDT in kerosene sprayed on the spider's web is lethal to the spider.

**Ticks and Mites.** Many species of ticks and several species of mites cause serious local irritation at the sites on the skin where they take blood meals. The most notorious mites are the chigger ("red bug") and the rat mite. These are particularly irritating for small children. The local lesion at the site of attachment can be effectively treated by application of phenolated camphor solution in pure mineral oil or Quotane ointment (containing 1[ $\beta$ -dimethylaminoethoxy]-3-*n*-butylisoquinoline hydrochloride). Dusting of DDT into socks and pants, or rubbing of dimethyl phthalate on the ankles and legs, will usually prevent infestation with these mites.

Certain ticks, as the Rocky Mountain wood tick, introduce saliva which may produce a flaccid ascending motor paralysis which begins in the lower extremities. Recovery is usually rapid and complete if the tick is removed quickly, but if it is allowed to remain, death may result from respiratory paralysis.

**Insects.** These include bees, wasps, ants, blister beetles, moth caterpillars and many bloodsucking insects. The honeybee worker introduces her stinger along with venom; the bumblebee retains her stinger. Bees, wasps and ants have both acid and alkaline frac-

tions as well as a histamine-like fraction in their venom. The stinger must be removed carefully after honeybee venenation. Hypersensitive persons who go into shock require prompt use of epinephrine, and then should be desensitized with whole bee extract made up in Coca's solution to minimize subsequent reactions.

Blister beetles produce a painful blister when their juices are brought in contact with the skin. Ammonia will partly neutralize the blister fluid, and calamine lotion will ease the pain. Certain caterpillars elaborate venom at the base of some of their hairs. When these hairs come in contact with the skin or mucous membranes, they produce a painful burn which heals slowly. The pain is partially eased by calamine lotion.

Many insects, such as mosquitoes, stable flies, fleas, lice and assassin bugs, introduce saliva into the skin before taking a blood meal. This foreign protein produces allergic manifestations in many persons. Since no method of treatment is eminently satisfactory, such hypersensitive persons must learn to protect themselves from these insects.

## TISSUE-INVADING ARTHROPODS

Among the arthropods which invade tissues the following are important: the itch mite (*Sarcoptes scabiei*), which produces scabies; the chigoe (*Tunga penetrans*); and the maggots or larval stage of many species of filth flies and their relatives, which cause myiasis.

**Scabies.** This disease, produced by *Sarcoptes scabiei*, is cosmopolitan in distribution and is most frequently found in lower economic groups whose personal hygiene is neglected. The adult mite is an eight-legged organism which burrows into the deeper layers of the skin and forms a tunnel nearly parallel to the surface. At the blind end of the tunnel the female lays about ten eggs a week for four or five weeks. In three to five days the eggs hatch, and six-legged larvae emerge. These young mites either make lateral tunnels or come out of the tunnel and form new ones. Since an entire life cycle may be completed in eleven to fifteen days, an infestation, once established, develops rapidly. The tunnel appears superficially as a slightly raised, reddened, somewhat sinuous track. (See page 1294 for clinical discussion.)

**Chigoe Infestation.** *Tunga penetrans*, a flea, is a common skin parasite of dogs, pigs and bare-footed persons in the American tropics and tropical Africa. The most common

sites of infestation are the spaces between the toes, into which the fleas burrow. The females swell to the size of a pea and produce painful, festering lesions. The gravid fleas should be removed with a sterile needle and the wounds painted with tincture of iodine to kill the remaining fleas and eggs. Since infestation is usually acquired from direct contact of the bare foot with dust or dirt harboring fleas from the feet of dogs or pigs, well-shod feet practically guarantee safety from attack.

**Myiasis.** This results from penetration of animal tissues by the larval stage of several species of flies. It may be specific, semispecific or accidental, depending on the species of fly. Myiasis may affect the skin, eye, nasopharynx, ear, intestine or urethra.

Specific myiasis refers to a natural tendency of the gravid fly to deposit eggs or larvae on unbroken skin or uninjured mucous membranes. Certain species, such as the tropical warble fly (*Dermatobia hominis*), the sheep bot (*Oestrus ovis*), the cattle bots (*Hypoderma* species), the horse bots (*Gasterophilus* species) and the primary screwworm (*Callitroga hominivorax*) are myiasis-producing forms.

Semispecific myiasis-producing species are those which deposit their eggs or larvae either on or in clean or ulcerated tissues. These include the flesh flies (*Sarcophaga* species, *Wohlfahrtia* species) and the common American screwworm (*Callitroga macellaria*). Both groups produce mutilating wounds, which consist of long, serpiginous tunnels under the skin (larva migrans), deep wounds more or less perpendicular to the surface, or excavating lesions which become secondarily infected. Children are the most frequent victims. Death may occur and be due to extensive deep penetration into the lungs, brain or abdominal viscera.

The third type of myiasis is purely accidental, and consists in the implantation of eggs or maggots in wounds, or their temporary lodgment in the intestine or urethra.

Maggots burrowing into tissues or breeding in wounds should be removed as soon as possible. The lesion should be irrigated, bacitracin applied, and covered with a sterile dressing. In intestinal myiasis frequent saline purgation and enemas may be helpful. Young children, particularly those around stock farms, should be protected from flies by screening or mosquito netting, and any discharges from the eyes, nares or skin lesions should not be allowed to accumulate, since

these attract myiasis-producing flies. Permanent control consists in eradication of breeding by these flies, especially around cattle, horses, hogs and domestic rabbits.

## ARTHROPODS AS TRANSMITTING AGENTS OF DISEASE

Arthropods serve in two ways to transmit disease-producing microorganisms to man: (a) mechanically and (b) as essential biologic hosts or incubators of pathogens.

**Mechanical Transmitters.** The most important group of mechanical transmitters is that of the filth flies, including the common housefly, the lesser houseflies, stable flies, greenbottles, bluebottles, blowflies, the flesh flies, the hover flies, fruit flies and the cluster flies. They are responsible for the transmission of typhoid and other salmonella infections, cholera and amebiasis. Evidence is less conclusive that they play a conspicuous role in the spread of poliomyelitis and epidemic conjunctivitis.

**Essential Transmitters.** Arthropods which are biologic vectors of pathogens include (1) the ticks, which transmit tick spotted fever, Q fever, Colorado tick fever, relapsing fever and tularemia; (2) red mites, which transmit scrub typhus, and mouse mites, which transmit rickettsialpox; (3) lice, which transmit epidemic typhus fever, trench fever and relapsing fever; (4) fleas, which transmit plague, murine typhus and several other infections; (5) mosquitoes, which transmit malaria, yellow fever, dengue, encephalomyelitis, filariasis and tularemia; (6) sand flies, which transmit kala-azar, cutaneous and mucocutaneous leishmaniasis, Oroya fever and pappataci fever; (7) *Glossina* flies, which transmit African trypanosomiasis; (8) black gnats, which transmit onchocercosis; and (9) assassin bugs, which transmit Chagas' disease.

Children are particularly susceptible to all these diseases. In some instances protection can be afforded by vaccine, as in yellow fever, Rocky Mountain spotted fever and typhus fever. In some, individual prophylaxis consists in avoiding endemic territory. In certain diseases the only practical safeguard consists in dusting the exposed person's clothing with DDT or using this insect toxicant as a residual spray. One or both of these procedures have been effective in the control of epidemic typhus fever, malaria and filariasis. Another method of attack is the destruction of the reservoir host (i.e., rats in the case of plague



and murine typhus). These arthropods are man's greatest enemy and today constitute his most serious challenge.

ERNEST CARROLL FAUST

## REFERENCES

### General

Belding, D. L.: Textbook of Clinical Parasitology. 2d ed. New York, Appleton-Century-Crofts, Inc., 1952.

Faust, E. C.: Human Helminthology. 3rd ed. Philadelphia, Lea & Febiger, 1949.

———: Animal Agents and Vectors of Human Disease. Philadelphia, Lea & Febiger, 1955.

Faust, E. C., and Russell, P. F.: Craig and Faust's Clinical Parasitology. 6th ed. Philadelphia, Lea & Febiger, 1957.

Mackie, T. T., Hunter, G. W., III, and Worth, C. B.: A Manual of Tropical Medicine. 2nd ed. Philadelphia, W. B. Saunders Company, 1954.

### Nematodes

Andrews, J.: Modern Views on the Treatment and Prevention of Hookworm Disease. Ann. Int. Med., 17:891, 1942.

Beaver, P. C.: The Detection and Identification of Some of the Common Nematode Parasites of Man. Am. J. Clin. Path., 22:481, 1952.

Beaver, P. C., and others: Chronic Eosinophilia Due to Visceral Larva Migrans. Pediatrics, 9:7, 1952.

Brown, H. W.: Recent Developments in the Chemotherapy of Helminthic Diseases. Proc. IV Congresses Trop. Med. and Malaria, II:966, 1948.

———: Use of Antibiotics in the Treatment of Helminthic Infections. New York Acad. Sc., 55:1133, 1952.

Caplan, J. P.: Creeping Eruption and Intestinal Strongyloidiasis. Brit. M. J., 1:396, 1949.

Dent, J. H., Nichols, R. L., Beaver, P. C., Carrera, G. M., and Staggers, R. T.: Visceral Larva Migrans. Am. J. Path., 32:777, 1956.

Etteldorf, J., and Crawford, L.: Treatment of Ascariasis in Children. Use of 1-Diethylcarbamyl-4-Methyl Piperazine Dihydrogen Citrate (Hetrazan). J.A.M.A., 143:797, 1950.

Garnham, P. P. C.: The Control of Onchocerciasis. Ann. Soc. belge de Méd. trop., 34:763, 1954.

Gould, S. E.: Trichinosis. Springfield, Ill., Charles C Thomas, 1945.

Hartz, P. H.: Contribution to the Histopathology of Filariasis. Am. J. Clin. Path., 14:34, 1944.

Hawking, F.: The Chemotherapy of Filarial Infections. Pharmacol. Rev., 7:279, 1955.

Jelliffe, D. B.: Oil of Chenopodium in the Treatment of Ascariasis. J. Trop. Med. & Hyg., 54:143, 1951.

Jones, C. A.: Clinical Studies in Human Strongyloidiasis. I. Semeiology. Gastroenterol., 16:743, 1950.

Jung, R. C.: The Predominance of Single-Brood Infections in Human Ascariasis. J. Parasitol., 40:405, 1954.

Jung, R. C., and Beaver, P. C.: Clinical Observations on *Trichocephalus Trichiurus* (Whipworm) Infestation in Children. Pediatrics, 8:548, 1952.

Kenney, M., and Hewitt, R.: Treatment of Bancrof-

tian Filariasis with Hetrazan in British Guiana. Am. J. Trop. Med., 29:89, 1949.

Knox, J. M.: Creeping Eruption (Larva Migrans) at Keesler Field Air Force Base. J. Louisiana M. Soc., 105:69, 1953.

Link, V. B.: Trichinosis: A National Problem. Proc. First Nat'l Conf. on Trichinosis, Chicago, 3-7, 1952.

Michael, P.: Filariasis among Navy and Marine Personnel. Report of Laboratory Investigations. U.S. Nav. M. Bull., 42:1059, 1944.

Rhoads, C. P., Castle, W. B., Payne, G. C., and Lawson, H. A.: Hookworm Anemia: Etiology and Treatment, with Especial Reference to Iron. Am. J. Hyg., 20:291, 1934.

Schöffner, W., and Swellengrebel, N. H. Retrofection in Oxyuriasis. A Newly Discovered Mode of Infection with *Enterobius Vermicularis*. J. Parasitol., 35:138, 1949.

Swartzwelder, J. C., and others: Dithiazanine, an Effective Broad-Spectrum Anthelmintic. Results of Therapy of Trichuriasis, Strongyloidiasis, Enterobiasis, Ascariasis, and Hookworm Infection. J.A.M.A., 165:2063, 1957.

Swartzwelder, J. C., and others: Therapy of Trichuriasis and Ascariasis with Dithiazanine. Am. J. Trop. Med. & Hyg., 7:329, 1958.

Swartzwelder, J. C., Miller, J. H., and Sappenfield, R. W.: The Treatment of Cases of Ascariasis with Piperazine Citrate. With Observations of the Effect of the Drug on Other Helminthiasis. Am. J. Trop. Med. & Hyg., 4:326, 1956.

White, R. H. R., and Standen, O. D.: Piperazine in the Treatment of Threadworms in Children. Brit. Med. J., 2:755, 1953.

Wilder, H. C.: Nematode Endophthalmitis. Tr. Am. Acad. Ophthalm., 55:99, 1950.

### Cestodes

von Bonsdorff, B.: *Diphyllobothrium latum* as a Cause of Pernicious Anemia. Exp. Parasitol., (Rev. Sec.), 5:207, 1956.

Miller, M. J.: Hydatid Infection in Canada. Canad. M. A. J., 68:423, 1953.

Neghme, A., and Faiguenbaum, J.: Nuevo Modalidad de Tratamiento en las Teniasis. Rev. Med. Chile, 75:54, 1947.

Sodeman, W. A., and Jung, R. C.: Treatment of Teniasis with Quinacrine Hydrochloride. J.A.M.A., 148:285, 1952.

Vogel, H.: Ueber den Entwicklungszyklus und die Artzugehörigkeit des europäischen Alveolarchinococcus. Deutsch. med. Wchnschr., 80:931, 1955.

———: Ueber den Echinococcus Multilocularis Süddeutschlands. I. Das Bandwurm-stadium von Stämmen menschlicher und tierischer Herkunft. Zeitsch. Tropenmed. u. Parasitol., 8:404, 1957.

### Trematodes

Alicata, J. E.: Human Fascioliasis in the Hawaiian Islands. Hawaiian Med. J., 12:196, 1953.

Amberson, J. M.: Schistosomiasis and Its Control in Egypt. U.S. Nav. M. Bull., 46:977, 1946.

Faust, E. C.: *Schistosomiasis Japonica*: Its Clinical Development and Recognition. Ann. Int. Med., 25:585, 1946.

Faust, E. C., and Meleney, H. E.: Studies on *Schisto-*

- somiasis Japonica*. Am. J. Hyg., Monogr. Ser., no. 3, 1924.
- Kuntz, R. E., and Wells, W. H.: Laboratory and Field Evaluation of Two Dinitrophenols as Molluscicides for the Control of Schistosome Vectors in Egypt. Am. J. Trop. Med., 31:784, 1951.
- Most, H., et al.: Schistosomiasis Japonica in American Military Personnel: Clinical Studies of 600 Cases during the First Year after Infection. Am. J. Trop. Med., 30:239, 1950.
- Olivier, L.: Schistosome Dermatitis, a Sensitization Reaction. Am. J. Hyg., 49:209, 1949.
- Sadun, E. H.: Studies on *Opisthorchis viverrini* in Thailand. Am. J. Hyg., 62:81, 1955.
- Sadun, E. H., and Maiphoo, C.: Studies on the Epidemiology of the Human Intestinal Fluke, *Fasciolopsis Buski* (Lankester) in Central Thailand. Am. J. Trop. Med. & Hyg., 2:1070, 1953.
- Arthropods*
- Atkins, J. A., Wingo, C. W., Sodeman, W. A., and Flynn, J. E.: Necrotic Arachnidism. Am. J. Trop. Med. & Hyg., 7:165, 1958.
- Auguston, G. F.: The Tropical Chigoe in California. Science, 96:581, 1942.
- Bishopp, F. C., and Philip, C. B.: Carriers of Human Disease. Insects, in Year Book, U.S. Dept. Agric., Washington, D. C., 1952, pp. 147-60.
- Bogen, E.: The Treatment of Spider Bite Poisoning. In "Venoms," Publ. 44, AAAS, Washington: 101, 1956.
- Buxton, P. A.: The Louse. An Account of the Lice Which Infest Man, Their Medical Importance and Control. London, 1939.
- Costa, J. A.: Tick Paralysis on the Atlantic Seaboard. Am. J. Dis. Child., 83:337, 1952.
- Harrell, W. B., and Moseley, V.: The Surgical Treatment of Subdermal Myiasis Due to *Dermatobia Hominis*. South. M. J., 35:720, 1942.
- Kirby-Smith, H. T.: Specific Treatment of Black Widow Spider Bite. South. M. J., 38:696, 1945.
- Kohls, G. M.: Vectors of Rickettsial Diseases. Ann. Int. Med., 26:713, 1947.
- Link, V. B., and Mohr, C. O.: Rodenticides in Bulbous Plague Control. Bull. WHO, 9:585, 1953.
- Lucas, T. L.: Poisoning by *Megalopyge Opercularis* (Puss Caterpillar). J.A.M.A., 119:877, 1942.
- Maretic, Z., and Stanic, M.: The Health Problem of Arachnidism. Bull. WHO, 11:1007, 1954.
- O'Rourke, F. J.: The Toxicity of Black Widow Spider Venom. In "Venoms," Publ. 44, AAAS, Washington:89, 1956.
- Parker, R. R.: Rocky Mountain Spotted Fever; Results of Fifteen Years Vaccination. Proc. Sixth Pacific Sci. Congress, V:589, 1942.
- Pipkin, A. C.: Filth Flies as Transmitters of *Entamoeba Histolytica*. Proc. Soc. Exper. Biol. & Med., 49:46, 1942.
- Schöttler, W. H. A.: On the Toxicity of Scorpion Venom. Am. J. Trop. Med. & Hyg., 3:172, 1954.
- Watt, J.: Fly Control and the Acute Diarrheal Diseases. Bol. Ofic. San. Panam., 28:249, 1949.
- Wolbach, S. B., Todd, J. L., and Palfrey, F. W.: The Etiology and Pathology of Typhus; Being the Main Report of the Typhus Research Commission of the League of Red Cross Societies to Poland. Cambridge, Harvard University Press, 1922.

## Tropical Eosinophilia

Unusually high, persistent or recurrent eosinophilia in the absence of a readily detectable cause suggests an occult helminth infection. A number of such infections are more or less well known. Trichinosis, visceral larva migrans, cryptic filariasis and sparganosis are all helminth infections in which eosinophilia may be conspicuous while the causative worms are inconspicuous and difficult to detect. Certain of the helminths, whose presence in the adult stage is easily detected by finding eggs or larvae in the feces, sputum or blood, are hidden in the tissues during some stage of larval development when they too may produce high, but transient, eosinophilia. Common examples are *Ascaris* and hookworms, which characteristically produce transient pulmonary infiltration and eosinophilia (Loeffler's syndrome) during the period of larval migration through the lungs.

In tropical countries, particularly in India and other southeastern countries of Asia, there occurs a syndrome known as tropical eosinophilia. It occurs more frequently in

adults than in children. This syndrome is hard to distinguish from eosinophilias resulting from hidden helminth infections; indeed, tropical eosinophilia is not at this time a clearly defined disease entity. In addition to hypereosinophilia, the outstanding features of tropical eosinophilia are chronic or recurrent bronchial asthma and pulmonary infiltration (eosinophilic lung), both of which are relieved by administration of organic arsenicals. Favorable response to arsenotherapy has been regarded as an essential diagnostic feature. It is now evident that diethylcarbamazine, given orally in daily doses of 12 mg. per kilogram of body weight in three divided doses for four days, is equally effective in relieving symptoms and in reducing eosinophilia to normal levels. Owing to its greater safety and ease of administration, it is replacing arsenicals.

The etiology of tropical eosinophilia is unknown. Observations just reported strongly suggest involvement of one or more undetermined species of filarial worms, but the relation of tropical eosinophilia to visceral



larva migrans and pulmonary ascariasis is not clear.

PAUL C. BEAVER

#### REFERENCES

Beaver, P.: Wandering Nematodes as a Cause of Disability and Disease. *Am. J. Trop. Med. & Hyg.*, 6: 433, 1957.

Beaver, P., and Danaraj, T. J.: Pulmonary Ascariasis Resembling Eosinophilic Lung. Autopsy Report with Description of Larvae in the Bronchioles. *Am. J. Trop. Med. & Hyg.*, 7:100, 1958.

Chaudhuri, R. N.: Tropical Eosinophilia. *J. Indian Med. A.*, 27:195, 1956.

Danaraj, T. J.: The Treatment of Eosinophilic Lung (Tropical Eosinophilia) with Hetrazan. *Proc. Alumni A. Malaya*, 9:172, 1956.

Danaraj, T. J., da Silva, L. S., and Schacher, J. F.: The Filarial Complement Fixation Test in Eosinophilic Lung (Tropical Eosinophilia). *Proc. Alumni A. Malaya*, 10:109, 1957.

Gault, E. W., and Webb, J. K. G.: Tropical Eosinophilia. Hepatic Lesions Related to Presence of Nematode Larvae. *Lancet*, Sept. 7:471, 1957.

## PROTOZOAN DISEASES

### MALARIA

The clinical vagaries attributed to malaria are more frequent in children than in adults. Only by an understanding of the variations in malarial infections can one explain what takes place in the individual patient.

Malaria is usually described as an infection with one of four species of protozoan parasites, termed "plasmodia." Though such a distinction exists, for practical clinical and diagnostic purposes, malaria may be regarded simply as *two* diseases: One disease, caused by *Plasmodium falciparum*, is potentially dangerous and sometimes fatal; it can produce a fantastic variety of clinical manifestations, but fortunately is readily cured.

The other disease, caused by *P. vivax*, *P. malariae* or *P. ovale*, is more paroxysmal and almost never fatal. It may recur weeks after an adequately treated primary attack in contrast to falciparum infections, which, in the absence of reinfection, rarely if ever recur after adequate treatment.

Thus the term "malaria," when used to identify a particular infection, should be preceded by an adjective which indicates the species of parasite involved. The old term "quartan" is used in reference to *P. malariae* infections. Otherwise the species names (falciparum, vivax and ovale) are used. *Ovale* malaria is exceedingly rare and seldom severe.

**Etiology. Pre-erythrocytic phase.** A malarial infection of any species is acquired when a previously infected female anopheles mosquito injects, with her saliva during the act of biting, tiny organisms called *sporozoites*. These sporozoites reach the sinusoids of the liver through the circulating blood and enter the cytoplasm of hepatic cells. Growth and nuclear division are rapid for some days with formation of small cysts containing hundreds or thousands of *merozoites*. These merozoites are similar to those of the same name which later result from development of the asexual forms in the red blood cells. It is at this stage that the falciparum infection first differs from the others.

At the end of approximately *six days* of development in the liver the falciparum cysts rupture, and many of the liberated merozoites enter red blood cells in the liver sinuses. In vivax infections the development

in the liver requires *eight days*, and some of the merozoites enter hepatic cells to pave the way for a relapse at a later date. The pre-erythrocytic stage of *ovale* has been proved to be *nine days*. The same phase of quartan malaria is estimated to be *nineteen days*.

**Erythrocytic phase.** Irrespective of species, the merozoites which invade red blood cells immediately begin to feed on hemoglobin and to grow. In stained thin blood smears they appear first as tiny signet rings of bluish cytoplasm with a dot of red chromatin (young trophozoite). As they become larger, variable amounts of yellow-brown hematin appear (later trophozoite). The shape may vary during growth until a round organism containing pigment almost fills the red blood cell. The mature parasite (early schizont) stops feeding, and its nucleus divides first in two and finally into eight or more pieces. The cytoplasm arranges itself around the new nuclei, the pigment aggregates into large clumps, and the completed *schizont* or segmenter contains eight to thirty merozoites similar to those formed in the liver. After a specific time the invaded erythrocyte ruptures, and naked merozoites, pigment and erythrocytic debris are freed in the plasma, where the merozoites which fail to enter fresh erythrocytes are phagocytized. Thus an asexual cycle is begun each time a new crop of merozoites invades red blood cells. Only the erythrocytic cycle occurs in infections induced artificially by injection or accidentally as in the transfusion of infected blood.

Malarial parasites are always intracellular except briefly during the transfer from one host cell to another. The malarial paroxysm does not take place until enough cycles have occurred to produce the amount of parasitic material, pigment and red cell debris required to induce febrile or other reactions.

Some of the growing parasites fail to divide. They require about the same time for maturation, but their nucleus remains intact. They become male or female forms which within the red blood cells continue to circulate in the blood stream for a number of days, after which they degenerate and disappear. These forms, called *gametocytes*, are the only forms capable of infecting the mosquito. Gametocytes never degenerate simul-



taneously in sufficient numbers to cause symptoms.

**Mixed infections and broods.** Although mixed infections with two species undoubtedly occur, one species almost invariably is responsible for the clinical picture. Falciparum strains usually dominate vivax, and vivax dominate quartan; only when sufficient immunity is developed to the dominant strain does the other one reach clinical status.

In an infection with a single species distinct broods may develop. Since the liver merozoites are not released simultaneously and the erythrocytic schizonts do not all rupture at the same time, some groups of new parasites begin their existence in red blood cells before or after the majority. When some which are about twelve hours ahead and others about twelve hours behind the majority mature about the same time, their numbers are frequently sufficient to produce an independent reaction, and a new brood is clinically evident. Dominant broods survive, and the others quickly disappear. In vivax or falciparum infections single broods will produce a febrile reaction every other day, whereas, if two broods develop, there will be daily paroxysms. Two broods of the quartan species can be responsible for fever two days out of three, but three broods are required for daily temperature rises. The impossibility of a "species" diagnosis on clinical grounds is apparent.

**Epidemiology.** Only in regions where people, especially children, have gametocytes within their red blood cells can the Anopheles mosquitoes become infected. These areas are chiefly tropical. The United States is now free of indigenous malaria, but infection of local mosquitoes can occur from infected persons.

When breeding of Anopheles mosquitoes is prevented, where the adult mosquitoes are kept from contact with man by screens or nets, or where adult infected mosquitoes are killed by natural enemies or insecticides before the sporozoites have had time to mature, infection of man does not occur. At present no drugs are known which can, with certainty, prevent invasion of the sporozoite, but some which may be toxic can stop the pre-erythrocytic development. Currently available drugs suppress chiefly the erythrocytic forms; when such suppression is effective, clinical disease is not manifest.

The term "congenital disease," as used for syphilis, does not apply to malaria, since merozoites or sporozoites, unlike spirochetes,

cannot pass the intact placental membrane. Only if infected maternal red blood cells mingle with red blood cells of the fetal circulation can infection of the fetus result. Severe falciparum infections of the pregnant woman may damage the placenta, resulting in death of the fetus or premature birth. Malarial infections rarely develop after antepartum or intrapartum separation of a part of the placenta even though the mother is infected at the time of delivery. However, the blood of newborn infants in malarial areas should always be examined for malarial parasites if the infants appear ill. Thus if a special diagnostic term were to be used, "neonatal malaria" would seem better than "congenital malaria." On the other hand, infants born during or shortly after an attack of malaria in the mother appear to acquire a natural infection more slowly than do infants born of healthy mothers. This apparent passive immunity may represent the suppressive effect of a diet consisting solely of milk on vivax malaria, and fetal hemoglobin may be less attractive to the falciparum parasite.

**Pathology.** In all malarial infections there is destruction of red blood cells; the extent depends upon the duration and severity of the infection. Thus the greatest concentration of malarial pigment is in the spleen, liver and bone marrow. At first the spleen shows congestion, then hyperplasia and sometimes necrosis of the follicles with tremendous amounts of pigment in the phagocytic cells. The liver becomes extremely congested, and the Kupffer cells contain large amounts of malarial pigment. Similar reactions occur in the bone marrow, placenta and other organs. Practically all descriptions of the pathology of malaria are of fatal falciparum infections.

The malignancy of falciparum malaria is peculiar to that species. Eight to eighteen hours after the falciparum parasite has entered the red blood cells these cells become increasingly sticky and tend to adhere to the endothelial lining of blood sinuses and vessels, especially where the circulation may be slow. A cross section of a small venule from a fatal case will usually reveal in each red blood cell around the periphery of the vessel a spot of pigment which is all that remains of the antemortem parasite, whereas of the many red blood cells in the lumen of the vessel only an occasional one will have evidence of a contained parasite. This phenomenon has no relation to "sludging" of the

blood seen in other diseases as well as in malaria, though doubtless it contributes to it.

The "sticky cell" is thus fixed and unable to return to the general circulation. Its contained parasite grows and matures, and at the end of forty-eight hours the cell ruptures, liberating its merozoites, which are capable of infecting new red blood cells. Interference with the function of the vessel may vary from slight to complete occlusion or to actual rupture. The site and extent of this interference with vascular function coupled with an unexplained, seemingly selective localization of parasitized cells in various organs or systems are responsible for the variety of symptoms from falciparum infections. Thus pneumonitis, encephalitis or enteritis may be manifest when the bulk of the infection is in the lungs, brain or intestinal tract.

The release of merozoites where the circulation is slowed facilitates the invasion of near-by red blood cells, so that falciparum parasitemias may be heavy in comparison with those of vivax and quartan, in which the rupture of the schizonts takes place in the active circulation.

Successful treatment stops the growth of parasites in one or all stages in the red blood cells, and immunity appears to increase the speed with which fixed and mobile phagocytic cells take up the naked merozoites and even parasite-containing red blood cells. Changes brought about by vivax and quartan malaria, as well as by the majority of falciparum infections, are completely reversible.

**Clinical Manifestations.** There are no clinical manifestations of malaria which can be said to be peculiar to children.

As with adults, children who acquire malaria fall in two groups: those who have not had previous contact with the disease and have no immunity, and those who have been exposed to repeated infection since birth and by eight to twelve years of age have acquired a high degree of tolerance. The former may quickly become severely ill, whereas the latter may have astonishing parasitemias with relatively few symptoms. In the partially immune child an intercurrent infection sometimes initiates renewed activity of an otherwise quiescent malarial infection.

About ten days after a nonimmune child has been in an infected area he should be observed for such changes in behavior as fretfulness, anorexia, unusual crying or disturbances of sleep. Fever may be absent or increase gradually for one or two days, or the onset may be sudden with temperature

up to 105° to 107° F. with or without a chill. After varying periods the temperature falls to normal or below and sweating occurs.

The paroxysm may be extremely short or may last for two to twelve hours. The child may complain of malaise, headache, nausea, generalized aching, particularly of the back, and occasionally of pain in the abdomen when the spleen has swollen quickly and is tender. In vivax and quartan infections dominated by a single brood the fever is the outstanding and characteristic manifestation, occurring at intervals of forty-eight hours in the former and at seventy-two hours in the latter. If convulsions occur, they abate when the fever falls. Herpetic lesions of the mouth are not uncommon.

In falciparum infections the fever is less characteristic and may even be more or less continuous; the fever may be overshadowed by severe manifestations related to such systems as the cerebral, pulmonary or intestinal ones. Severe nausea and vomiting, jaundice, diarrhea, bronchitis and pneumonitis, delirium, convulsions and coma are common. The red blood cell count and hemoglobin level may decrease rapidly.

The spleen is more commonly enlarged in vivax than in falciparum infections, but the liver is likely to be palpable or tender in both. The behavior of a particular strain of any species of malaria can be deduced only from observation of a large number of patients, since the variations are so great.

Whatever the signs and symptoms, if they disappear with the parasitemia in response to therapy, it may be assumed that they were caused by the malarial infection.

**Blackwater fever.** The dreaded blackwater fever is now seen only rarely. The essential lesion is an intravascular hemolysis of varying degree. It is observed only following attacks of falciparum malaria. Therapy with quinine has been thought to be a causative factor; the disappearance of it in areas where Atabrine has replaced quinine in therapy strongly suggests a causal relationship.

If falciparum parasites are present in the blood during an attack, the child may be treated with amodiaquine, chloroquine or quinacrine; otherwise treatment of the malarial infection is postponed until the hemoglobinuria has abated.

**Diagnosis.** The diagnosis of malaria depends upon identification of parasites in the blood. In the blood smear stained for a differential count, the parasites within the red cells have a red chromatin and bluish cyto-



plasm, but *only* if the nuclei of leukocytes have been stained so that they have a rich blue-violet color. The parasites need never be confused with platelets, which have different densities of the same color.

A thick blood film is most suitable for identification of the parasite. Specific medication should be withheld until parasites are demonstrated; if necessary, examinations should be made morning and evening for three successive days. Thick films are made by spreading blood on a clean, grease-free slide so that, when tilted at a right angle, the blood does not quickly form a drop at the lower border, but spreads slowly to the low point. The slide is then placed flat and permitted to dry without heating. The dry film is dipped in methylene blue phosphate solution for one second only. After washing gently in distilled water until the excess blue is removed, it is placed *face downward* on a curved staining plate, and a freshly prepared solution of buffer water, containing 1 drop of Giemsa stain per milliliter, is run under the slide and allowed to act for six to eight minutes. The slide is again dipped in distilled water, drained and dried with heat. The slides are examined under the oil immersion lens with blue-white light and with an eyepiece of 6 to 8 magnification.\*

**Treatment.** Treatment should not be undertaken until the diagnosis has been established. Owing to the importance of the falciparum infection, it is essential to determine whether this species is present; otherwise species identification is not important.

The adequacy of any drug is based on its ability to control the immediate attack and to eliminate the falciparum infection. During World War II quinacrine was proved to be the first drug capable of accomplishing both. It is not practical to attempt to eradicate all vivax infections at the time of the primary attack, especially if there is the potentiality of reinfection. The fourteen-day treatment should be reserved for patients with vivax infections who have had at least one relapse.

\* Methylene blue phosphate solution is prepared by dissolving 1 gm. of the following mixture in 300 cc. of distilled water and filtering (suitably covered, it may be used for many examinations): Medicinal methylene blue, 1 part; anhydrous disodium phosphate, 3 parts; potassium dihydrogen phosphate, 1 part. Buffer water can be made by dissolving 1 gm. of the same phosphate salts in 1 liter of distilled water in proportion of 6 gm. of disodium acid phosphate (anhydrous) to 5 gm. of potassium dihydrogen phosphate.

If good Giemsa stain is not available, 0.75 gm. of Wright's stain powder is thoroughly shaken several times daily for two days with 65 cc. of pure methyl alcohol and 35 cc. of pure glycerin and ten glass beads. Any glass dish with a depression of 4 mm., as the bottom of a mason jar, may replace the curved staining plate.

Gametocytes of vivax and quartan malaria disappear simultaneously with the asexual forms after treatment with the usual drugs. If the falciparum infection is treated early enough and adequately, gametocytes may never appear. On the other hand, falciparum gametocytes may not appear until after the asexual forms have been absent for some days and may then persist for two to three weeks. No treatment is required unless Anopheles mosquitoes are prevalent, when it may be advisable to follow the regular treatment with a gametocidal drug, owing to the potential danger of the patient to the community.

Ice caps and tepid sponging are indicated when the temperature is over 104° F. The fluid and electrolyte balance should be maintained. Water, fruit juices and other fluids should be offered in small amounts at frequent intervals. Salt tablets may be used if sweating is excessive. No purgation should be given, and the child should be allowed considerable latitude in the selection of his diet. Some form of vitamin B<sub>1</sub> may be given, and, when the acute phase is passed, ferrous sulfate may be prescribed.

Children with severe falciparum infections require much more consideration. When markedly dehydrated with or without shock, they should receive intravenous fluids, including blood. The child should be hydrated, out of shock and urinating as an evidence of restored renal function before antimalarial drugs are given. Injections of Atabrine to markedly dehydrated or even to severely malnourished children may be attended by serious consequences. Malnourished children should receive relatively small doses of antimalarial drugs and then only after initial hydration.

Parenteral administration of drugs may be indicated for children who are vomiting persistently, who are in coma or who cannot be induced to swallow. Only drugs especially prepared for parenteral administration should be used, except in grave emergencies. If quinine is the only drug available, 0.5 gm. may be given intramuscularly every four hours. When coma or convulsions are present, quinacrine hydrochloride as a sterile powder freshly dissolved in 3 to 10 cc. of distilled water, or 3 to 5 cc. of chloroquine dihydrochloride (50 mg. per cubic centimeter) may be given. The doses stated are average ones for a child three years of age. Such intravenous injections should not be given faster than 1 cc. per minute.

**Suppressive medication.** Suppressive medi-

Table 80. Malarial Drugs\*

Key	Drug (U.S.P.)	Synonyms	Tablet Size (Mg.)	Length of Treatment in Days	Total Number of Tablets	How Administered
a	Amodiaquine	Camoquin	200	1	3	Single or divided doses
b	Chloroquine	Aralen	250	3	10	† at time of diagnosis; 2 six hours later; 2 daily for 2 days
		Resorchin	250	3	10	
		Nivaquine	200	3	10	
c	Quinacrine	Atabrine	100	7	24	2 two hours apart on diagnosis;
		Mepacrine	100	7	24	3 daily for 6 days
		Metoquine	100	7	24	
d	Chlorguanide	Paludrine	100	7	21	3 daily for 7 days, plus a, b or c
		Proguanil	100	7	21	for 2 days
		Guanatol	100	7	21	
e	Primaquine	Similar to	15	14	14	1 daily after a or b for vivax
		Pamaquin				
		Plasmochin				
		Pentaquin		1	3	Single dose after a or b for falciparum gametocytes

\* The doses are for nonimmune adults weighing approximately 70 kg. Members of races of less stature and especially those who have been exposed to malaria from birth are adequately treated with two thirds of the doses listed. Outpatients may safely be given the daily dose of the drug as a single administration. Children 12 years of age are treated as adults. For those under 12 years the doses may be modified as follows:

0 to 1 year	$-\frac{1}{4}$ adult dose	Doses to be adjusted to the nearest $\frac{1}{4}$ -tablet.
1 to 3 years	$-\frac{1}{3}$ adult dose	
3 to 6 years	$-\frac{1}{2}$ adult dose	
6 to 12 years	$-\frac{3}{4}$ adult dose	

cation is not recommended for children, since in case of failure the parasites may not be detectable microscopically and a prompt diagnosis is impossible.

In endemic areas infants and preschool children should be protected by screens or nets during the hours of mosquito activity. When ill, irrespective of symptoms, every child from a suspect area should have his blood examined on three successive days.

When medical facilities are lacking, it may be desirable to give a drug for suppressive or prophylactic purposes. Such therapy should never be undertaken casually, and rigid adherence to periodic administration is absolutely essential. It should be continued for six to eight weeks after exposure has ended. In localities of great risk larger doses and more frequent administrations may be indicated. After discontinuance of the drug any mild disorder appearing within the next three months should be suspected as being malaria hitherto masked by the suppressive therapy.

The usual suppressive doses for adults are as follows: amodiaquine, 2 tablets every two weeks; chloroquine, 2 tablets weekly; quinacrine, 1 tablet daily; chlorguanide, 1 tablet (100 mg.) daily, or 1 tablet (250 mg.) weekly or twice weekly.

A. J. WALKER

## KALA-AZAR IN CHILDREN

Three different clinical entities, kala-azar (visceral leishmaniasis), oriental sore (cutaneous leishmaniasis) and espundia (nasal leishmaniasis), are associated with what morphologically appears to be the same organism. Leishmania, a protozoal parasite, which in the human body is a small ovoid or roundish organism measuring 2 to 4 microns in diameter, multiplies in the reticuloendothelial cells of the host. In the sand fly vectors and in cultures the Leishmania assume an elongated, motile, flagellated form.

There is some evidence that the Leishmania responsible for the three above-mentioned clinical conditions are not identical, because dogs which have recovered from oriental sore acquire immunity to the sore, but are not immune to kala-azar. This assumption is further supported by the distinctly different geographic distribution of the three diseases.

**Epidemiology.** Kala-azar is endemic in some parts of the eastern region of India (Assam, Bengal and Madras) and in areas of Africa and China. It has also been reported from some areas of South America (Paraguay, Argentina and Brazil). In certain of the Mediterranean countries and islands kala-azar occurs mainly in infants and is



termed "infantile kala-azar." The causative protozoan, however, is the same *Leishmania donovani* responsible for the Indian, African and American cases. There is no satisfactory explanation for this predilection for infants in the Mediterranean area.

The incidence of kala-azar is declining in the endemic areas. The disease is transmitted by the sand fly, which breeds in cracks and rubble, flies low and only for short distances. Multiple infections in the same household are common. Sand fly control is not difficult to achieve with residual insecticides and other measures; early diagnosis and specific treatment of the human host have also contributed to the decline in incidence. Dogs have been incriminated as animal reservoirs in the Mediterranean area, but they do not seem to be important reservoirs for human infection in other parts of the world.

**Clinical Manifestations.** Fever occurs for prolonged periods, sometimes with afebrile intervals. In the chronic form common in adults and older children, low grade remittent or intermittent fever, rarely over 102° F., is more or less persistent, often with two remissions in the twenty-four hour period. The spleen is usually enlarged within a fortnight after the onset, whereas the liver does not become appreciably larger for some months. Some lymphadenitis, especially cervical, is often present, but is less common in the Indian cases. In the well established disease, splenomegaly, emaciation and anemia produce a typical appearance. In many long-standing cases the skin acquires a strange, earthy gray pigmentation, especially on the feet, hands and abdomen. Hence the name, kala-azar, which, translated from the Indian dialect, means "black sickness." The hair is likely to become sparse and brittle. A peculiar feature in adults and older children is that in spite of the systemic infection the appetite remains good, the tongue is clean, and the patient is often unaware that he has fever. Leukopenia with a relative increase of monocytes and lymphocytes is characteristic. Anemia is often present, but is rarely severe. Purpura, gingivitis and stomatitis are common. Leukopenia, with a relative lymphocytosis, thrombocytopenia and anemia are common and are probably due to displacement of the hemopoietic elements of the bone marrow by parasitized reticuloendothelial cells. Cancrum oris may occur in neglected cases, though most cases of it in children in India are unassociated with kala-azar. Progressive alteration of the plasma proteins

occurs early; the globulin is increased considerably, and the albumin is decreased.

In children the onset is often abrupt with typhoid-like fever and toxemia. Hence they are more apt to receive medical attention early. If untreated, they are more liable than adults to intercurrent infections, such as bronchopneumonia or dysentery, which may prove fatal. For these reasons young children do not reach the stage of gross splenomegaly as often as adults do. Kala-azar in older children in the Mediterranean area runs a subacute course unless terminated by bronchopneumonia or cancrum oris.

The onset in *infantile kala-azar* is acute with high fever and vomiting. Agranulocytosis, which is common, is responsible for the tendency to secondary infections and cancrum oris. Untreated infantile kala-azar is invariably fatal; sudden death may be due to hyperpyrexia, intense dyspnea or hemorrhage. Light-skinned children show pallor rapidly with slight generalized edema resembling that of subacute nephritis. The lymph nodes are usually enlarged.

**Diagnosis.** The diagnosis is established by finding the protozoan (1) in a smear of the peripheral blood, which is rather unusual, (2) in a blood culture on N.N.N medium, (3) in smears or cultures from aspirated bone marrow, and (4) in aspirated material from the liver or spleen. Splenic puncture gives the highest percentage of positive results, but must not be lightly undertaken on account of the risk of fatal hemorrhage, especially when there is anemia and a bleeding tendency. The "formol-gel" test, performed by adding 1 drop of 30 per cent formalin to 1.0 ml. of clear serum of the patient and observing for jellification with opacity, is useful in chronic and subacute cases, but is often negative in the early stages of the acute forms in children. Other presumptive evidence includes leukopenia with decrease of the granular elements, the characteristic fever with double daily remissions when present, and splenomegaly. The early stage may be confused with malaria and typhoid fever, and prolonged or recurring fever may resemble tuberculosis, brucellosis and amebic abscess of the liver. The chronic stage may be confused with Banti's syndrome or with Indian childhood cirrhosis.

**Treatment.** The susceptibility of kala-azar to specific drug therapy appears to vary considerably in different parts of the world. The disease in India is most easily cured by pentavalent antimonials; only an occasional

antimony-resistant case is encountered which requires one of the aromatic diamidine drugs such as pentamidine or stilbamidine, drugs which may be toxic. Visceral leishmaniasis of the Sudan is highly resistant to therapy. The Chinese and Mediterranean forms are

intermediate in their response to therapy. Besides specific treatment, it is important to combat the malnutrition present in these children. Strict oral hygiene is essential to prevent stomatitis and cancrum oris.

S. T. ACHAR

## INTESTINAL PROTOZOA

Unlike most of the worm infections, the severity of disease produced by protozoa is not necessarily proportional to the size of the inoculum. Though protozoa are capable of developing colonies of limitless size, the ultimate population is limited by the area of suitable habitat, immunity and perhaps by other extrinsic factors. Once the colony is established, its reproductive potential is in part used for production of transfer-stages which infect other hosts.

The life cycle of an intestinal protozoan colony typically begins with a single cell, a *trophozoite* (vegetative stage), with one or more nuclei and with specialized structures for locomotion. The trophozoite grows and reproduces by binary fission (*Isospora* excepted). The vegetative functions of some of the trophozoites are interrupted; an enveloping membrane is secreted by the organism and, thus immobilized, is eliminated in the feces. In this stage it is referred to as a *cyst* and is not to be confused with the eggs of higher animals or spores of other organisms. The protozoan cyst is fairly resistant to external conditions, but it rarely reaches a new host in a viable state except in relatively cool, moist media. When the cyst is ingested and reaches its normal habitat in the intestine, the membrane ruptures, and the organism resumes its vegetative functions. By a succession of generations a new colony is formed and the cycle is repeated.

The cyst is passive in its transfer from host to host; thus cysts from the feces of man may be ingested by other animals, and cysts eliminated from other animals may be ingested by man. It was thought that the cysts or the escaping trophozoites were either destroyed in the "abnormal" host or passed through the intestine unchanged and that each host had its individual species. It is now recognized that some intestinal protozoa inhabit a variety of hosts.

Of the ten species of protozoa commonly found in the human intestine, five are ame-

bae (*Entamoeba histolytica*, *Entamoeba coli*, *Endolimax nana*, *Iodamoeba bütschlii*, *Dientamoeba fragilis*), three are flagellates (*Giardia lamblia*, *Chilomastix mesnili*, *Trichomonas hominis*), one is a ciliate (*Balantidium coli*) and one a sporozoon (*Isospora* species). Only two, *Entamoeba histolytica* and *Balantidium coli*, produce serious disease in man, although *Dientamoeba fragilis* and *Giardia lamblia* are frequently classified as pathogens. *Isospora* infection rarely occurs in man. It usually produces only mild symptoms and tends to be self-terminating.

### AMEBIASIS

**Etiology.** Amebiasis is usually regarded as synonymous with *Entamoeba histolytica* infection. *Dientamoeba fragilis* and *Iodamoeba bütschlii* have infrequently been considered pathogens, but neither produces a distinct disease. If either is suspected of producing symptoms, the disease may be treated as infection with *E. histolytica*.

*Entamoeba histolytica* inhabits the colon. It is frequently found in symptomless carriers and is thought by some to be a harmless commensal in the majority of instances. It is potentially a pathogen, however, capable of deep invasion of the bowel wall and of being transported to other organs, especially the liver, where it causes serious damage.

**Epidemiology.** Amebiasis is found in all parts of the world, especially in the tropics, but, like other filth-borne diseases, its distribution and prevalence correlate more closely with standards of personal hygiene and sanitation than with climate. Infection rates may approach 100 per cent in densely populated unsanitary areas and may be extremely low in well sanitated groups. Faust (1953) estimated that the incidence of amebiasis in the general population of the United States may be about 10 per cent; 5 per cent is regarded as a safe estimate. In the United States amebiasis is probably most prev-



alent in the South Central States. In the Charity Hospital at New Orleans routine examinations during the years 1945–56 recorded *E. histolytica* in 3 to 4 per cent of stools from children one to eleven years of age and in 3 to 5 per cent from adults. Possibly because amebiasis is more difficult to diagnose in children than in adults, surveys usually show a higher incidence in the latter. Infrequently the disease appears in epidemic form as in Chicago in 1933, when there were 1400 cases and 100 deaths. The mortality rate in the United States is about 0.1 per 100,000 population.

Infective cysts passed in stools vary from too few to be detected by ordinary means to many millions per day. Stools from ten consecutive patients averaged 241 cysts per milligram of feces. A housefly or cockroach may ingest much more than a milligram of feces, the amebic cysts passing through its intestine unharmed.

Cysts are killed immediately by desiccation and by temperatures above 55° C., but may survive for months in water at temperatures below 20° C. In feces at room temperature they die rapidly after one or two days. They are killed by all commonly used disinfectants, but not by ordinary chlorination of water. Five parts per million of chlorine residual for thirty minutes, however, renders water safe. It has not been shown that contaminated soil is important in the spread of amebiasis through the medium of uncooked vegetables. However, since cysts may survive in moist soil, amebiasis may be contracted by children from dooryard soil. There are no important animal reservoirs of amebic infection, although monkeys, apes and dogs may harbor natural infections, and other animals are readily infected in the laboratory. Amebic infection in dogs is relatively common, presumably owing to their tendency to eat human feces, but they rarely pass cysts in their stools and therefore are not an important source of human infection.

Infection is passed from person to person by means of relatively nonresistant but extremely abundant cysts in feces which, in diverse but mostly unproved ways, contaminate food and water.

**Pathology.** Some strains of *E. histolytica* are more pathogenic than others, and some which fail to produce symptoms in one person may readily produce disease in another. Infection may exist without evidence of disease, other than an abundance of cysts in the stools, and later develop into frank dysen-

tery. Conversely, dysentery may be followed by a carrier state without evidence of disease.

Although massive colonization over its unbroken surface may deleteriously affect the mucosa, the only known means by which amebae produce disease is by tissue destruction in the colon or in other organs secondarily colonized by way of the blood stream. The colon is most frequently invaded at the cecal and sigmoidorectal levels, but the ascending colon, the hepatic and splenic flexures and the appendix are also frequently affected. Involvement varies greatly in area and in depth, the extreme being the full length of the organ and all layers even to, or through, the serosa. Generally, the muscular layers are resistant to invasion. Thus the typical lesion, which tends to be microscopic, develops vertically and secondarily extends laterally, simulating the shape of a flask as the more resistant layers are encountered. Bacteria may be absent from newer lesions, and inflammatory cells may be scant or absent. Older lesions, however, complicated by secondary bacterial invasion, show various degrees of inflammation and suppuration. Microscopically, there is nothing diagnostic in the lesion of the colon except the presence of *E. histolytica* trophozoites.

The hepatic lesion is more characteristic. Trophozoites diffusely distributed through the liver parenchyma produce multiple microscopic areas of necrosis which may coalesce to form a macroscopic lesion, the amebic liver abscess. It usually contains a characteristic pasty brownish material. Occasionally this material is mixed with purulent exudate, and the demonstration of amebae, essential for positive diagnosis, is more difficult.

**Clinical Manifestations.** The 'signs and symptoms of intestinal amebiasis are largely those of nonspecific regional ulcerative colitis. Varying from mild irritation to extensive destruction of the bowel wall, from involvement of one or more local areas to that of the entire organ and from transient minor clinical disturbances to severe chronic disease, the manifestations of amebic infection are so diverse that intestinal amebiasis can never be ruled in or out without the aid of a microscope. Any abnormal bowel activity, unusual stools, abdominal complaints or physical findings suggestive of colonic disease should be an indication for microscopic examination of stools for amebae.

In severe amebic diarrhea, in contrast to bacillary dysentery in that in the former the

onset is less likely to be sudden, fever and leukocytosis are slight or lacking, and the stools lack the odor and appearance of containing pus; i.e., the mucus is clear instead of being whitish or yellowish, and the odor is reminiscent of autolytic rather than suppurative processes. In this latter respect, the diarrheas caused by *E. histolytica* and by whipworm (*Trichocephalus trichiurus*) infections are identical.

Amebic abscess of the liver is uncommon in children. The manifestations are the same as in adults, except possibly more pronounced. Chills, fever, leukocytosis and right upper quadrant tenderness or pain, especially if accompanied by physical signs or roentgenographic evidence of a bulging mass, suggest the possibility of a liver abscess. The demonstration of colonic amebiasis would be supportive evidence, but other causes should be considered. In regions where *Ascaris lumbricoides* is endemic, abscess formation around adult worms in the liver, or enlargement and tenderness of the liver resulting from migrating larvae, is much more frequent in children than hepatic amebiasis.

**Diagnosis.** The diagnosis of parasitic infections by stool examination presents two distinct problems: the detection of some stage of the organism and its identification. The following suggestions may be helpful.

Since all stages of amebae in all types of feces or other material retain their normal appearance longer at room temperature than at body temperature and even longer under refrigeration (but not frozen), stools should be refrigerated promptly if examination is to be delayed more than one hour. Even trophozoites may occasionally remain identifiable for several days.

Abnormal elements in stools, such as mineral oil, fats, bismuth, kaolin, barium, certain foods such as bananas and milk and excessive amounts of undigestible pulpy fruits and vegetables, diminish the chances of finding amebae in the stools.

The advantage in the specimen obtained by purgation, saline enema or proctoscopy is its delivery fresh and on convenient schedule. If watery, it may contain more amebae, but they perish more quickly than in the usual stool. Of twenty-six infections studied by Hood, three were detected by proctoscopic examination, five by stool examination and the remainder by both methods.

Reliability of negative findings is increased proportionally with the number of

stools examined, provided the stools vary in kind as well as in time. Time should not be taken to examine unsatisfactory specimens. It is important that laboratory reports include a description or an evaluation of the material examined.

A large specimen permits selection of favorable samples, but overemphasis of this factor may delay diagnosis, especially of waning dysentery. An ideal microscopic preparation contains only 1 to 2 mg. of feces, and most concentration methods require less than 1 gm. A fleck of feces obtained from the rectum on the gloved finger or from a saline enema may be sufficient.

If reliable diagnostic service is not locally available, fecal specimens and material aspirated from the colon or from liver abscesses may be satisfactorily preserved and mailed to distant laboratories by using one of the procedures described below. The material *must* be freshly collected, diluted with 5 parts or more of the fixative-preservative and must be well comminuted.

**Methods for preservation of stools.** (1) Ritchie (1948) found that 1 part of full-strength commercial formaldehyde solution diluted with 9 parts of water is a good general fixative-preservative. One cubic centimeter of feces in 10 cc. of fixative is an adequate specimen. On reaching the laboratory the material is strained, mixed with ether and concentrated by centrifugal sedimentation. This is not as satisfactory as other techniques for dysenteric stools and aspirates, but it is probably the choice for mushy or formed stools.

2. Brooke and Goldman (1949) described a fixative-preservative prepared by adding 5 gm. of powdered polyvinyl alcohol ("Elvanol" 90-25, E. I. du Pont de Nemours) to 1.5 cc. of glycerin, 5 cc. of glacial acetic acid and 93.5 cc. of Schaudinn's solution (2 parts of saturated aqueous solution of mercuric chloride to 1 part of 95 per cent ethyl alcohol), heated to about 75° C. and stirred until clear. One cubic centimeter of feces in 5 cc. of fixative is an adequate specimen. On its reaching the laboratory, slides are prepared and stained with iron-hematoxylin.

3. Saper, Lawless and Strome (1951) use a fixative-preservative consisting of two solutions, stored separately and mixed immediately before use. Solution I is 40 parts of tincture of Merthiolate (Lilly), 5 parts of formaldehyde (U.S.P.) and 1 part of glycerin. Solution II is freshly prepared Lugol's solution (5 per cent iodine in 10 per cent aqueous potassium iodide solution). For use, combine 15 parts of solution I with 1 part of solution II. One cubic centimeter of feces in 8 to 10 cc. of preservative is an adequate specimen. Wet smears of the mixed specimen or the sediment are examined microscopically without further staining.

Cultures of fecal or aspirated material are generally not practical. Although mul-



tiplication of amebae is often obtained in cultures, experienced workers have little confidence in negative findings.

Complement fixation is not a dependable test.

**Prognosis.** Once a diagnosis of colonic amebiasis has been made, early eradication of the parasite is a definite probability. In the absence of reinfection, chronic refractory infections requiring long, varied and multiple treatments are exceptional. With proper corrective and supportive measures even severe dysentery usually can be controlled within a few days and cured within two or three weeks. Except for amebic abscess of the brain, which is rare even in adults, the prognosis is also good in early diagnosed extraintestinal infections.

**Prevention.** Contaminated water and food are probably the only important sources of amebic infection in adults. In children the transfer of infection occasionally may be more direct, and contaminated dooryard soil is a possible though unproved source of infection. Water and certain foods may be made safe by boiling or scalding. When boiling of water is impractical, hyperchlorination or halogenation with iodine by means of commercially available preparations is possible. Thoroughly dried foods may be regarded as safe. Rooty vegetables and fruits can be washed and peeled, and leafy vegetables can be safely eaten after thorough washing and immersion in full strength vinegar (5 per cent acetic acid) for fifteen to twenty minutes at room temperatures. The prophylactic use of glycobarsol or Diodoquin in doses of one sixth to one third of the therapeutic ones has been recommended. Sterilization of dooryard soil is not feasible.

**Treatment.** For children with acute dysentery or severe diarrhea due to *E. histolytica*, Milibis (glycobarsol) is a relatively safe, inexpensive and effective drug. Tetracycline or emetine may be given for speedier control of symptoms, but, because of cost, toxicity, and cure rates, they usually are not used as curative drugs. Milibis is administered orally in 250- or 500-mg. tablets three times daily with meals for eight days, the single dose being 500 mg. for adults and for children over six years of age and 250 mg. for younger children. Though generally nontoxic, treatment should be interrupted if such untoward symptoms as dizziness, severe headache, abdominal cramps or neuritis are noted. Tetracycline may be given alone or simul-

taneously with Milibis. The dosage for children is 5 to 10 mg. per pound of body weight three times daily for two to four days, or until acute symptoms subside. Emetine similarly administered may be more effective and is less expensive than the tetracyclines (see below for dosage). Although somewhat less effective than Milibis, some of the older drugs such as Diodoquin, chiniofon (Anayodin, Yatren) and carbarsone are often satisfactory.

Three or four stool examinations should be made at weekly intervals after discontinuance of treatment. If symptoms persist despite negative findings on satisfactory fecal specimens, efforts should be made to discover causes other than amebic infection. Because amebae may appear in the stools within a few days after reinfection, positive findings on treated outpatients should not be interpreted as necessarily indicating failure of treatment.

Hepatic amebiasis, apparent or presumed to be highly probable, in the presence of demonstrated colonic infection, usually is treated with chloroquine phosphate. The drug is administered orally in 250-mg. tablets and may be given simultaneously with the treatment for colonic infection. The dose for children under six years of age is 250 mg. twice daily for two days followed by 125 mg. twice daily for twelve additional days; for older children and adults the dose is doubled. When chloroquine fails in the treatment of amebic liver abscess, emetine is used. It is obtainable in 1-cc. ampules containing 65 mg. of emetine hydrochloride and is injected subcutaneously in doses of 0.5 mg. per pound of body weight per day for not more than ten days, and never in excess of 6.5 mg. per day. Emetine may produce neuritis or irreversible myocarditis, so that its use should not be repeated in less than one month.

## GIARDIASIS

*Giardia lamblia* is most frequently found in the tropics and subtropics, its distribution seeming to vary with economic, hygienic and sanitary conditions. Faust and Headlee observed a high incidence in white children in New Orleans, 8.6 per cent at one year of age, 19.3 per cent in the seventh year and 13.8 per cent in the tenth year. Though the parasite may be transmitted by food and water and by houseflies, it is most commonly carried directly from person to person.

The flagellate usually lives in the duodenum and upper jejunum, where it may persist for years, or disappear spontaneously, especially in older children and adults. Trophozoites die within a few hours outside the body, but cysts may remain viable for as long as sixty days.

The pathogenicity of *Giardia lamblia* has not been satisfactorily demonstrated. It has frequently been demonstrated in stools of children with a variety of complaints referable to the abdomen in general and to the intestinal tract in particular. Proof of its connection with the clinical disturbances, however, is still lacking. Observations in this country do not support the contention that the organism is responsible for significant disturbances. The experience of Véghelyi in Hungary has been the most convincing in support of the pathogenicity of *Giardia*. He reported a high incidence of abdominal and intestinal symptoms among children infected with *Giardia*. The clinical disturbances were mainly abdominal pain and diarrhea, but a significant number also had manifestations of the celiac syndrome. The disappearance of the symptoms after eradication of the parasite by treatment with acetarsone he regarded as proof that *Giardia* was the etiologic agent.

Fortunately the infection is easily eradicated by drugs that are neither expensive nor very toxic. Quinacrine dihydrochloride (Atabrine) administered orally in 0.1-gm. tablets for five days in the following dosage rarely if ever fails to result in complete removal of *Giardia*: for adults and children over eight years of age, 1 tablet three times daily; for children four to eight years,  $\frac{1}{2}$  tablet on the same schedule; and for younger children,  $\frac{1}{2}$  tablet twice daily.

## BALANTIDIASIS

*Balantidium coli* is a parasite which, like *E. histolytica*, colonizes the colon. More often than in man it is found in monkeys and pigs, both of which tolerate the infection without apparent damage. Although *Balantidium coli* is the only ciliate protozoon known to parasitize the human colon, numerous morphologically similar organisms are frequent in stools as contaminants and may lead to errors in diagnosis. Diagnosis is established by the presence of either the more or less uniformly ciliated, large, rapidly motile trophozoites or the large spherical cysts.

Balantidiasis is rare in the United States,

but is relatively common in Puerto Rico, Mexico and various parts of South America. Most of the human infections apparently are derived from pigs. Under crowded or unsanitary conditions, especially in institutions, person-to-person transfer of infective cysts commonly occurs. As a rule, however, cysts are formed only sparingly or not at all in the human intestine.

Typically, the infection is of short duration, producing in children a disease similar to amebic dysentery. The pathologic changes are likewise similar, both in distribution and character. The chief difference is the greater tendency of balantidiasis toward spontaneous cure. This factor has led to variable interpretations of the curative value of tested drugs. Carbarsone, regarded as the drug of choice, frequently fails to effect cures. Satisfactory results appear to be obtained with tetracycline given orally in doses of 8 to 10 mg. per pound of body weight three times daily for ten days, the total dose not to exceed 2 gm.

PAUL C. BEAVER

## REFERENCES

### General

- Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases. An Atlas. Philadelphia, W. B. Saunders Company, 1945.
- Craig, C. F.: Laboratory Diagnosis of Protozoan Diseases. 2d ed. Philadelphia, Lea & Febiger, 1948.
- Faust, E. C., and Russell, P. F.: Craig and Faust's Clinical Parasitology. 6th ed. Philadelphia, Lea & Febiger, 1957.
- Otto, G. F.: Diseases and Infections Due to Intestinal Protozoa; in Maxcy: Rosenau's Preventive Medicine and Hygiene. 7th ed. New York, Appleton-Century-Crofts, Inc., 1951, p. 227.

### Amebiasis

- Anderson, H., Bostick, W., and Johnstone, H.: Amebiasis. Pathology, Diagnosis and Chemotherapy. Springfield, Ill., Charles C Thomas, 1953.
- Beaver, P., and Deschamps, G.: The Viability of *E. histolytica* Cysts in Soil. Am. J. Trop. Med., 29:189, 1949.
- : The Effect of Acetic Acid on the Viability of *Endamoeba histolytica* Cysts. Am. J. Trop. Med., 29:193, 1949.
- Beaver, P., Jung, R., Sherman, H., Read, T., and Robinson, T.: Experimental Chemoprophylaxis of Amebiasis. Am. J. Trop. Med. & Hyg., 5:1015, 1956.
- Brooke, M., and Goldman, M.: Polyvinyl Alcohol-Fixative as a Preservative and Adhesive for Protozoa in Dysenteric Stools and Other Liquid Materials. J. Lab. & Clin. Med., 34:1554, 1949.
- Bundensen, H.: The Chicago Epidemic of Amebic Dysentery. Pub. Health Rep., 49:1266, 1934.
- Craig, C. F.: The Etiology, Diagnosis, and Treat-



- ment of Amebiasis, Baltimore, Williams & Wilkins Company, 1944.
- Faust, E. C.: Amebiasis. Springfield, Ill., Charles C Thomas, 1953.
- Hoare, C. A.: The Commensal Phase of *Entamoeba Histolytica*. *Exper. Parasitol.*, 1:411, 1952.
- Hood, M., Sodeman, W., and Akenhead, W.: Comparison of the Effectiveness of the Examination of Multiple Stools and Proctoscopic Material for the Detection of Amebiasis. *Am. J. Trop. Med. & Hyg.*, 1:539, 1952.
- Jones, M.: Studies on Treatment of Fresh Vegetables Contaminated with Cysts of *Entamoeba Histolytica*. I. Acetic Acid. *Am. J. Trop. Med. & Hyg.*, 1:576, 1952.
- Jung, R., and Beaver, P.: Clinical Observations on *Trichocephalus Trichiurus* (Whipworm) Infestation in Children. *Pediatrics*, 8:548, 1951.
- Miller, M.: The Experimental Infection of *Macaca Mulatta* with Human Strains of *Entamoeba Histolytica*. *Am. J. Trop. Med. & Hyg.*, 1:417, 1952.
- Ritchie, L.: An Ether Sedimentation Technique for Routine Stool Examinations. *Bull. U. S. Army Med. Dept.*, 8:326, 1948.
- Sapero, J. J., Lawless, D. K., and Strome, C. P. A.: An Improved Iodine-Staining Technique for Routine Laboratory Diagnosis of Intestinal Protozoa. *Science*, 114:550, 1951.
- Wright, W.: The Public Health Status of Amebiasis in the United States, as Revealed by Available Statistics. *Am. J. Trop. Med.*, 30:123, 1950.

#### Giardiasis

- Berberian, D.: Treatment of Lamblasis with Acrinin. *Am. J. Trop. Med.*, 25:441, 1945.
- Hartman, H., and Kyser, F.: Giardiasis and Its Treatment: A Clinical Study. *J.A.M.A.*, 116:2835, 1941.
- Véghelyi, P.: Giardiasis in Children. *Am. J. Dis. Child.*, 56:1231, 1938.
- : Giardiasis. *Am. J. Dis. Child.*, 59:793, 1940.

#### Balantidiasis

- Negme, A., Miranda, M., Agosin, M., and Sanz, R.: Contribucion a la Quimoterapia del *Balantidium coli*. II. Estudio clinico. *Bol. Inform. Parasitol. Chilenas*, 6:7, 1951.
- Shookhoff, H.: *Balantidium Coli* Infection, with Special Reference to Treatment. *Am. J. Trop. Med.*, 31:442, 1951.
- Swartzwelder, J. C.: Balantidiasis. *Am. J. Digest. Dis.*, 17:173, 1950.
- Tsuchiya, H., and Kenamore, B.: Report on a Case of Balantidiasis. *Am. J. Trop. Med.*, 25:513, 1945.
- Weinstein, P., Garfenkel, B., and Miller, M.: Treatment of a Case of Balantidial Dysentery with Terramycin. *Am. J. Trop. Med. & Hyg.*, 1:980, 1952.

### TOXOPLASMOSIS

The parasite *Toxoplasma gondii* was first described by Nicolle and Manceau and by Splendore in North Africa and in Brazil, re-

spectively, in 1908. In 1939 Wolf, Cowen and Paige isolated the organism from infants who had died of congenital encephalomyelitis, demonstrating for the first time that *Toxoplasma* could produce human illness. It soon became apparent that the disease could be acquired in utero, termed the congenital form, or at any time postnatally, the acquired form. Acquired toxoplasmosis was encountered either as an acute encephalitis or as a rickettsial-like illness with pneumonitis and a maculopapular rash. Sabin devised a rabbit neutralization test with which specific serologic studies could be performed, and also pointed out that congenital toxoplasmosis frequently produced chorioretinitis, cerebral calcification, psychomotor retardation, hydrocephaly or microcephaly and convulsions. With the development of the dye, complement fixation and skin tests in 1948, practical specific methods became available for intensive study of the disease. Among the unanswered questions are those concerned with the sources and the pathogenesis of human infections.

**Etiology.** *Toxoplasma gondii* is considered to be a protozoon, but its precise classification remains in some doubt. It is a delicate, oval or crescent-like organism measuring 2 to 4 by 4 to 7 microns. It divides by binary fission and is best stained with either Giemsa or Wright stain. *Toxoplasma* is unique in that it may invade any tissue (with the possible exception of the erythrocyte) of mammals and birds; multiplication has been noted only in the presence of living cells. *Toxoplasma* does not withstand freezing, except under special conditions, and sediments readily during ordinary centrifugation. There is only one *Toxoplasma* species, and all strains isolated to date have been serologically homogeneous.

**Epidemiology.** The prevalence of *Toxoplasma* antibodies among normal populations varies considerably in different parts of the world. Significant titers of dye test antibodies may be present in 50 per cent or more of the inhabitants of some localities, so that the interpretation of serologic findings in older children and adults in such areas is almost impossible unless real changes in titer are demonstrated in serial samples. Among various animal species surveyed by the author approximately 30 per cent of swine and cats had significant amounts of antibody, and half or more of goats and dogs were positive. This relatively high rate of specific antibody titers among animals makes it difficult to

determine the relationship of a particular animal to a specific human infection.

Any of the clinical manifestations of congenital toxoplasmosis may be produced by other diseases. Hence any single finding or combination of findings is not sufficient in itself to establish the diagnosis. For example, in our experience, of children suffering from chorioretinitis, only 41 per cent of those under one year of age, 49 per cent of those between one and four years, and 62 per cent of those between five and nine years were found to have satisfactory serologic criteria for congenital toxoplasmosis. Thus, in at least half or more of childhood cases of chorioretinitis, congenital toxoplasmosis could not be incriminated. These data, however, may not be applicable in all sectors. A similar tabulation was made among children with cerebral calcifications; approximately half of the children nine years of age or younger were found not to have congenital toxoplasmosis.

**Pathology.** In the congenital form histologic changes are most frequent in the central nervous system, but may be found in almost all tissues, as is the case in the acquired type. The retina and choroid are usually involved in the congenital form, and such lesions have recently been noted in a few cases of acquired toxoplasmosis. Gross or microscopic areas of necrosis may be found in many tissues, especially in the heart, lungs, skeletal muscle, liver and spleen. *Toxoplasma* may be seen as pseudocysts (particularly within muscle) or as individual organisms, often with surprisingly little tissue reaction. Single or multiple areas of calcification, both large and small, may be present in necrotic areas of brain in the congenital form, but have not been found in acquired cases. The lesions of toxoplasmosis are not sufficiently characteristic to permit a specific diagnosis in the absence of other information or of demonstration of parasites. Recently, parasites have been identified in sections of lymph nodes; their presence in nodes has also been confirmed by animal inoculation.

**Clinical Manifestations.** Human toxoplasmosis may occur as a congenital or acquired disease. Although there is no evidence that the congenital disease is ever inapparent, most acquired infections occur in a clinically non-recognizable form, and presumably account for the fetal infections.

**Congenital toxoplasmosis.** The fetus infected with *Toxoplasma* may be stillborn or born prematurely or at term. Illness which

is apparent at birth or does not become evident for several days may manifest itself with malaise, fever, maculopapular rash, icterus, lymphadenopathy, hepatomegaly, splenomegaly, hydrocephaly, microcephaly, microphthalmia and convulsions. The cerebrospinal fluid may be xanthochromic and contain an increased number of cells (sometimes eosinophils) and protein. Cerebral calcifications and chorioretinitis may be present at birth or develop in ensuing weeks. Congenital toxoplasmosis may be diagnosed in this stage by demonstration of parasites in smears from the sediment of cerebrospinal or ventricular fluid. There is a high dye test titer in both mother and infant, but though the maternal complement fixation test is positive, the infant's may or may not be. Active congenital toxoplasmosis may terminate fatally in days or weeks, or the illness may regress, leaving varying degrees of disability such as hydrocephaly or microcephaly, chorioretinitis, psychomotor retardation, ocular palsies or convulsions. The full impact of the infection may not become evident until some weeks or months after apparent recovery. Live parasites were isolated from the brain of a child with a congenital infection who died in his fourth year.

In a large group of cases of congenital toxoplasmosis collected by the author, 31 per cent of the infants were born prematurely, of whom 27 per cent died. Of those born at term, 12 per cent died. In this series chorioretinitis was noted in 99 per cent, cerebral calcification in 63 per cent, psychomotor retardation in 56 per cent and hydrocephaly or microcephaly in about half of the cases. Neither the cerebral calcification (single or multiple) nor the chorioretinitis was sufficiently characteristic to permit an etiologic diagnosis. Chorioretinitis was bilateral in 85 per cent of the cases and almost equally distributed between the left and right eyes in the remainder.

There is suggestive evidence that fetal infection occurs only after the placenta has been formed. All offspring in a multiple pregnancy are infected, although the degree of damage of each may vary.

Toxoplasmosis does not appear to be important as a cause of prematurity, cerebral palsy, blindness or "uncomplicated" mental retardation. The disease apparently occurs only once among the offspring of a given mother.

**Acquired toxoplasmosis.** Acquired toxoplasmosis most frequently is unrecognized



clinically. Parasitemia probably occurs in such infections and presumably is the mechanism by which the fetus becomes infected in the pregnant woman. With the exception of occasional instances of lymphadenopathy, no indication of maternal infection has been noted.

Symptomatic acquired toxoplasmosis may occur at any age and with almost any combination of the following manifestations: malaise, fever, myalgia, maculopapular rash, generalized lymphadenopathy, splenomegaly, encephalitis, pneumonia and myocarditis. The illness may be symptomatic for a few days or for some weeks. The incubation period, source of infection and mortality rate are unknown, but most patients seem to recover spontaneously. If chorioretinitis occurs during the acute, acquired form, it must be rare.

**Laboratory Diagnosis.** The best evidence of infection is the demonstration of parasites in wright- or giemsa-stained impression smears of tissues or in films made from the sediments of centrifuged cerebrospinal or ventricular fluids. Final identification depends upon isolation of the parasites in animals; the laboratory-reared mouse is ideal. The inoculation should be made with suspensions of fresh tissue or body fluids.

The dye test, a sensitive, reliable indicator of *Toxoplasma* antibody in human or animal serums, is performed by incubating mixtures of various dilutions of inactivated serum of the patient with living parasites (mouse peritoneal exudate) which have been suspended in fresh, antibody-negative human serum. The latter serves as a source of a heat-labile serum component (activator) which is necessary for the action of the specific antibody. After incubation at 37° C. for one hour, alkaline (pH 11.0) methylene blue is added to the test mixture, which is then examined under the microscope. If antibody is absent, the parasites are stained blue; if present, their cytoplasm will be unstained. The dilution of serum in which 50 per cent of the parasites are unstained represents the end point (titer) of the specimen. *Toxoplasma* antibody, as determined by the dye test, tends to appear early in the infections and to remain in high titer for some months or years; the titer then diminishes gradually, but some antibody persists for years, if not for life. Titers of 1:1000 to 1:16,000 are usual for at least some months in the serums of mothers and of infants or young children with congenital disease. If the infant's antibodies have been

acquired by passive transfer, there will be a sharp decline in titer by three months of age and almost total disappearance by six months.

The complement fixation test, which has been used less widely than the dye test, offers additional aid. It becomes positive more slowly, so that early in the disease there may be a strongly positive dye test with a negative complement fixation one. Conversely, the complement fixation reaction tends to decrease relatively quickly, so that within months or several years after the illness (or birth) there again may be a negative complement fixation reaction and a positive dye test. An infant born with active disease may have a negative complement fixation test but a positive dye test, despite the mother's serum having high titers by both procedures.

A skin test (antigens from either egg or mouse peritoneal fluid) is available, but of questionable aid in a specific situation, since positive reactors are prevalent in the general population. The time required for the development of skin sensitivity is unknown, but positive reactions have not been encountered in children under four years of age in any survey among the general population.

Two new methods for demonstrating antibodies for *Toxoplasma* have been reported recently. One of these is a hemagglutination test in which sheep erythrocytes treated with tannic acid serve as the vehicle for a soluble *Toxoplasma* antigen. The results seem to parallel those obtained with the dye test, but the usefulness of this test must await further experience.

The second test is somewhat more complex. The antibody content of a serum is measured by its ability to interfere with the fluorescent staining of killed *Toxoplasma* by a fluorescein-labelled antiserum. It has been proposed as a screening procedure before performing the dye test. Its advantages remain to be determined.

**Treatment.** Eyles has observed that the combination of pyrimethamine (Daraprim) and sulfadiazine is superior to either drug alone in the treatment of experimental mouse infections and has suggested a trial of this combination in human infections. A number of patients now have been treated in this way, and although the results are promising, the inability to predict the natural course of the disease makes critical analysis rather difficult. Nevertheless, this combination appears to be the best form of therapy currently available. Sulfadiazine should be administered in usual therapeutic doses with

the pyrimethamine in divided doses on the basis of 1 mg. per kilogram of body weight per day. Treatment should be continued for about two weeks, and leukocyte counts should be repeated frequently, since pyrimethamine, an antifolic agent, as well as the sulfonamide may produce severe leukopenia.

HARRY A. FELDMAN

#### REFERENCES

- Feldman, H. A.: The Clinical Manifestations and Laboratory Diagnosis of Toxoplasmosis. *Am. J. Trop. Med. & Hyg.*, 2:420, 1953.
- Feldman, H. A., and Miller, L. T.: Serological Study of Toxoplasmosis Prevalence. *Am. J. Hyg.*, 64:320, 1956.
- Feldman, H. A., and Sabin, A. B.: Skin Reactions to Toxoplasmic Antigens in People of Different Ages without Known History of Infection. *Pediatrics*, 4:798, 1949.
- Frenkel, J. K., and Friedlander, S.: Toxoplasmosis. Pathology of Neonatal Disease. Pathogenesis. Diagnosis and Treatment. Washington, D. C., U.S. Government Printing Office, Public Health Service Publication No. 141, 1951.
- Goldman, M.: Staining *Toxoplasma gondii* with Fluorescein-Labelled Antibody. II. A New Serologic Test for Antibodies to Toxoplasma Based upon Inhibition of Specific Staining. *J. Exper. Med.*, 105:557, 1957.
- Gronroos, P.: Studies on Toxoplasma and the Serology of Toxoplasmosis. *Ann. Med. Exp. et Biol. Fenniae*, 33, Sup. 11, 1955.
- Jacobs, L., and Lunde, M. N.: Hemagglutination Test for Toxoplasmosis. *Science*, 125:1035, 1957.
- Sabin, A. B.: Complement Fixation Test in Toxoplasmosis and Persistence of the Antibody in Human Beings. *Pediatrics*, 4:443, 1949.
- Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoan Parasite (*Toxoplasma*). *Science*, 108:660, 1948.
- Sabin, A. B., Eichenwald, H., Feldman, H. A., and Jacobs, L.: Present Status of Clinical Manifestations of Toxoplasmosis in Man. Indications and Provisions for Routine Serologic Diagnosis. *J.A.M.A.*, 150:1063, 1952.
- Various Authors: Some Protozoan Diseases of Man and Animals: Anaplasmosis, Babesiosis, and Toxoplasmosis. *Ann. New York Acad. Sc.*, 64:154, 1956.



# The Digestive System

## THE ORAL CAVITY

### EXAMINATION

The condition of the oral cavity has considerable influence on the nutritional status and psychologic development of the child. The physician should know what constitutes good oral hygiene and adequate management of oral disturbances. He should develop skill in examination of the oral cavity so that he can perform it with the least possible discomfort to the child. At best it is likely to be the most disturbing part of the physical examination and should be left until last. Examination of the anterior part of the mouth should occasion no discomfort and should be completed before the throat is examined. In the older child, gagging can be avoided if he breathes actively through his mouth during the examination of the throat. Infants, of course, must be held by an attendant, who, standing at the head of the infant, extends the arms beside the head and holds the arms and the head together by cuffing his (the attendant's) hands over the infant's elbows in such a way that his fingers are directed toward the occiput and the thumbs are at the temple area.

Good intraoral lighting is essential; the otoscope or a flashlight with a condensing or "spotlight" lens is satisfactory. The ordinary wooden tongue blade is too big and clumsy for the small mouth of the infant and young child; it may also produce trauma. The straight blade tends to push the base of the tongue back against the postpharyngeal wall, whereas a curved spoon handle or a mouth mirror placed on the base of the tongue enables the physician to pull the tongue down and forward.

### ORAL HYGIENE

**Natural Means.** Oral hygiene is largely a mechanical cleansing process, and can be achieved by natural mastication, provided the diet includes hard, coarse and fibrous foods

which must be chewed thoroughly before they can be swallowed. The action of the tongue, the labial musculature and the saliva aid the cleansing action of such foods.

At six to eight months of age the child can be given some hard food such as zwieback which will assist in the cutting of the teeth. Later, raw apples, oranges and other fruits become splendid tooth cleaners, but cakes and starchy and sticky foods are noncleansing, tend to adhere to the teeth and thus favor food stagnation and decomposition.

**Artificial Means.** Before the teeth are erupted, artificial cleansing of the healthy mouth is superfluous. Because the oral mucosa is thin and easily injured in the infant and young child, brushing of the teeth should not be started before the third year. Until that time the crowns of the teeth may be occasionally cleansed with a cotton-tipped applicator soaked in saline solution or a dilute sodium bicarbonate solution. During the third year the mother should start the brushing of the child's teeth and by the fifth year the child usually assumes the responsibility. Modern man needs to brush his teeth to remove collections of soft and sticky foods; brushing helps to control dental caries and periodontal disorders, but cannot entirely prevent them.

The child should be taken to the dentist at the age of three years and should return every six months. The first visits permit early recognition of decay that can be treated easily and painlessly and also minimize any tendency to fear the dentist.

**Oral Hygiene in the Sick Child.** Oral hygiene is especially important for the sick child. The nurse should free the mouth of its debris by cleansing the oral mucosa and the teeth at least twice daily with gauze placed around her index finger and soaked in a mild antiseptic. This should be followed by rinsing the mouth with iodosaline (1 per cent tincture of iodine in warm saline solu-

tion). No oral care is necessary for the sick infant beyond that of an adequate intake of water.

The convalescent child should be taught

the technique of brushing teeth. Iron or acid preparations in liquid form should be taken through a straw to avoid discoloration or dissolution.

## DISTURBANCES OF THE TEETH

**Life Cycle of the Tooth.** Each tooth undergoes four successive periods of development during its life cycle: growth, calcification, eruption and attrition. All the common developmental aberrations of the teeth may be classified according to the developmental stage affected (Table 81, p. 621). The earlier the tooth is affected, the more severe the result.

### DISTURBANCES IN GROWTH

#### INITIATION OR ABNORMALITIES IN NUMBER OF TEETH

**Deficient Number of Teeth.** *Anodontia* may be complete or partial and results from a lack of initiation or from an arrest in proliferation. Clinical absence of teeth, however, is not sufficient evidence to warrant a diagnosis of anodontia, and roentgenographic examination is essential before failure in eruption can be excluded.

The third molars, the upper lateral incisors and the lower second bicuspid are, from an evolutionary point of view, vestigial organs, and abnormalities or absence of them has no clinical significance. The congenital absence of other teeth, however, is likely to be associated with such congenital dysplasias as cleidocranial dysostoses, arachnodactyly and congenital ectodermal dysplasia.

**Supernumerary Teeth.** An excessive number of teeth usually results from continued budding of the enamel organs of the preceding teeth. Supernumerary deciduous teeth are much less common than supernumerary permanent ones.

#### PROLIFERATION

Proliferative malformations may have a variety of forms and causes.

**Cysts.** Cysts may originate from abnormal proliferation of the oral epithelium or more commonly from proliferation of epithelial rests in the periodontal membrane.

**Ameloblastomas.** These tumors arise from the enamel organ (see p. 1369).

**Odontomas.** When abnormally proliferating cells of the enamel organ undergo partial

or complete differentiation, calcified toothlike masses are formed which are termed odontomas. These may range from small calcific nodules to well formed teeth. They usually do not erupt and are never malignant.

#### HISTODIFFERENTIATION—

##### ABNORMALITIES IN STRUCTURE OF ENAMEL AND DENTIN

**Amelogenesis Imperfecta (Brown Teeth).** When the ameloblasts (enamel-forming cells) fail to differentiate properly, a thin layer of enamel is deposited, and the underlying brown dentin is readily visible. The condition is hereditary.

**Hereditary Opalescent Dentin (Dentinogenesis Imperfecta).** Brown opalescence of the teeth and marked abrasion characterize hereditary opalescent dentin. The roentgenographic appearance is pathognomonic, the pulp chamber being entirely absent and the pulp canals showing progressive decrease in size. The roots are usually shorter than normal. Both the deciduous and permanent teeth are affected. The dentin is abnormal in formation and calcification, and the tubules are reduced in number and are irregular in arrangement. The pulp cavity is completely obliterated by excessive dentin formation. The teeth wear rapidly, and their protection by special restoration is indicated as soon as they appear.

Dentinogenesis imperfecta is hereditary and often accompanies other congenital mesodermal dysplasias, particularly osteogenesis imperfecta. Each may occur separately, but in combination the condition is termed *congenital mesodermal dysplasia*.

**Abnormalities in the Color of Teeth. Intrinsic stains.** The brown teeth characteristic of dentinogenesis imperfecta and amelogenesis imperfecta are described above. A greenish color of the enamel being formed at birth may result from intense neonatal jaundice, and the deciduous teeth may be completely green except for the portions formed postnatally. In congenital porphyria the teeth are often stained pink. Hemorrhage into the pulp after trauma may cause a gray to black discoloration of the crown.



Table 81. A Classification of Aberrations in Tooth Development

CHARACTER OF DISTURBANCE	GROWTH				CALCIFICATION	ERUPTION	ATTRITION
	INITIATION	PROLIFERATION	HISTO-DIFFERENTIATION	MORPHO-DIFFERENTIATION			
DEFICIENT DEVELOPMENT	ABNORMAL NUMBER	ATYPICAL STRUCTURE	ATYPICAL FORMS & SIZES	ABNORMAL AMOUNT	ABNORMAL HARDNESS	ABNORMAL ERUPTION	ABNORMAL WEARING
	Anodontia - partial or complete Congenital absence of lateral incisors, third molars, bicuspids, etc.	Amelogenesis Imperfecta (Ameloblasts) Dentinogenesis Imperfecta (Odontoblasts) Vitamin A Deficiency (Odontogenic Epithelium)	Peg teeth Hutchinson's incisor Mulberry molars Microdontia	Hypoplasias - systemic or local Chronologic enamel hypoplasia Localized enamel pits Dentin hypoplasia (Pulpal inclusions)	Hypocalcification Mottled (chalky) enamel Malacotic enamel Interglobular dentin	Delayed Eruption of teeth single or multiple Submerged denture teeth Submerged teeth (ankylosis) Impacted teeth Malposed teeth	Deficient Wear Restricted lateral excursion
EXCESSIVE DEVELOPMENT	Epithelial Rests	Odontogenic Epithelium	Extra cusps and roots Dens in Dente Macrodonia	Enamel nodules Simple compound and complex odontomes	Sclerotic Dentin resulting from age, injury or caries	Malocclusions Excessive mesial and occlusal drift of teeth Supraocclusion of teeth	Excessive Wear Night grinding (Bruxism)

From Massler and Schour: Atlas of the Mouth. American Dental Association, Chicago.

**Extrinsic stains.** Green stain occurs on the labial surfaces of the anterior teeth near the gingivae in children who lack satisfactory oral care. It is probably caused by chromogenic bacteria which adhere to gingival mucous plaques or to remnants of the enamel epithelium (Nasmyth's membrane) which have not been worn off in the protected gingival areas. This stain is firmly attached to the enamel and can be removed only by the dentist.

Black stains on the teeth may result from ingestion of iron compounds if a drinking tube is not used to prevent contact with the teeth.

#### MORPHODIFFERENTIATION—

##### ABNORMALITIES IN FORM AND SIZE OF TEETH

**Peg Teeth.** Peg teeth are cone-shaped and small in size. They occur frequently in the congenital dysplasias and may be familial. The upper lateral incisors are most commonly affected.

**Macroteeth or Microteeth.** Excessively large or small teeth are usually hereditary.

**Hutchinson's Incisor.** The incisor has a screwdriver appearance as a result of convergence of the mesial and distal sides (see Syphilis, p. 475).

##### ABERRATIONS IN APPPOSITION

**Enamel Hypoplasia (Pitted Enamel).** This is a developmental defect which appears clinically as a pitting or grooving of the enamel surface and occurs in 5 to 10 per cent of the population. It is a permanent record of a systemic disturbance which injured the enamel-forming cells and caused a premature cessation of their activity. Severe systemic upsets such as congenital syphilis and prolonged diarrhea or vomiting in the first year of life may result in enamel hypoplasia. Many children with persistent cerebral disorders have enamel hypoplasia. Most of the enamel hypoplasias are formed during infancy and may be recognized roentgenographically before eruption of the teeth.

Enamel hypoplasia may also be of local origin and confined to a single tooth. An infection at the root of a deciduous molar may injure the subjacent developing crown of its permanent successor and produce a permanent defect in its enamel.

*A knowledge of the time of tooth formation facilitates chronologic assessment of enamel hypoplasia.* All the deciduous teeth start forming in utero, but are not completed

until about two and a half years of age. The first permanent molar begins its formation at birth and is the first permanent tooth to erupt (about six years of age). It is frequently mistaken for a deciduous tooth and thus often inadequately cared for.

The roots of the permanent teeth usually do not complete development until about three years after eruption of the tooth.

#### DISTURBANCES IN CALCIFICATION

**Interglobular Dentin.** Deposition of mineral salts, as in bone, follows closely the deposition of the matrix. Slight disturbances in calcification are evidenced as interglobular dentin, or *chalky enamel*. Such alterations represent relatively mild systemic disturbances and are often the result of subclinical variations in calcium metabolism (see Mottled Enamel).

The calcification of the enamel and dentin is characteristically different during the various developmental periods (Table 82). It is so sensitive to metabolic changes that these tissues reflect the developmental pattern of the child and serve as a graphic record of past systemic disturbances.

**Mottled Enamel (Dental Fluorosis).** In contrast to normal enamel, which is hard, glossy and translucent, mottled enamel is opaque and, in severe cases, chalky and crumbles easily. It is usually caused by ingestion of excessive amounts of fluorides (more than one part per million of water) during the period of calcification of the developing teeth. The fluorides are usually derived from drinking water from artesian wells in endemic areas. In mild cases there are white opaque areas involving up to 50 per cent of the tooth surface. In moderate cases the entire surface is affected, and brown staining occurs secondarily from oral pigments. In severe cases there is extensive mottling and discrete or confluent hypoplastic pitting.

#### THE TEETH IN DIETARY DEFICIENCIES

The importance of nutrition varies with the developmental stage of the tooth and the particular dental structure. Nutrition is of greatest significance in the infant and younger child when most of the teeth are undergoing formation and calcification. As the teeth erupt into the oral cavity, nutritional factors become relatively less important, and finally play no direct role. It is



Table 82. Effects of Developmental Disturbances in the Structure of Teeth

Normal Structure		Enamel Hypoplasia
Prenatal period		
(4½ months to birth).....	Optimal calcification of enamel and dentin	Often associated with congenital cerebral disorders (especially athetosis or spastic diplegia)
Neonatal period.....		
	Microscopic line of arrested growth demarcating prenatal and post-natal tissue; due to physiologic adaptation and trauma incident to birth	Present in children suffering from excessive birth trauma and brain damage due to anoxia, etc. ("spastics" and mentally deficient children)
Infancy period		
(1-10 months).....	Poor calcification of enamel and dentin	Chronic hypoplasia from birth to 11 months most common form of enamel hypoplasia; usually due to disturbances in calcium metabolism Acute hypoplasia at 10-11 months also common; etiology unknown
Childhood period		
(1-5 years).....	Improved calcification of enamel and dentin from 1 to 2½ years; poorer calcification from 2½ to 5 years	Acute hypoplasias seen occasionally; may be associated with acute illnesses

useless to add calcium or vitamins to the diet to treat enamel hypoplasia or caries. By contrast, the growth of the gingivae, the alveolar bone and the other periodontal structures is influenced by nutrition throughout life.

A diet adequate for general health is also adequate for dental health. Special attention, however, should be given to the physical make-up of the food and its local detergent action and to avoidance of excess sugar.

*Vitamin A deficiency* is rarely sufficiently severe to cause enamel hypoplasia, although in experimental animals it produces striking disturbances.

*Vitamin D deficiency* results in disturbed calcification of the growing alveolar bone and the dentin and occasionally is responsible for enamel hypoplasia. A causal connection between deficiencies of vitamin D and/or calcium and the occurrence of caries has not been proved.

*Vitamin C deficiency* is responsible for hemorrhages in the oral mucosa and gingivae. The use of vitamin C for bleeding gums, postoperative hemorrhage and in oral infections cannot be expected to be beneficial, however, except in the presence of a deficiency of vitamin C.

*Deficiencies of the B complex vitamins*, particularly of riboflavin and nicotinic acid, favor the occurrence of specific infections in the oral cavity. The characteristic changes

of the tongue and other oral tissues are discussed on pages 365 to 367.

DISTURBANCES IN THE ERUPTION OF TEETH

The appearance of the tooth in the oral cavity is only one phase of the eruptive process, which continues throughout life, but at a decelerating rate. The time of the eruption of the teeth is a valuable clinical index of the rate of maturation of a child (Tables 83, 84). The lower teeth usually erupt before the corresponding upper ones, and

Table 83. Time of Eruption and Shedding of the Deciduous Teeth\*

<i>Eruption</i>			<i>Shedding</i>	
	Lower	Upper	Lower	Upper
	Age (Months)		Age (Years)	
Central incisor.....	6	7½	6	7½
Lateral incisor.....	7	9	7	8
Cuspid.....	16	18	9½	11½
First molar.....	12	14	10	10½
Second molar.....	20	24	11	10½
Incisors.....	Range ± 2 mos.		Range ± 6 mos.	
Molars.....	Range ± 4 mos.			

\* From Massler and Schour: Atlas of the Mouth. American Dental Association, Chicago.

Table 84. Time of Eruption of the Permanent Teeth\*

	<i>Lower</i> Age (Years)	<i>Upper</i> Age (Years)
Central incisors.....	6- 7	7- 8
Lateral incisors.....	7- 8	8- 9
Cuspids.....	9-10	11-12
First bicuspid.....	10-12	10-11
Second bicuspid.....	11-12	10-12
First molars.....	6- 7	6- 7
Second molars.....	11-13	12-13
Third molars.....	17-21	17-21

\* From Massler and Schour: Atlas of the Mouth. American Dental Association, Chicago.

teeth usually erupt earlier in girls than in boys. There is also a normal variation according to constitutional type: Thus teeth tend to erupt earlier in slender children than in stocky ones. Disturbances in eruption of permanent teeth are more common than disturbances in their formation and calcification, and are usually caused by premature extraction of deciduous teeth.

PREMATURE ERUPTION

Occasionally one or two deciduous teeth in the lower central incisor area are erupted at birth or soon after (natal teeth). These may be normal or supernumerary teeth. The latter are exfoliated before the normal teeth erupt and are characterized by looseness, lack of root formation and defective structure. They should be removed if they interfere with nursing or if there is danger of aspiration.

DELAYED ERUPTION

Within normal limits the first deciduous tooth may not appear until the age of one

year. Further delay in eruption suggests a systemic disturbance of nutritional or endocrine origin. Cretinism, rickets, mongolism and congenital syphilis are among the more likely causes. The possibility of total or partial anodontia must be ruled out by roentgenographic examination.

DIFFICULT ERUPTION OR TEETHING  
(DENTITIO DIFFICILIS)

In the early part of this century a great number of disorders (fever, convulsions, diarrhea, croup) were often mistakenly attributed to dentitional difficulties. Eruption is a physiologic process and is not related to the many temporary systemic disturbances that frequently occur during infancy and childhood. There is little basis for the view that eruption of a tooth causes fever. There are instances when the process of teething appears to irritate the child and may be associated with fretfulness, disturbed sleep, salivation and a tendency to put the hand constantly into the mouth. Reassurance to the parents and elimination of other diagnostic possibilities are helpful.

The gingivae at the point of emergence of the tooth may become inflamed and sensitive to touch. Overambitious care by the mother should be discouraged. The inflammation will usually subside with the eruption of the tooth. Lancing of the gingivae to facilitate eruption usually aggravates the situation and is rarely indicated. A clean, smooth, firm and unbreakable teething object with which the child can aid the cutting of the gums is usually helpful.

Premature Exfoliation of Teeth. Exfoliation of the deciduous teeth is a physiologic

Table 85. Differential Diagnosis and Treatment of Dental Pain (Odontalgia)

<i>Pulpal Pain (Pulpitis)</i>	<i>Periapical Pain (Periodontitis)</i>
Sharp, lancinating and intermittent. Aggravated at night when lying down Not tender to percussion	Dull, throbbing ache
Difficult to localize. Pain may be referred to any other tooth	Tender to percussion; tooth feels high and strikes first in occlusion Easily localized
Very sensitive to changes in temperature and to sugar No swelling	Relieved by heat or cold Swelling may occur as a localized "gum boil" or generalized swelling of face
TREATMENT	
Remove carious material and food debris and insert eugenol on cotton pellet or, preferably, in zinc oxide paste	Apply heat or counterirritation (3 per cent iodine) to localize infection in oral vestibule Incise and drain (do not use local anesthesia)



process. Premature exfoliation of teeth has been observed in association with a skeletal disorder resembling rickets and an almost complete lack of plasma alkaline phosphatase activity (see p. 1224).

## DISTURBANCES IN ATTRITION OF TEETH

Attrition, the normal wearing of the teeth, begins as soon as the opposing teeth come into occlusion. The amount of attrition varies with the physical composition of the food. Deciduous teeth wear somewhat faster than permanent ones.

*Night grinding (bruxism)* results in especially rapid attrition. Bruxism should be regarded as a symptom of emotional disturbance in the child, and the cause sought. It frequently occurs in patients with cerebral palsy. Subclinical nutritional deficiencies should also be considered.

## DENTAL CARIES

Dental caries is a progressive lesion of the calcified dental tissues (enamel, dentin or cementum) characterized by loss of tooth structures.

**Etiology.** Irrespective of the many factors which influence the rate of caries progress, all available evidence points to bacteria as the active etiologic factor.

The bacteria involved are generally classified into three groups according to the role they play in the production of dental decay: (1) acidogenic and aciduric organisms, which produce the acids upon the tooth surface that decalcify the hard tissues, *Lactobacillus acidophilus* and certain streptococci being the most frequent ones; (2) proteolytic organisms, which digest the organic matrix after its decalcification and produce the characteristic discoloration and odor of caries; and (3) leptotrichiae organisms, which apparently play no primary role, but form plaques on the smooth surfaces of the teeth where acidogenic and proteolytic organisms are harbored.

**Contributory factors.** **AGE.** Although no age is immune to dental decay, caries is primarily a disease of childhood and adolescence. The periods of greatest carious activity are five to eight years in the deciduous dentition and twelve to eighteen years in the permanent dentition. The latter is the period of highest susceptibility, when 90 per cent of all rampant caries occurs.

**DIET.** The most important factor contribut-

ing to dental decay is excessive ingestion of sticky refined carbohydrates *between meals* which remain on the tooth surface for long periods of time. Acidogenic bacteria quickly produce acid from these sugars. Sugars ingested at mealtime are not as injurious, since the buffering capacity of the saliva tends to neutralize the acid.

**ORAL HYGIENE.** Lack of oral hygiene provides the food (debris) upon which the bacteria feed.

**STATE OF HEALTH.** Saliva is normally bacteriostatic, but in adverse systemic conditions the quality of the saliva as well as its quantity may be altered so that caries activity is increased. The majority of persons with chronic debilitating diseases have an increase in caries activity. In such cases oral hygiene after each meal is even more important and necessary than in the healthy person.

**Clinical Manifestations.** Caries occurs most often in areas where food debris may become impacted and stagnate, as in the pits and fissures on the occlusal surface of the posterior teeth (pit and fissure decay), less often at the contact areas between the teeth (interproximal decay) and at the neck of the tooth (gingival decay), usually only in badly neglected mouths.

The carious lesions may be acute and penetrate rapidly through the substance of the tooth, or their progress may be intermittent and slow and may even become arrested. Rapidly burrowing caries is characteristic in children; the slow, intermittent caries predominates in middle age.

**Prevention.** Since dental caries is a disease of a tissue which cannot regenerate or repair itself, the disease is likely to be cumulative. It is sometimes self-limiting (arrested caries), but never self-reparative. Caries can usually be treated adequately by the dentist and can be kept minimal by good oral hygiene and an adequately balanced diet. Simple caries is merely a problem of early detection and repair by the dentist. Neglected caries is usually a problem in oral hygiene.

Because new carious lesions appear suddenly and in numerous areas and since the lesions progress rapidly, *the usual six month interval between dental examinations is inadequate for the rapidly growing child*; examinations, particularly of the teen-age child, should be made at least at two to three month intervals. If special care is not observed during this period, extensive decay will occur with disastrous results, which will be reflected throughout adulthood.

Fluorine inhibits enzymatic activity and thus prevents bacterial action and may reduce the progress of caries at the *site of action* if present in sufficient concentration. Fluorine may be ingested in small amounts in the communal drinking water or may be applied topically by the dentist.

The physician can help to minimize dental problems in children if he will:

Encourage frequent visits to the dentist.

Discourage between-meal eating of all foods and candies containing refined sugars; and substitute fresh fruits.

Encourage brushing the teeth or at least rinsing the mouth immediately after each meal.

Encourage the application of topical fluorides on newly erupted teeth or the fluoridation of the communal water supply.

### PERIAPICAL INFECTION

**Routes of Infection.** If dental caries is allowed to progress unchecked, an infection of the pulp is inevitable. Pulpal infection spreads through the apical foramen into the surrounding periapical tissues. Such periapical infections, when not localized by natural or artificial means, may spread (1) directly, (2) along fascial planes, (3) by the lymphatics, and (4) through the venous system.

**Direct extension** may be by invasion and infection of the bone (osteomyelitis) or adjacent structures such as the maxillary sinus, the orbit, the floor of the nose and the ethmoids, and the floor of the mouth, which may result in parapharyngeal space infections.

**Fascial planes are potential spaces** which are ideal sites for the collection of pus and the development of cellulitis. The spaces most commonly involved in dental infections are (a) the masticatory, temporal and parotid spaces in the cheek, (b) the floor of the mouth (sublingual space), submaxillary space and the carotid sheath in the neck, and (c) the pharyngomaxillary (parapharyngeal) space in the pharynx.

**The lymphatics** of the periodontal structures drain into the submaxillary lymph nodes, except those from the lower anterior region, which drain into the submental lymph nodes and then into the deep cervical ones. Periapical infections may therefore cause a lymphadenitis, and, if the infection is virulent, cellulitis may result. Sinus tracts

may be formed which perforate the skin, especially in the submandibular area, and continue to drain until the infected tooth is removed and the soft tissue infection is eradicated by antibiotic therapy.

**Blood-borne** bacteria from peripheral and focal infections may be responsible for localized lesions in other parts of the body.

**Periapical infections** of the upper anterior teeth (particularly in children) may involve the lip or floor of the nose and extend by way of the anterior facial vein to the cavernous sinus. Infections of the posterior teeth may invade the pterygoid plexus of veins and by retrograde extension reach the cavernous sinus. About 4 per cent of the fatal cases of thrombosis of the cavernous sinus in children are of dental origin. The dangers of spreading a mild infection of the upper lip or nose by "squeezing" or "picking" are well known; the fact that periapical infection of the upper anterior teeth may follow the same route is less appreciated.

**Treatment.** The majority of periapical infections point into the oral cavity, owing to the warm and moist environment. Nature can be aided by increasing the intraoral heat by means of hot mouth washes. Extraoral heat may favor the spread of the periapical infection into the cheek, leading to perforation of the skin and a disfiguring scar. Antibacterial therapy is the most effective means for the control of these infections. The oral surgeon should be consulted as early as possible, since removal of the tooth permits maximal drainage of the infection.

**Dental Infections and Systemic Disease.** At one time teeth were overemphasized as foci of infection, and there were many unwarranted extractions. It is well to realize, however, that dental infections may on occasion provide a focus for systemic disease. Periapical infections in children constitute the major dental foci from which infections may spread. In adults gingival disease constitutes another source of dentogenic infections.

Many diseases cannot be successfully treated if the child has an infected tooth or a spreading periapical infection; hypochromic anemia and diabetes mellitus are examples. Because transient bacteremia is frequently associated with dental extractions, prophylactic antibacterial therapy, preferably with penicillin, is indicated when this procedure is to be undertaken.



## DISTURBANCES OF THE FACE AND JAWS

### MALOCCLUSIONS OF THE TEETH

Normal occlusion of the teeth and jaws is essential to a pleasing appearance and to efficiency in mastication. Abnormal occlusion may result from abnormal positioning of the teeth alone or from an abnormality in the growth of the jaws.

**Physiologic Spacing of the Anterior Teeth.** Fortunately, malocclusion is not common in deciduous teeth. The spacing of the anterior deciduous teeth by about four to six years of age is a physiologic condition and should not be mistaken for malocclusion. Similarly, the newly erupted permanent anterior teeth are often "spaced," incorrectly inclined, and even partially rotated when they first erupt. This condition is temporary and is self-corrected through the action of the tongue and labial-buccal musculature.

During the transition from deciduous to permanent dentition (from six to twelve years) the permanent teeth often appear disproportionately large and are frequently crowded or "spaced" and abnormally inclined. These conditions are usually self-corrective and merely represent a transitory stage in the development of dentition. It is often difficult to determine whether progress will be toward the normal or the abnormal. In case of doubt an orthodontist should be consulted.

Malocclusions of the teeth are frequently caused by (1) premature extraction of teeth, particularly the deciduous molars and the first permanent molar; (2) prolonged retention of deciduous teeth which prevents their permanent successors from coming into correct position; (3) thumb-sucking, which interferes with the normal molding action of the tongue and lips; and (4) mouth-breathing, which may disturb the formation of the jaws.

**Effects of Loss of a Tooth.** The dental arch is not static, but is in a state of dynamic balance. The removal of a single element upsets this equilibrium. The first permanent molar is the keystone of the dental arch. The extraction of the lower one without immediate replacement, especially after eruption of the second permanent molar, may result in shifting of the teeth, malocclusion, periodontal injury and caries.

The deciduous teeth serve not only in the mastication of food, but also as space main-

tainers for their permanent successors. The effects of early loss of a deciduous cuspid or molar tooth may be disastrous, since malocclusion of the entire permanent arch may result. The loss of deciduous incisors rarely has serious consequences.

**Thumb-Sucking.** The orthodontist, the pediatrician, the psychiatrist, the teacher and the parents are all concerned with the problem of thumb- or finger-sucking in a child. It may be considered a normal habit in the first two years of life, but should gradually be given up by the end of this period except on occasions of fatigue or unusual emotional disturbance. Its persistence beyond the third year usually reflects a problem in emotional development (see p. 77). Occasionally a child who has given up thumb-sucking regresses to such behavior when emotional disturbances develop (for example, after the appearance of a newborn sibling). When the habit persists abnormally, the sucking is usually vigorous and may therefore distort the deciduous dental arch. It is usually more effective to direct attention toward relieving the emotional disturbance than to call attention to the habit. In unusually severe cases psychiatric consultation may be necessary. If help is effective and thumb-sucking ceases before the sixth year, the dental deformity will be remolded and corrected in about 75 per cent of all cases.

If thumb-sucking continues after six years of age, the dental deformity which may result is usually severe, since the incisors are newly erupted and the entire anterior segment is easily displaced. Efforts to correct the underlying psychologic disturbance should continue while orthodontic care is undertaken.

**Mouth-Breathing.** The consequences of mouth-breathing are more serious to the health of the child and to the development of his teeth and jaws than those of thumb-sucking. The effects of thumb-sucking rarely extend beyond the dental arches, but mouth-breathing may affect the entire facial skeleton. The face becomes markedly elongated and narrowed because of the dropping of the mandible into an open position and because of the constriction of the upper arches and palate. The nostrils become narrowed and pinched from disuse. The facial expression becomes dull and drawn.

The tongue, assisted by the labial and buccal musculature, is nature's orthopedic appliance for correct molding of the dental arches. When the child has normal nasal function, the tongue lies against the palate, within and supporting the upper arch, so that symmetrical molding of the arch results. The lower arch lies within the upper one and is molded by it.

In the child whose normal nasal function is obstructed so that he is obliged to breathe through his mouth, the following changes may occur:

1. The gingivae frequently are hypertrophied and inflamed in the cuspid-to-cuspid region.
2. The tongue is suspended between the arches or on the floor of the mouth instead of on the roof, so that the molding action of the tongue is lost to the upper buccal segments, leaving them unopposed to the action of the buccal musculature.
3. The maxillary arch becomes V-shaped, owing to contraction of the buccal segments and protrusion of the anterior teeth. The palate seems high as a result of contraction of the alveolar arches.

Mouth-breathing may result from nasal obstruction or from habit. It occurs most frequently in long-faced (dolichofacial) persons in whom the pharyngeal space is normally long and narrow.

Infants and young children normally sleep with the lips apart; this should not be confused with the mouth-breathing habit. The physician should test for mouth-breathing with a wisp of cotton.

*Treatment* consists in surgical removal of the obstruction and in muscular exercises to strengthen the lips and to maintain closure. Orthodontic treatment is frequently necessary to make the closed-mouth position comfortable.

## FACIAL ASYMMETRY

Molding of the head during birth is possible because the bones of the cranium are not fused and can override. No such mechanism of adjustment to the narrow birth canal is present in the face. The mandible is the only movable bone in the face and is attached to the cranium only at its condylar head by the muscles of mastication. Facial asymmetries resulting from excessive molding of the cranium or from displacement of the mandible during breech or face presentations are fairly common and are usually self-correcting. Facial asymmetry resulting from injury to the growing cartilage of the condylar head during birth, infancy or early childhood is also common, but the effects may be more permanent. Traumatic injuries may occur during

birth from the placing of obstetrical forceps over the area, or may result from blows on the chin during infancy and childhood.

Such injuries, acute infections or rheumatoid arthritis of the growing condylar cartilage may result in a partial (fibrous) or complete (bony) *ankylosis of the temporomandibular joint* and failure of that side of the mandible to grow. The normal side, meanwhile, continues to grow and pushes the midline toward the affected side. The midline deviation is exaggerated during mouth opening. Roentgenograms of the affected side reveal a markedly increased pre-angular notch. Bilateral injuries to the growing cartilage result in failure of the mandible and chin to grow downward and forward, causing the entire mandible to be considerably smaller than normal and markedly distorted.

## FRACTURED INCISORS

Injuries to the anterior teeth, especially protruding upper incisors, are frequent in children. Even a minor blow to the teeth should be cause for careful observation, since the tooth often turns dark later, indicating hemorrhage into the pulp. Every traumatized tooth should be x-rayed. Chipping of the enamel may not require treatment, but fractures which expose the dentin should be covered with a sedative dressing, or the exposed dentin will become sensitive and death of the pulp may result. If the pulp is exposed, immediate capping is imperative. Even a dislodged tooth can be reimplanted if it is done immediately. Removal of the dead pulp and sealing the root canal are essential to success. A delay of more than twenty-four hours will usually result in resorption of the root and loss of the tooth. Prevention of injuries to the teeth during contact sports can be accomplished by wearing a moulded mouthguard. Discolored or fractured upper incisors present cosmetic problems and may be associated with psychologic problems.

## CLEFT LIP AND CLEFT PALATE

### (HARELIP)

Fusion of the maxillary and premaxillary processes normally occurs between the fifth and eighth weeks of intrauterine life; the palatal processes fuse approximately one month later. A failure in fusion may result in a cleft lip and/or cleft palate.

The incidence of cleft lip or cleft palate is approximately one per 800 population.



The cause is not known, although studies have indicated a genetic influence in many cases. Animal studies suggest that a variety of other influences may also be responsible for clefts if applied at a critical organogenetic period in a susceptible host. Associated congenital deformities may occur in any of the other organ systems developing at the same time with a higher incidence in the structures derived from the first branchial arch.

### CLEFT LIP

Cleft lip is more frequent in males than in females and may vary from a small notch in the vermilion border to a complete separation extending into the floor of the nose. Clefts may be unilateral (more often on the left side) or bilateral and usually involve the dental ridge. Deformed, supernumerary or absent teeth are additional anomalies. The nasal alar cartilage may also be displaced or deformed, producing a noticeable deformity of the nasal orifice. Bilateral clefts of the lip are frequently associated with a deficiency of the columella and an elongation of the vomer producing a protrusion of the anterior aspect of the cleft premaxillary process (Fig. 184).

Operation should be performed by a qualified plastic surgeon. The operation is usually performed at a month or two of age, but only after the infant is stabilized, gaining weight satisfactorily, and is free of any oral, respiratory or systemic infection.

There are several standard methods for repair of the cleft lip. The most common technique utilizes a staggered suture line to minimize notching of the lip from retraction of scar tissue. A Logan clamp, which is a wire bow attached by adhesive to the cheeks, is applied immediately after operation to take tension off the suture line. The initial operation in early infancy may be followed by revisions at four to five years of age. In most instances corrective surgery on the nose is better delayed until the teen-age period. The cosmetic results are dependent upon the extent of the original deformity, absence of infection and the skill of the surgeon.

### CLEFT PALATE

**Types.** Clefts of the palate may occur alone or in association with cleft lip. The former is more frequent in females than in males. Isolated cleft palate occurs in the midline and may involve only the uvula or extend into or through the soft and hard palates to the incisive foramen. When asso-

ciated with cleft lip, the palatal defect may involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate.

An isolated cleft palate may occur in association with an abnormally small mandible (Pierre Robin syndrome). There is commonly a glossoptosis, which results in a partial respiratory obstruction.

**Management.** The immediate problems of the infant with a cleft lip and/or palate are concerned with feeding and prevention of aspiration and infection. Most infants can be adequately managed by feeding them in an upright position, using softened nipples with slightly enlarged nipple openings. A lamb's nipple may be of value. In some instances a medicine dropper or gavage feedings may be used to advantage. Special cleft palate nipples and plastic palatal coverings are not necessary.

**Surgery.** In the past, palatal operation was often performed in infants less than one year of age. Not infrequently such early operation resulted in a deformed maxillary arch, especially when multiple palatal operations were necessary or excessive scarring was produced. At present the tendency is to delay operation so that the surgeon can take advantage of the palatal changes which occur with growth. Since clefts of the palate vary considerably in size, shape, and degree of deformity, the timing for operation should be individualized. Criteria such as width of the cleft, adequacy of the palatal parts, the morphology of the surrounding areas (such as the width of the oropharynx) and the

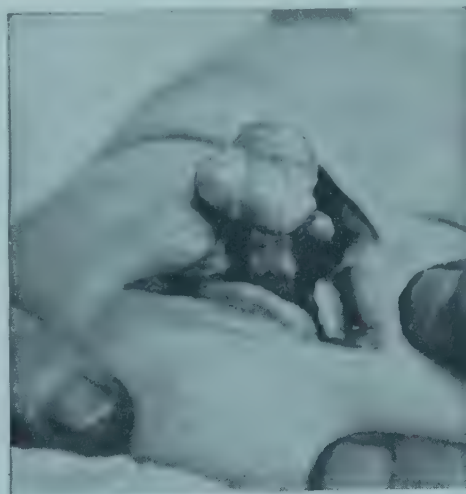


FIG. 184. Double cleft lip and cleft palate in an infant 2 months of age. Note the intermaxillary process between the clefts.

neuromuscular function of the soft palate and pharyngeal walls should affect the decision. The goals of operating are union of the cleft parts, intelligible and pleasant speech, and avoidance of injury to the growing maxilla. The optimal time for palatal surgery varies from one to five years of age. When operation is best delayed beyond the third year, a dental speech appliance can be prescribed to help the child develop intelligible speech.

**PREOPERATIVE AND POSTOPERATIVE MANAGEMENT.** Even the suspicion of any existing infection is a contraindication to operation. Bleeding and clotting times should be determined before the operation. If the child is in good nutritional state and in fluid and electrolyte balance, feeding may be permitted to within six hours of the operation. Fluid therapy is discussed on page 195.

During the immediate postoperative period *special nursing care is essential*. Gentle aspiration of the nasopharynx minimizes the hazards of the common complications of atelectasis and/or of pneumonitis. The primary considerations in the postoperative care are maintenance of a clean suture line and elimination of strain on the sutures. For these reasons the infant is fed with a medicine dropper, and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for three weeks, and feeding is with a dropper or spoon. The patient's hands as well as toys and other foreign bodies must be kept away from the palate.

**Complications.** Recurrent otitis media and hearing loss are frequent complications. Excessive dental decay is not unusual and requires special care. Displacement of the maxillary arches and malpositions of the teeth usually require orthodontic correction.

**Speech.** Speech defects may be present even after good anatomic closure of the palate. Such speech is characterized by emission of air from the nose and by a quality of hypernasality when certain sounds are made. The speech defect before and, at times, after palatal surgery is due to inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve which functions to separate the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such ex-

plosive sounds as p, b, d, t, h, g or the sibilants s, sh, ch, and such words as "cat," "boats" and "sisters" are not intelligible. After operation or the insertion of a speech appliance it may be necessary to institute speech therapy to lessen the persisting speech defect.

A *complete program of habilitation* for the child with a cleft lip and/or palate may require many years of special medical, surgical, dental and speech treatment. Representatives of the specialties involved function more effectively on a team basis than individually.

A pediatrician, plastic surgeon, otolaryngologist, children's dentist, prosthetic dentist, orthodontist, speech pathologist, medical social worker, psychologist, child psychiatrist and public health nurse may make up such a *cleft palate team*. The child's physician may need to avail himself of such a group, usually located in the larger medical centers; most states have programs for financial assistance for the medical care when the economic status of the family warrants. Parental counselling by the physician and members of the cleft palate team is an important aspect of care.

## PALATOPHARYNGEAL INCOMPETENCE

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities in the oral and pharyngeal areas. The common denominator is the inability to form an effective muscular seal between the oropharynx and nasopharynx during swallowing or phonation. The anomaly may be in the bony structures of the palate or pharynx or in the muscles attached to these structures. An adenoidectomy may precipitate the speech defect in a child who previously spoke normally, and the defect may be attributed to a previously unrecognized submucous cleft palate. In such instances it is assumed that the adenoid had a static function as a mass protruding into the epipharynx, allowing the soft palate to make contact with it when elevated; this became impossible after removal of the adenoids. If there is sufficient reserve neuromuscular function, compensation in palatopharyngeal movement may take place and the speech defect disappears, although often some symptoms of palatopharyngeal incompetence may persist. In other instances slow involution of the adenoids may allow for gradual compensation in palatal and pharyn-



geal muscular function. This may explain why a speech defect does not become apparent in some children who do have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

#### *Organic Factors Producing Palatopharyngeal Incompetence*

- I. Congenital anomalies (alone or combined)
  - A. Overt cleft palate
  - B. Submucous cleft palate
  - C. Hypoplasia of hard and/or soft palate
  - D. Extreme variations of nasopharyngeal space
    1. Depth factor—occipitalization of the atlas (platybasia)
    2. Width factor—widespread pterygoid plates
  - E. Intracranial defects with motor impairment of the palatopharyngeal muscles
- II. Acquired disturbances
  - A. Loss of palatal tissue due to infection, trauma or malignancy
  - B. Neuromotor disorders
    1. Bulbar poliomyelitis
    2. Brain injury due to infection, trauma, malignancy or vascular disease
- III. Associated or precipitating factors
  - A. Acquired disturbances superimposed on congenital anomalies
  - B. Adenoidectomy
  - C. Changes in structure with growth
 

The palate is gradually positioned lower in the oral cavity with growth changes. In the adolescent and adult soft palate contact with the pharynx occurs below the adenoid mass
  - D. Inadequate muscular compensation, especially following adenoidectomy or growth changes

#### *Manifestations of Palatopharyngeal Incompetence*

1. Hypernasal speech defect especially noted in the articulation of pressure consonants, such as p, b, d, t, h, v, f, s
2. Conspicuous constricting movement of the nares during speech
3. Inability to whistle, gargle, blow out a candle or inflate a balloon
4. Loss of liquid through the nose when drinking with the head down
5. Otitis media and hearing loss

#### *Signs on Oral Inspection*

1. Cleft palate or a relatively short palate with a large oropharynx
2. Absent, grossly asymmetric or minimal muscular activity of the soft palate and pharynx during phonation or gagging
3. A submucous cleft, as evidenced by the following pathognomonic signs
  - (a) Bifid uvula
  - (b) Translucent membrane in midline of soft palate revealing lack of continuity of muscles

- (c) Palpable notching in posterior border of hard palate instead of a posterior nasal spinous process
- (d) Forward or V-shaped displacement of grooving on the soft palate during phonation or gagging

The *symptoms* of palatopharyngeal disturbances are largely similar, although clinical signs will vary. The *diagnosis* can usually be made without difficulty if there is sufficient awareness of the entity. Palatopharyngeal incompetence can be demonstrated roentgenographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel "u" as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, while in palatopharyngeal incompetence such contact is obviously absent.

*Treatment* of palatopharyngeal incompetence is either surgical or prosthetic. In selected cases the palate may be retropositioned or a pharyngoplasty performed, utilizing a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. *Adenoidectomy should be avoided when there is a submucous cleft palate or a potential palatopharyngeal incompetence.*

### **HYPOPLASIA OF THE MANDIBLE**

The congenital deformity of an abnormally small mandible is not uncommon. The defect may be symmetric or asymmetric. The asymmetric variety is generally associated with other congenital anomalies on the same side, such as a small ear lobe. The mandibular ridge fails to contact the maxillary ridge and rests within the contour of the hard palate, producing a typical "Andy Gump" type of deformity. Apart from the cosmetic aspects, there are problems associated with respiration and feeding.

When the hypoplasia is marked, the tongue may be displaced posteriorly (glossoptosis) and partially obstruct respiration. When a cleft palate is associated, it is known as the Pierre Robin syndrome.

In relatively mild cases the infant may be placed in the prone position to alleviate the respiratory distress. If the feeding is undertaken carefully and slowly, improvement may occur with growth. Although a variety of splints and traction devices have been de-

signed to pull the mandible forward, they have not been successful. In extreme situations, where obstruction of the airway is nearly complete, performance of a tracheotomy may be necessary. If adequate respiration and nutrition are established, sufficient mandibular growth usually occurs within a few months to relieve the glossoptosis and permit removal of the tracheotomy tube. Suturing of the tongue to the lower lip (Beverly Douglas) may be helpful in the less severe cases. Since these patients have potentialities for mandibular growth, plastic surgical procedures are preferably delayed and are often unnecessary.

Unilateral hypoplasia of the mandible is sometimes part of an anomaly complex that includes partial paralysis of the facial nerve, macrostomia, blind fistulas between the angles of the mouth and the ears, and deformed ear

lobes. Because of the absence or hypoplasia of the mandibular condyle on the affected side, severe facial asymmetry and malocclusion develop. Experience has indicated that when there is early roentgenographic evidence of congenital condylar deformity, the deformity will increase with age. Plastic surgical procedures may be indicated early to minimize the deformity.

The symmetric mandibular deformity in mandibulofacial dysostosis (Treacher-Collins syndrome; Franceschetti-Klein syndrome) differs from the Pierre Robin syndrome in that the over-all shape of the mandible is grossly deformed and is associated with other facial anomalies. Furthermore, in mandibulofacial dysostosis there is no basic improvement in facial appearance as mandibular growth proceeds. Plastic surgical procedures are indicated to minimize the deformity.

## DISEASES OF THE GUMS AND GINGIVAE

The gingivae cover the necks of the teeth and are continued as the gums over the alveolar bone holding the teeth.

Gingivitis may be caused by local irritants or trauma, such as calculus, food debris or malocclusion; by systemic conditions such as acute infectious diseases, deficiency states and blood dyscrasias; or by a combination of local and systemic conditions. Gingival disease, if neglected, gives rise to periodontitis and periodontoclasia (pyorrhea). In the adult more teeth are lost as a result of periodontal diseases than as a result of caries. Gingivitis is rare in the healthy child, but common in the adult and in the sick child.

A transient gingivitis sometimes occurs when the deciduous tooth first erupts (*eruption gingivitis*); it is much less common with the eruption of the permanent teeth. The marginal gingival collar surrounding the tooth is often the site of inflammatory lesions in *vitamin C deficiency* and in *gingival drug reactions* such as those associated with Dilantin therapy.

*Crowding of the teeth* causes pressure upon the interdental papillary gingivae. In children this often leads to inflammation and hypertrophy of the gingival papillae. These areas become even more severely inflamed and hypertrophied when systemic factors such as those previously mentioned interfere with cellular metabolism.

So-called *filth gingivitis* is usually caused by lack of oral hygiene or by local irritants. The free margins of the gingivae become inflamed, violaceous and edematous. The interdental papillae in particular become engorged and covered with an exudate. There is usually no pain. If the condition is allowed to become chronic, the gingival tissue may become hyperplastic, or the underlying alveolar bone may be invaded, and a periodontoclasia results, particularly if any systemic factor intervenes.

The impact of cold air in long-continued *mouth-breathing* results in an irritation of the oral tissues. In mild cases the gingivae merely become inflamed, but in severe cases they may become hypertrophied. The incidence is much higher in the mentally deficient with dirty mouths than in healthy children with clean mouths. The mandible is usually retruded, and a severe malocclusion is present. (See Mouth-Breathing, p. 627.)

### LATERAL ABSCESS (GUM BOIL)

A small abscess or fistulous tract may occur on the gums about the level of the apex of the tooth. It is an extension of a periapical infection. As soon as the infection is localized on the gum it should be incised and allowed to drain before the tooth is extracted.



## DISEASES OF THE ORAL MUCOSA

The term "stomatitis" is frequently used to include the various inflammatory lesions that occur in the mouth. The term is not a good one, since it implies a diffuse inflammation of the various organs and tissues of the mouth, a condition which is actually rare. So far as possible it is preferable to designate specifically the area affected—i.e., gingivitis, buccal mucositis, glossitis, cheilitis. Any infection of the gingivae, lips or tongue may extend to the oral and pharyngeal mucous membranes. Such infections are less common but more serious than infections limited to the gingivae. They are far more painful and are often attended with toxic symptoms. Thus the site of the infection is as important as the cause of the infection.

**HERPETIC STOMATITIS** (See p. 491.)

(ACUTE INFECTIOUS [HERPETIC] GINGIVOSTOMATITIS, ULCEROMEMBRANOUS STOMATITIS, APHTHOUS STOMATITIS, VINCENT'S STOMATITIS)

It would appear that a large number of the oral lesions identified by the foregoing designations are an etiologic entity produced by the virus of herpes simplex.

**OTHER APHTHOUS LESIONS****ALLERGIC APHTHAE**

Allergic persons may have repeated attacks of aphthae. In appearance and course the lesions are similar or identical to those of herpetic aphthae.

**TRAUMATIC APHTHAE**

Traumatic aphthae often result from biting the mucous membrane, from accidental injuries by toys, hard foods or the toothbrush, and from irritations by sharp edges of carious teeth and broken fillings. The lesion resembles that of herpetic aphthae, but is of shorter duration and less painful. The injured area may be covered with tincture of benzoin compound.

**BEDNAR'S APHTHAE**

Superficial abrasions or erosions on the posterior part of the hard palate in the newborn infant may be caused by mechanical abrasion. They are usually caused by the gauze-covered finger of the mother or nurse during an attempt to cleanse the infant's mouth, but

may arise from friction by the nipple. The erosions generally heal within a week after the source of irritation has been removed.

**THRUSH**

(ORAL MONILIASIS)

(See also pp. 330, 798, 1293.)

The condition known as thrush is a mild infection of the skin and mucous membranes characterized by the formation of pearly-white, curdlike lesions. It is caused by the fungus *Candida* (*Monilia*) *albicans*.

**Etiology.** *Candida albicans* (*Saccharomyces albicans*, *Oidium albicans*) is a saprophyte in the normal mouth (except in the newborn infant) until such time as tissue resistance is sufficiently impaired by improper diet or disease, at which time the organism gains a foothold and assumes a pathogenic role. Thus premature and weak infants, undernourished children and old people with low resistance are especially susceptible.

A positive relationship between maternal vaginal and infantile oral moniliasis has been demonstrated; this maternal source appears to be the principal means for infection of healthy newborn infants. Infection of other healthy newborn infants may occur from imperfectly sterilized bottles or nipples, from the mother's breast or the attendant's hands. Familial cross infection may occur via the patient's oral secretions or stools and from dust. Suppression of the natural oral flora by long-term antibacterial therapy enhances the development of moniliasis as well as other fungus infections.

**Clinical Manifestations.** The lesions which are characteristic may be found wherever warmth and moisture favor growth of the fungus (the mouth, anal region, genitals, interdigitally and under the breasts). In the mouth the lesions usually appear on the gingivae, the sides of the tongue, the buccal mucosa and the throat. The superficial, strandlike lesions become confluent and form pearly-white, elevated patches which resemble milk curds; when forcibly removed, they leave a raw surface. The lesions are painless with little or no swelling, usually self-limited, and after treatment heal within a few days by exfoliation of the epidermis.

If the infection is localized to the mouth, the systemic symptoms are mild; otherwise



FIG. 185. Gangrenous stomatitis, beginning in the lip.

they may be severe. Esophagogastritis and pneumonitis may complicate the oral infection. Extensive spread of the infection is usually the result of an underlying debilitating condition. The organism is commonly found in the lesions of *perlèche*.

**Diagnosis.** Budding yeasts and rudimentary branching filaments can be seen in fresh smears by adding a drop of 10 per cent potassium hydroxide solution. Cultures made on Sabouraud's medium are diagnostic; the filaments are long and thin, with little branching, but with short lateral buddings.

**Treatment.** At present there is no completely effective agent. Nystatin, in doses of 200,000 units per 1 ml. applied locally three to four times daily with a soft cotton swab, allowing the infant to swallow whatever portion remains, is effective in eliminat-

ing the lesions. The rate of recurrence of moniliasis following its use, however, is similar to that following such topical therapy as 1 per cent aqueous gentian violet solution and 1:1000 aqueous solution of benzalkonium chloride (Zephiran), each of which is moderately effective.

## NOMA

(GANGRENOUS STOMATITIS, CANCRUM ORIS, INFECTIVE GANGRENE OF THE MOUTH)

Noma is a relatively rare progressive gangrene of the buccal mucosa which results in a perforating ulcer of the cheek (Fig. 185).

**Etiology.** Noma is caused by invasion of the buccal tissues by fusospirochetal organisms and other bacteria in children whose resistance has been lowered by a concurrent disease or a nutritional deficiency.

**Clinical Manifestations.** The lesion usually begins as a small ulcer with few constitutional symptoms, but soon results in a gangrenous, greenish-black area on the gums, buccal mucosa or mucocutaneous borders. The tissues then become swollen and characteristically fetid. The gangrenous area spreads slowly but inexorably until the cheeks are perforated and the jaws denuded.

**Treatment.** Intensive antibacterial therapy (penicillin or other agents, the selection being based on susceptibility tests *in vitro*) should be instituted as soon as the diagnosis is made and continued until all necrotic tissue, whether soft tissue or bone, has sloughed. Since malnutrition is frequent in these patients, an adequate diet should be introduced gradually with special emphasis on adequate amounts of protein and vitamins. Parenteral fluid therapy is usually necessary in the acute stage. Plastic surgical procedures may be indicated when healing is complete.

## DISTURBANCES OF THE LIPS

### FISSURES

#### CHEILITIS

Dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation is common in children. It is usually caused by sensitivity to contact substances (from toys and foods) plus a photosensitivity to the sun's rays. It is aggravated by the habit of alternate wetting with the tongue and drying by the wind, especially in cold weather. Cheilitis also often occurs in association with fever.

### ANGULAR FISSURES

#### (PERLÈCHE)

Maceration and fissuring at the angles of the mouth may be caused by an infection with *Candida albicans* (*perlèche*; moniliasis, see p. 633). It is contagious, but causes no constitutional symptoms or pain. The infection usually extends inside the mouth. Treatment with a mild antiseptic is successful.

When fissuring is caused by a nutritional deficiency, it is termed *cheilosis*. Cheilosis is



an early sign in riboflavin deficiency and is often accompanied by moniliasis.

Fissuring also occurs in mentally deficient children who drool (rhagades in mongolism).

## HERPES SIMPLEX

(HERPES LABIALIS, COLD SORE, FEVER BLISTER)

Herpes simplex (see p. 490) is an aggregate of small transparent vesicles on an inflammatory base and is accompanied by itching or burning. It usually affects the mucocutaneous junction, but may affect the skin of the face or the mucous membrane of the mouth. It is self-limited, disappearing in eight to fourteen days.

## ALLERGIC ERUPTIONS

Certain substances such as lipsticks and toothpastes may produce eruptions where

they come in contact with the lips. The lesions may be vesicular or elevated reddish wheals (urticaria), and there may be a glossitis. There is usually a history of other allergic manifestations.

## ANGIONEUROTIC EDEMA

A variety of urticaria which may be responsible for a sudden diffuse swelling of short duration (one to two days) in children with allergic tendencies is angioneurotic edema. It often itches, but seldom is painful. There is no erythema, and the tissues appear to be normal in color, firm, and do not pit.

## MUCOUS RETENTION CYST

A mucous retention cyst is a single teatlike projection covered by a thinned-out mucous membrane and filled with a clear fluid. It is caused by occlusion of the orifice of a labial or buccal mucous gland, resulting in retention of the secreted fluid.

# THE TONGUE

The tongue in certain instances may assume an unusual appearance without having an undue clinical significance. The patient is often not aware of the unusual appearance.

## FISSURED TONGUE

The pattern may be foliaceous (leaflike) or cerebriform. The tongue may be somewhat enlarged and show imprints of the teeth at the sides. Fissured (scrotal) tongue is usually congenital, but may be acquired, especially in mongolism. Occasionally, fissuring may follow certain diseases such as scarlet fever, syphilis or typhoid fever.

## BLACK HAIRY TONGUE

(LINGUA NIGRA)

This condition is characterized by an elongation of the filiform papillae into hairlike projections as long as  $\frac{1}{2}$  to 1 inch. It is generally concentrated in a triangular area in front of the V-shaped line of circumvallate papillae. The patch may vary from brown to black. The condition is usually chronic, but often disappears spontaneously.

A similar condition also occurs in cases of chronic intraoral hemorrhage, as in purpura and hemophilia. The filiform papillae become hypertrophied and are colored dark brown

by the blood pigments. There is always a characteristic fetor ex ore, owing to the presence of blood in the mouth.

Hairy tongue may occur during prolonged antibiotic therapy, especially with oral troches.

## GEOGRAPHIC TONGUE

(WANDERING RASH)

This benign lesion of the tongue is characterized by one or more smooth, bright red patches often showing a yellowish, grayish or whitish membranous margin upon the dorsum of an otherwise normally roughened tongue. The patches represent areas in which the filiform papillae have become completely desquamated, leaving a smooth, slick surface. The patches may be single or multiple, discrete or confluent (maplike). They travel by an extension of desquamation of the papillae at one edge and a regeneration of the normal papillae at the other. A single cycle may last two to seven days. The condition is usually chronic and has been attributed to allergy.

Temporary smooth red patches on the dorsum of the tongue simulating geographic tongue are frequent in children with low grade fevers, particularly those accompanying the common cold and chronic systemic infections.

## TONGUETIE

A short lingual frenum making it impossible to protrude the tongue to the normal extent usually causes no symptoms and requires no treatment. In *extremely rare* instances the lingual frenum is short and fibrous and may interfere with sucking and later with articulation. Treatment consists in nicking the edge of the frenum with blunt-pointed scissors and then separating the remaining membrane.

## MACROGLOSSIA

The tongue in infants is often proportionately larger than the other oral structures because it grows at a relatively faster rate and is not confined by the teeth. In stocky infants the tongue is frequently so large and unconfined that it protrudes from the mouth, and occasionally has been mistaken for a manifestation of hypothyroidism. As the infant grows, the other oral structures gradually catch up and confine the tongue, so that its relative size is decreased.

A true hypertrophy of the tongue is rare. It may exist congenitally as a diffuse lymphangioma or as a muscular hypertrophy (rhabdomyoma). The tongue may reach such a size that it cannot be retained in the mouth, with the result that nursing and, later, speech are interfered with. In such cases the teeth are pushed into a malocclusion by the action of the tongue.

*Treatment* is surgical, although some relative adjustment usually occurs as the child grows older.

Hemangiomas and cysts may be responsible for a diffuse or localized enlargement of the tongue. Enlargement of the tongue is also present in cretinism, acromegaly, mongolism and occasionally gargoylism.

## TONGUE-SWALLOWING

See Hypoplasia of the Mandible (p. 631).

## THE TONGUE IN SYSTEMIC DISTURBANCES

The tongue reflects changes in the physical state of the body, at times in a diagnostic manner.

### WHITE COATED TONGUE

The accumulation of food debris and bacteria among hypertrophied filiform papillae

causes a *moist coated tongue*. The filiform papillae are present at birth, but are much shorter than even the fungiform papillae until about five years of age, so that the tongue appears smooth. Thus in the young child the cause should be sought for any coating of the tongue.

The condition of *furry tongue* is seen early in states of mild dehydration and low grade fever. The "fur" is actually the hypertrophied filiform papillae. The tongue seems dry.

Failure of secretion by the salivary and lingual glands results in a *dry coated tongue*. Dryness of the tongue is one of the best clinical evidences of dehydration. The color may vary from white to brown.

A transitional stage from the white coated tongue to the raw, red tongue is known as the *white strawberry tongue* (Fig. 111, p. 407). The appearance is that of an unripe strawberry. The engorged and enlarged fungiform papillae appear prominently above the level of the white, desquamating filiform papillae. It is seen early in scarlet fever and other acute febrile states.

### RAW RED TONGUE

#### (GLOSSITIS)

When the filiform papillae of the "white strawberry tongue" or the coated tongue are shed, leaving the engorged fungiform papillae raised above the smooth, denuded surface of the tongue, the condition is known as "red raspberry" or "red strawberry tongue." This is seen often in the later stages of febrile states and about the sixth or seventh day of scarlet fever (Fig. 113, p. 407).

When the papillae become flattened and edematous (mushroom-shaped), but not atrophied or shed, the *raw pebbly tongue* results. The color is a characteristic purplish-red (magenta) instead of pink. Edema of the tongue is common, and the indentations of the teeth can easily be seen. The edges of the tongue often become denuded and raw, resulting in a burning, painful sensation. Fissuring is common. Magneta glossitis occurs in ariboflavinosis in association with cheilosis, photophobia and lacrimation.

Complete atrophy of both the filiform and fungiform papillae results in a *smooth atrophic tongue*. The tongue also shrinks in size. The desquamated surface is usually dry and extremely sensitive to painful stimuli (glazed tongue). Atrophic glossitis with a fiery red (scarlet) coloration of the tongue is characteristic of niacin deficiency (pellagrous glossitis), especially when accom-



panied by infection. Atrophic glossitis with a pale salmon coloration of the tongue (Hunter's glossitis) occurs in pernicious anemia, and also in sprue, achlorhydria and hypochromic anemia.

## TRAUMA

Accidental biting of the tongue, irritation by carious teeth, injuries by sharp objects placed in the mouth, and burns by hot foods occur frequently in children. Such injuries may result in a simple blister or ulcer which disappears in a few days, but even superficial ulcers are painful. In extreme cases the tongue may become swollen and edematous; ice may be used to reduce the swelling. The food should be cool and in liquid form; it may be necessary to feed young infants

through a nasal tube. A mild antiseptic mouthwash such as 1 per cent tincture of iodine in physiologic saline solution may be used.

Accidental injuries and burns resulting from ingestion of poisons are not uncommon in young children. Immediate care is determined by the poison ingested and the extent of the injury. In severe cases particular attention should be given to adequacy of the airway; occasionally tracheotomy is essential as a lifesaving measure.

Ulcerations of the frenum and the margins of the tongue are usually the result of herpetic infection; those limited to the frenum may be secondary to biting the tongue during paroxysms of coughing in pertussis. Such ulcers have also been observed in association with familial autonomic dysfunction.

## SALIVARY GLANDS

### SALIVATION

#### (DROOLING)

The newborn infant does not secrete much saliva, since many of the cells of the salivary glands do not mature until about three to six months of age. About three months of age the flow of saliva is increased, and drooling occurs because the child has not learned to swallow it. Drooling becomes more evident with the cutting of the first teeth. Drooling is common in idiots because of failure to swallow the saliva.

### EXCESSIVE SECRETION OF SALIVA

#### (PTYALORRHEA, PTYALISM)

Excessive secretion of saliva occurs frequently in children as a reflex during the process of teething; it may also occur as a reflex to anticipated pain, from irritation of lesions in the mouth or from nausea. It is also seen after administration of mercurial compounds and in certain nervous affections such as encephalitis and chorea. In uncontrolled diabetes mellitus sugar is excreted in the saliva and predisposes to rampant caries.

### XEROSTOMIA

#### (DRY MOUTH)

Temporary dryness is relatively common. In even mild fevers, the quantity of saliva is quickly reduced. Xerostomia is often accompanied by dry, cracked and burning lips (cheilitis) and a burning sensation in the mouth, and there is often a characteristic

fetid odor. The nurse should relieve the dryness and burning by frequent moistening of the mouth with cooled liquids and by the application of a bland ointment to the lips. Measures must, of course, be taken to replenish the loss of water from the tissues.

*Congenital xerostomia* rarely occurs. The entire mouth becomes glazed and dry and filled with epithelial and food debris. The condition responds well to administration of pilocarpine, indicating a hypoplasia rather than plasia of the major salivary glands.

## ENLARGEMENTS OF THE SALIVARY GLANDS

*Malformations* of the salivary glands are rare, and *tumors* are seldom encountered in children. *Cysts* are usually the result of an obstruction of the duct by inflammation or stone. *Hemangioma* is the most common tumor of the parotid gland in infants and children and is treated by surgical excision.

### SUPPURATIVE PAROTITIS

#### (INFECTIOUS PAROTITIS, SECONDARY PAROTITIS)

Hematogenous or retrograde (through Stensen's duct) infection is not an uncommon complication in weak, poorly nourished children, and may occur in infants during the first week of life. Prematurity of birth and trauma to the oral tissues and salivary glands

in delivery or resuscitation may be contributing factors. *Staphylococcus aureus* seems to be the most frequent pathogen.

The process is usually unilateral. The gland becomes swollen, tender, inflamed and painful. If the child's general condition improves rapidly, resolution usually occurs in a few days. However, if therapy is ineffective, a deep-seated suppurative process can develop which may lead to necrosis of the upper jaw and terminate in death from sepsis.

*Treatment* should be prompt and continuous. Specific antibacterial therapy is of greatest importance. For older children warm, saline mouth washes are helpful and should be supplemented by hot wet packs extraorally until the pus is evacuated through Stensen's duct or the buccal mucosa. Intraoral localization is important to prevent facial scarring. When there is fluctuation and the abscess does not drain spontaneously, surgical incision is required.

### RECURRENT PAROTITIS

Recurrent swelling of the parotid gland in otherwise healthy children from the ages of eight months to twelve years constitutes a fairly characteristic clinical syndrome. The condition is not associated with any systemic disease or any local condition in the mouth and is not contagious. The swelling is usually unilateral, although both parotid glands may be involved simultaneously or at alternate intervals. Ten or more recurrences may be observed in an individual child. There is little pain associated with the swelling, which is limited to the parotid glands. The duration of swelling is usually two to three weeks; subsidence is spontaneous and may be complete or partial. The incidence appears to be higher in the spring. Allergy and spasm of Stensen's ducts have been postulated as etiologic factors, but there is no proof.

No specific therapy is known. Surgical drainage is usually unnecessary. Antibacterial therapy may shorten the attacks and should be selected on the basis of bacteriologic findings. Roentgen therapy has been used and seemed to shorten the attack and to decrease the number of recurrences. Owing to radiation hazards in a growing child, this should be considered only in difficult cases.

### RANULA

This term is applied to a retention cyst of the sublingual and occasionally of other salivary glands in the floor of the mouth. The retained saliva pushes up the mucosa of the mouth, giving it the appearance of a frog's belly. The occlusion of the sublingual duct may be caused by a plug composed of bacteria and many thread-forming organisms (*Leptothrix*) or by concretions of calculi (*sialolithiasis*) in the salivary ducts. A secondary infection or abscess formation occasionally occurs. Complete resection of the cyst wall is the only satisfactory method of treatment.

### MIKULICZ'S DISEASE

This is a term applied to bilateral, painless enlargements of the parotid and lacrimal glands of unknown etiology and usually associated with dryness of the mouth and an absence of tears. These manifestations may also occur as a syndrome in specific diseases such as tuberculosis, leukemia and lymphosarcoma.

JULIUS B. RICHMOND  
MAURY MASSLER  
ISAAC SCHOUR

### REFERENCES

- Beckman, A. J., and Navarro, J. E.: Pneumonia Complicating Oral Thrush Treated with Mycostatin, a New Antifungal Antibiotic. *J. Pediat.*, 46:587, 1955.
- Bigler, J.: Recurrent Suppurative Parotitis. *Tr. Chicago Pediatric Soc.*, Feb., 1945.
- Brown, J. B., and Fryer, M. P.: Diseases of the Mouth and Adnexa; in Brennemann, J., ed.: *Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 3, Chap. 1.
- Huebner, R. J., and others: Importance of Coxsackie Viruses in Human Disease. *New England J. Med.*, 247:249, 1952.
- Massler, M., and Schour, I.: *Atlas of the Mouth and Adjacent Parts in Health and Disease*. Chicago, Bureau of Public Relations of the American Dental Assoc., 1944.
- Pruzansky, S., and Richmond, J. B.: Growth of Mandible in Infants with Micrognathia. *A.M.A. Am. J. Dis. Child.*, 88:29-42, 1954.
- Richmond, J. B., Ed.: *Symposium on The Child's Mouth*. *Pediatric Clin. North America*, 3:845, 1956.
- Via, W. F., Jr., and Churchill, J. A.: Relationship of Cerebral Disorder to Faults in Dental Enamel. *A.M.A. J. Dis. Child.*, 94:137, 1957.



## TUMORS OF THE NECK

For other swellings of the neck, see Goiter (p. 1169), Diseases of the Lymph Nodes (p. 991), Tuberculosis (p. 466) and Mumps (p. 505).

### THYROGLOSSAL DUCT CYST

A thyroglossal duct cyst may be located anywhere from the base of the tongue at the foramen caecum to the isthmus of the thyroid gland along the course followed by this gland in its descent into the neck. Usually the duct atrophies; when it does not do so, a cystic swelling may appear superficially, usually in the midline of the neck just below the hyoid bone. The swelling usually develops before puberty as a painless, progressively enlarging, movable mass. The cyst moves upward when the tongue is protruded or during swallowing. The cyst may become infected during the course of an upper respiratory infection and may rupture spontaneously. Recurring inflammation or a discharging fistula cause the patient to seek medical attention. The discharge is intermittent and slight except when activated by infection. The cyst and the entire tract, including the midportion of the body of the hyoid bone, must be completely excised to the base of the tongue. Incision and drainage are at all times contraindicated.

### BRANCHIAL CLEFT CYST

(LATERAL CERVICAL CYST)

The branchial cleft cyst is found in the neck anterior to the sternocleidomastoid muscle, but, in contrast to the thyroglossal duct cyst, not in the midline. The branchial cleft cyst represents a remnant of a right or left branch of a branchial cleft. Although the cyst may not be recognized until adolescence, it or its anlage has been present since birth. It grows slowly, is oval-shaped and may become extremely large. It is usually smooth, fluctuant, moderately movable and may be attached to the skin.

The cyst is sometimes mistakenly diagnosed as an abscess and incised and drained. Injection of radiopaque substances into the fistula may reveal a tract opening into the tonsillar area, and the patient may complain of a bitter taste. Incision and drainage, curettage and the use of caustics only result in the establishment of a fistula. The cyst should be excised completely.

### CYSTIC HYGROMA COLLI

See page 1360.

JULIUS B. RICHMOND

### REFERENCE

Ward, G. E., and Hendrick, J. W.: *Diagnosis and Treatment of Tumors of the Head and Neck*. Baltimore, Williams & Wilkins Company, 1950.

## THE ESOPHAGUS

Symptoms suggestive of esophageal disease in infants and children are dysphagia, complete inability to swallow, pain on swallowing, regurgitation of undigested food or fluids, and hematemesis. The esophagus may be examined directly with the esophagoscope and roentgenographically. Barium is the usual contrast medium used for roentgen examinations unless a tracheo-esophageal fistula or a complete esophageal obstruction is suspected, when an iodized oil should be used to avoid aspiration of barium into the trachea or bronchi. An esophagoscopic examination can

be made without anesthesia at any age.

Table 86. Average Measurements of the Esophagus

Age	Teeth to Cricoid	Teeth to Bifurcation	Teeth to Cardia
Birth.....	7 cm.	12 cm.	18 cm.
1 year.....	9 cm.	14 cm.	21 cm.
3 years.....	10 cm.	16 cm.	23 cm.
5 years.....	11 cm.	17 cm.	25 cm.
10 years.....	12 cm.	19 cm.	27 cm.
15 years.....	14 cm.	23 cm.	33 cm.
Adult.....	16 cm.	25 cm.	40 cm.

## CONGENITAL ANOMALIES

The esophagus is developed from the first part of the primitive gut, its upper part from the retropharyngeal segment, and the lower from the pregastric segment. As the neck differentiates and the heart and lungs push the stomach caudad, the esophagus elongates rapidly. Vacuoles appear by the eighth week in the epithelium to form a lumen. During the fourth week the laryngotracheal groove develops to become the larynx and trachea and the primordia of the lungs. Two furrows course longitudinally along the sides of this respiratory primordium and cut inward deeper and deeper until they separate it from the esophagus. This separation progresses in a cephalic direction, the lung bud first becoming free. Congenital anomalies develop through a failure of one of these critical steps to be completed correctly, and vary from complete absence of the esophagus to duplication throughout its length.

### ATRESIAS AND FISTULAS

**Etiology.** Atresias are the most common of the congenital anomalies and result from failure of the pharyngeal and gastric outpouchings to unite or establish a satisfactory lumen. These defects may be due to a mechanical development deviation of the septum between the trachea and esophagus, or to altered cellular growth along the septum. Absence of growth along the septum results in a fistula to the trachea, and deficient growth of entodermal cells of the dorsal wall of the foregut results in atresia.

**Clinical Forms.** Of the four principal types of complete atresias (Fig. 186), the most common (90 per cent) consists of an upper segment which ends in a blind pouch about the level of the bifurcation of the trachea or slightly above it, and a lower segment from the stomach which is connected to the trachea by a short fistulous tract. The *symptoms* are characteristic. The first swallow or two by the newborn infant is normal; then suddenly the fluids return through the nose and mouth; the child coughs, struggles, turns cyanotic and may stop breathing. The cycle is repeated with each attempt at nursing, and between feedings there is a constant drooling from the dependent corner of the mouth. The stomach becomes distended with air, and bile and gastric secretion may be collected from

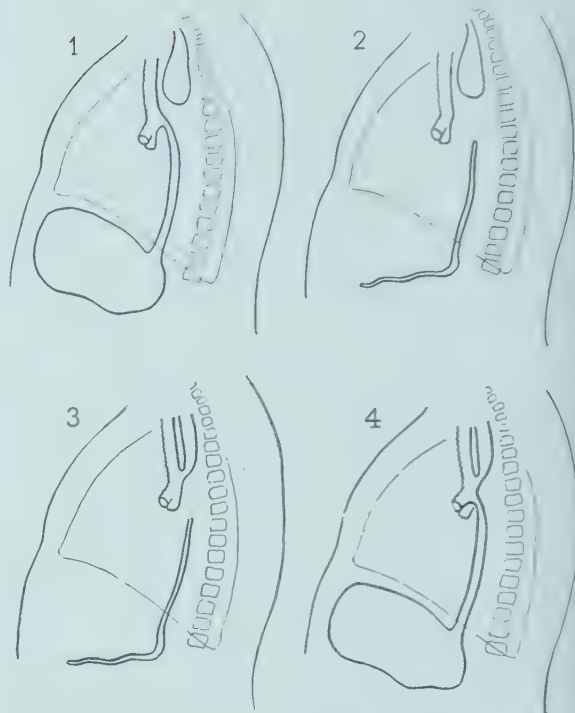


FIG. 186. Diagrams of the 4 most commonly encountered anomalies associated with congenital atresia of the esophagus in order of frequency. 1, (90%) Upper blind sac, lower esophageal segment communicating with the trachea to permit air to enter the stomach. 2, Both upper and lower esophageal segments are blind. No air enters the stomach; this is of considerable clinical significance and is apparent on the roentgenographic film, since no gas is visible below the diaphragm. 3, Upper segment communicates with the trachea, lower segment blind. Asphyxia usually occurs with the first attempt at feeding. 4, Both upper and lower segments communicate with the trachea.

the regurgitated material, owing to the fistula between the lower segment and trachea.

In the second commonest type both segments are blind, neither being connected to the air passages. The *symptoms* are like those of the first type, but the roentgenogram shows an opaque abdomen devoid of the usual gas bubbles in the stomach and intestines. Since no gastric juice can enter the tracheobronchial tree, the pulmonary symptoms are produced entirely by overflow of milk and saliva from the esophagus, so that postural drainage and catheter or bronchoscopic suction of the trachea are effective in clearing the obstruction. The lower segment is often rudimentary, and generally primary anastomosis is difficult to accomplish.

In the third type the upper segment opens into the trachea, and the lower is a blind pouch. In this type the infant may "drown"



with the first feeding, or a fatal aspiration pneumonia develops within a day or two.

*Tracheo-esophageal fistula without atresia*, the so-called H type (Type 4, Fig. 186; Fig. 187), is a relatively rare but important anomaly. It may be suspected in infants who show signs of respiratory embarrassment, and choking and coughing associated with feedings. There is usually gastric distention. There may be excessive amounts of mucus in the oropharynx, and repeated episodes of pneumonitis are common. The diagnosis is established endoscopically and roentgenographically by using contrast media; techniques have been described (see References). The fistula may be found at any point from the level of the cricoid cartilage to the mid-esophagus. The opening is usually at a higher level in the trachea than in the esophagus. Treatment is surgical.

**Diagnosis.** The diagnosis of congenital atresia is evident from the difficulty in swallowing, choking, cyanosis or regurgitation with the first or second swallow of food, and may be confirmed by roentgenologic, catheter or esophagoscopy evidence of atresia. Iodized oil rather than barium should be used as the contrast medium for roentgenologic studies to avoid the danger of aspiration of barium. One-half cubic centimeter given by mouth with a medicine dropper is adequate for diagnostic purposes.

The roentgenogram taken in the upright position shows the round blind end of the esophagus at the level of the tracheal bifurcation, or it may demonstrate the fistulous tract into the trachea or the absence of air below the diaphragm, depending on the type of malformation (Fig. 186).

**Treatment.** Most of the malformation can be corrected surgically. The success of operation is dependent on early diagnosis, before bronchopneumonia, dehydration and inanition have progressed to an irreversible degree. The transpleural approach rather than the extrapleural one is recommended for ligation of the fistula and anastomosis of the esophageal segments. Some surgeons perform a gastrostomy more or less routinely as a part of the procedure to permit early feeding and to avoid reflex flow of gastric secretions. When a gastrostomy is not performed, a polyethylene tube is passed through the esophagus into the stomach for the purpose of feeding. The condition of the lower segment occasionally does not permit establishing a satisfactory lumen, since its lumen may be

too contracted or too short. In such cases the cardia is ligated, a gastrostomy is performed, and the upper segment is exteriorized to avoid the otherwise inevitable aspiration pneumonia.

Adequate preoperative and postoperative management is essential for successful outcome. The operation should be deferred until the infant's condition is deemed satisfactory. The following preoperative factors are considered important: (1) preliminary broad-spectrum antibiotic therapy for the prevention or treatment of pneumonia; (2) constant drainage of the upper esophageal pouch through an indwelling catheter, the tip of which should be maintained just above the lower end of the pouch; (3) maintenance of the infant in an upright position to avoid reflux of gastric juice into the trachea and lungs; (4) parenteral administration of water and calories, preferably by slow, continuous intravenous drip of 5 to 10 per cent glucose solution in water (no saline solution is required during the first two or three days); (5) strict isolation technique (an Isolette is ideal and also permits maintenance of an increased oxygen concentration when necessary); (6) constant nursing supervision and care. Immediately before operation a cannula

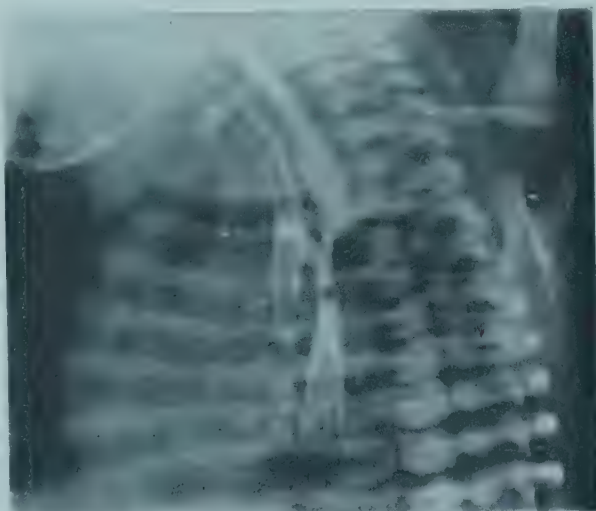


FIG. 187. Tracheo-esophageal fistula without esophageal atresia. The infant was born prematurely; birth weight was 3 pounds 14 ounces. Respiratory distress appeared soon after birth and was progressive; it was accentuated when liquids were swallowed. The possibility of esophageal atresia was eliminated by passing a catheter into the stomach. The large fistula was demonstrated after the tip of the catheter had been positioned in the upper esophagus and contrast material introduced through it. There is slight narrowing of the esophagus at the site of the fistula.

should be placed in a vein for administration of blood during the operation and of water, electrolytes and calories for a day or two postoperatively. Bronchoscopic aspiration may be required preoperatively or postoperatively if atelectasis persists. Right upper lobe atelectasis is a common associated finding.

Postoperatively, the infant should be placed in an oxygen tent or enclosed incubator. Feedings through the gastrostomy tube or through the esophageal-passed polyethylene tube may be started in two or three days. The first two or three feedings should consist of 0.5 per cent physiologic saline solution and then of 5 per cent glucose solutions. If these solutions are tolerated, a milk formula of gradually increasing strength may be given. Oral feedings are usually tolerated eight to ten days after the operation. Prophylactic antibiotic therapy should be continued for five to six days postoperatively.

Stenosis at the operative site is not uncommon. At times the diagnosis is delayed because the diet is entirely liquid. Fluoroscopic studies of the esophagus will establish the diagnosis; early esophageal dilatations of the soft stenosis at the point of anastomosis are more successful in maintaining a satisfactory lumen than later dilatations of fibrous scars.

### SHORT ESOPHAGUS

This anomaly consists of a short esophagus with a portion of the stomach displaced upward through the diaphragm into the thoracic cavity. Occasionally, temporary obstruction by a foreign body leads to a roentgenologic study which reveals a stricture in the mid-thorax. This stricture is at the cardia in the midthorax with the short esophagus above it and true gastric mucosa with rugae below. These rugae can be followed through the diaphragm as a continuation of the rugae of the subdiaphragmatic stomach. The fact that the cardia becomes stenotic accounts for the symptoms. A partial thoracic stomach is more frequent than is generally supposed, and though it is a frequent cause of vomiting, there is often no stricture. It has been suggested that the stricture may be the result of reflux of gastric contents due to an incompetence of the gastroesophageal mechanism as described under *Chalasia*. The clinical picture is characterized by dysphagia, regurgitation, malnutrition and frequent attacks of complete obstruction of the esophagus.

**Treatment.** When there is no evidence of stricture, treatment consists in propping the

infant in an erect position after feeding, as described for *chalasia*. When there is stenosis, repeated dilatations are indicated, the lesion is peculiarly resistant to therapy, and occasionally one must resort to gastrostomy and retrograde dilatation. Ulcers in the supra-diaphragmatic stomach should be treated in a manner similar to other gastric ulcers.

### STENOSIS

Congenital stenosis of the esophagus without fistula formation can be found at any point along the esophageal lumen as either a web or a long segment of esophagus with only a threadlike lumen. The *symptoms* are those of esophageal obstruction, usually first apparent when the infant begins to eat semi-solid or solid food. *Diagnosis* is made by roentgenologic and esophagoscopy examinations. The *treatment* is esophagoscopy dilatation. These strictures respond more readily than does that of a congenitally short esophagus.

### EXTERNAL COMPRESSION

Obstruction of the esophagus may be caused by compression from congenital cardiac or vascular anomalies and by mediastinal tracheal or bronchial cysts. A double aortic arch (vascular ring), anomalies of the subclavian vessels and occasionally a patent ductus arteriosus may cause dysphagia. Barium fluoroscopic studies of the esophagus and recognition of both esophageal and tracheal compression by esophagoscopy and bronchoscopy assist in establishing the diagnosis. Angiocardiography is of value in questionable cases in which symptoms are severe. *Treatment* consists in surgical relief of the obstructive phenomenon.

### NEUROGENIC SWALLOWING DYSFUNCTION

Congenital anomalies of the medulla or cerebral birth injuries occasionally result in a complete lack of nervous stimulation of the muscles of deglutition. The infant is unable to swallow, and food and mucus constantly fill the pharynx and trachea. Esophagoscopy, gavage and roentgenograms show the esophageal lumen to be entirely patent. Similar symptoms occur in extreme cases of *amyotonia congenita* and *bulbar poliomyelitis*. Death usually results from aspiration pneumonia.

**Treatment.** Postural drainage and constant aspiration of mucus are necessary to prevent aspiration pneumonia. Feedings must be entirely by gavage or gastrostomy.



## CARDIO-ESOPHAGEAL RELAXATION

## (CHALASIA)

This clinical syndrome consists in vomiting following feeding when the infant is in the horizontal position. The vomiting is the result of persistent relaxation of the lower end of the esophagus. The *etiology* appears to be varied, but in most instances is not demonstrable. The course is most often limited, and for this reason chalasia has often been assumed to be the result of a temporary neuromuscular imbalance. In one instance chalasia was observed in an infant with a hemangioma at the cardia; in other instances in which vomiting has been persistent it has been associated with cerebral defects.

The vomiting begins within a few days after birth, is more or less effortless, and can usually be avoided if the infant is maintained in the erect position. Vomiting may occur during the feeding, but usually begins after the infant has been returned to the crib. In unrecognized and hence untreated cases the infant loses weight and becomes dehydrated. It may be that an occasional instance of rumination is the result of chalasia.

The *diagnosis* is established by observing the swallowing of barium under the fluoroscope. Persistent relaxation of the esophageal hiatus is observed with retrograde filling of the esophagus during inspiration or with increase of intra-abdominal pressure.

*Therapy* consists in feeding a relatively thick milk formula mixture and in maintenance of the infant in an erect (propped sitting) position for two or three hours after feedings. Permanent relief is usually obtained after a month or two of such management.

## ACQUIRED DISEASES

## ESOPHAGITIS

Acute esophagitis may complicate practically any acute infectious disease; it may be associated with inflammation of other parts of the digestive tract or may follow lacerations produced by swallowing of foreign bodies or injuries caused by ingestion of hot liquids. The lesions generally last but a few days, and the prognosis is favorable. Symptoms may be substernal pain on swallowing, dysphagia and hematemesis, or they may be entirely absent. However, some benign esophageal strictures seen in later life originate from acute esophageal ulcers associated with infectious diseases in childhood.

Chronic esophagitis is not rare in early life. It may follow an acute process or be the result of venous congestion in chronic pul-

monary or cardiac disease. Most commonly it is associated with congenital stricture or with a short esophagus.

Other infrequent causes of secondary esophagitis include diphtheria, thrush, variola, and varicella, perforation by a caseous lymph node and ulcers associated with cerebral lesions. Recognition is often impossible during life.

*Inflammatory strictures* may follow any of the conditions mentioned as esophagitis. *Symptoms* and *treatment* are those of corrosive strictures. The *diagnosis* must be established from the history and from the roentgenologic and esophagosopic appearances.

## CORROSIVE STRICTURES

The most common type of stricture of the esophagus follows ingestion of some caustic such as lye, Clorox, Drano or ammonia, or acids such as nitric or muriatic (used in soldering pastes). Even lactic acid, when given by mistake in full strength, will cause stenosis. The lesions vary from superficial pharyngitis and esophagitis to ulceration and necrosis of the esophageal or gastric wall, with a chemical mediastinitis or peritonitis which may result in death in a few hours.

**Clinical Manifestations.** When a child swallows lye, the first mouthful causes intense burning and pain, making further swallowing impossible, but the damage has already been done. The lips, chin, tongue and pharynx become edematous and covered with exudate, and similar changes occur in the esophagus. If death does not occur within the first few hours or days, the edema subsides, and swallowing may be resumed. In many instances the swallowing function returns to normal in two to four weeks. Though the ensuing period may be symptomless, it is a latent period, and a stricture usually develops within weeks or months.

Difficulty in swallowing recurs insidiously, increasing in severity over several months as strictures develop in the burned areas. At first the child has difficulty in swallowing solid food. Eating becomes slow, food is frequently regurgitated, and, later, difficulty in taking liquids becomes apparent. Often the child is considered a "feeding problem" because the accident has been forgotten and the dysphagia is so gradual in its progress. Roentgenograms then reveal strictures of the esophagus, most pronounced in the areas of anatomic narrowing: the cervical region, the cardia, and the point at which the left bronchus crosses the esophagus. Children with long-standing esophageal strictures have num-

erous evidences of nutritional deficiencies.

**Treatment.** Treatment immediately after ingestion of a caustic consists in administration of its antidote in dilute form. To administer a strong acid solution in an effort to neutralize a strong alkali adds to the injury. Olive oil applied to the denuded surface areas and administered by mouth, and analgesics administered intramuscularly are needed to relieve pain.

Gastric lavage is contraindicated because of the danger of esophageal or gastric perforation. In most instances it will be necessary to feed the child intravenously initially. A gastrostomy or jejunostomy may be necessary for continued feeding in the acute phase. A gastrostomy with the tube directed toward the cardia is most satisfactory, since this facilitates subsequent dilatation. Severe burns from ammonia or by other means occasionally cause laryngeal edema which may be obstructive enough to necessitate a tracheotomy.

The main problem in the treatment of caustic burns of the esophagus is the prevention of strictures. The Salzer technique of early management should be used in all instances of caustic esophageal burns no matter how slight the burn may appear. The technique consists in the passage of graduated shot- or mercury-filled bougies daily for two weeks, beginning twenty-four to forty-eight hours after the accident, and then gradually increasing the interval between dilatations to twice a week, once a week, once in two weeks, once a month and finally one dilatation a year for several years. Dilatations may be begun with a no. 16 French mercury-filled bougie and gradually increased to a no. 30 or 32 bougie in a small child. There is almost no danger of perforation of the esophagus by this method.

Corticosteroid therapy in conjunction with a broad-spectrum antibiotic, begun shortly after the swallowing of lye and continued for approximately ten days, has some therapeutic value in cases of severe burns. Prolonged use with high doses, however, has been associated with esophageal and gastric perforations. Further clinical investigation is needed to determine the relative efficacy of this therapy.

In the absence of early treatment, stricture formation or actual atresia may become apparent within two to four months; in some instances many years elapse before the stricture becomes severe enough to produce dysphagia. The generally accepted method of

treatment of definitely formed strictures consists in esophageal dilatations which may be guided by a swallowed string, or visually through an esophagoscope. If the stricture is extremely tight, retrograde dilations are preferred, the bougies being guided by a string advanced through a gastrostomy. When complete atresia of the esophagus follows ingestion of a caustic, endoscopic efforts at recannulization are generally successful, but occasionally external surgical procedures must be considered. Replacement of the esophagus by a section of colon or small bowel is preferred to resection of the stricture and gastroesophageal anastomosis.

#### SPASM OF THE ESOPHAGUS

Esophagospasm, including cardiospasm, may be present even in newborn infants. Esophagospasm is usually characterized by severe sudden obstruction to swallowing and reverse peristalsis and is usually initiated by emotional stress. *Cardiospasm* (achalasia, pre-ventriculosis) is the syndrome of nonorganic obstruction of the cardia associated with dilatation and hypertrophy of the esophagus. It is generally considered to be a failure of coordination of the mechanism at the cardia, preventing normal passage of food from the esophagus to the stomach. In long-standing cases there is fibrosis and disorganization of musculature of the lower end of the esophagus.

**Clinical Manifestations.** These are difficulty in swallowing, regurgitation of undigested food and fluid, cough from overflow of fluids into the larynx, especially at night, and failure to gain or loss of weight. The diagnosis is made by fluoroscopy or roentgenograms, which demonstrate the barium column in the dilated esophagus terminating in a fine point as it approaches the diaphragm.

**Treatment.** In uncomplicated cases treatment consists in dilatations of the cardia by a pneumatic bag accurately placed under fluoroscopic guidance, by a Hurst mercury bougie, by an esophagoscope or by string-guided olive-tip bougies. Psychotherapy should be considered. In advanced cases retention of food and fluids produces esophagitis, periesophageal inflammation and fibrous strictures at the cardia. Bronchiectasis may be an associated condition due to the constant overflow of food from the esophagus into the larynx and bronchi. Surgical intervention may become necessary in extreme situations; such procedures as an esophagocardial myotomy (similar to the Fredet-Ramstedt opera-



tion for pyloric stenosis) or an esophagogastrostomy may give permanent relief. Unfortunately, however, reflux esophagitis often leads to a recurrence of the symptoms and of the stricture itself, necessitating a return to dilatations or reoperation. Belladonna derivatives may be of some benefit if administered early, but are apparently of no avail in advanced cases.

### ESOPHAGEAL VARICES

Esophageal varices may occur in children with portal hypertension (Banti's disease) (p. 986) as one of the evidences of the attempt to return blood to the heart by circumventing the liver. The principal symptoms of the varices are recurrent, profuse hematemesis of bright red blood, tarry stools and systemic signs of severe hemorrhage. Careful roentgen studies with barium may outline the varices. Their presence may be confirmed by esophagoscopy examination.

**Treatment.** Treatment of portal hypertension is discussed elsewhere. Acute hemorrhage may at times be controlled by some form of tamponade. The varices may be injected with sclerosing solutions, special long needles being used through the esophagoscope. These procedures are palliative in most instances, but prolong life, reducing the number and severity of the hemorrhages.

### RETROESOPHAGEAL ABSCESS

The most frequent cause of retroesophageal abscess is extension of a retropharyngeal abscess downward to the retroesophageal component of this single, potential space; other causes are esophageal perforations, foreign bodies, spinal caries, pleuritis, pericarditis, ulceration from an intubation or tracheotomy tube, diphtheria of the pharynx or suppurating mediastinal lymph nodes. The abscess forms behind and around the esophagus and often displaces it to one side, while at the same time it compresses the more firmly seated trachea.

The symptoms are dyspnea, brassy cough, dysphagia and, as the trachea is pushed forward, swelling of the neck. Toxemia, pain, tenderness on palpation of the neck, and cervical emphysema may be present. The increased retrotracheal space can be demonstrated on lateral roentgenograms of the neck without the use of contrast medium. With its use distortion of the esophagus may be demonstrated; but if the abscess is due to esophageal perforation, barium is contraindicated.

**Prognosis.** Recovery is possible. The ab-

cess may rupture into the pleura, trachea or lung. Death may result from pressure of the abscess upon the vagus nerve or on the trachea with consequent asphyxia, or by an erosion into the great vessels of the neck with exsanguinating hemorrhage.

**Treatment.** Prompt surgical drainage is indicated. If the abscess is high, the retroesophageal space may be opened in the neck along the anterior border of the sternocleidomastoid muscle. Drainage here is effective to the level of the fourth dorsal vertebra. In retroesophageal abscesses occurring below this point a posterior mediastinotomy is generally indicated. In either instance broad-spectrum antibacterial therapy should be used. It should be recognized that such therapy could mask an advancing mediastinal infection, and only repeated lateral roentgenograms of the neck and chest will indicate the situation in the post-tracheal area.

### FOREIGN BODIES IN THE ESOPHAGUS

Infants and children swallow an unlimited variety and number of inedible objects which in most instances reach the stomach and pass through the gastrointestinal tract without complications. Occasionally they lodge in one of the three anatomically narrow points of the esophagus, from which they must be extracted.

The point of lodgment of most foreign bodies is the cervical esophagus, immediately below the cricopharyngeus muscle (Fig. 188). Here the musculature is weak in comparison with the strong muscles immediately above. The narrowing at the hiatus of the diaphragm and the cardia constitutes the second most common site for the lodgment of foreign bodies, although few lodge there. The third and infrequent site for lodgment is the normal narrowing of the esophagus at the level of the arch of the aorta.

Strictures of the esophagus, congenital or acquired, are often responsible for the lodgment of foreign bodies which would pass through the normal esophagus. Open safety pins are found most frequently in infants seven to fifteen months of age, and coins, small toys, buttons, marbles and jackstones in children from three to six years.

**Clinical Manifestations.** Initial symptoms of coughing, gagging, choking and dyspnea usually occur with ingestion of an object, no matter where it lodges. If it remains in the esophagus, pain localized in the region of the thyroid cartilage, dysphagia and drooling may

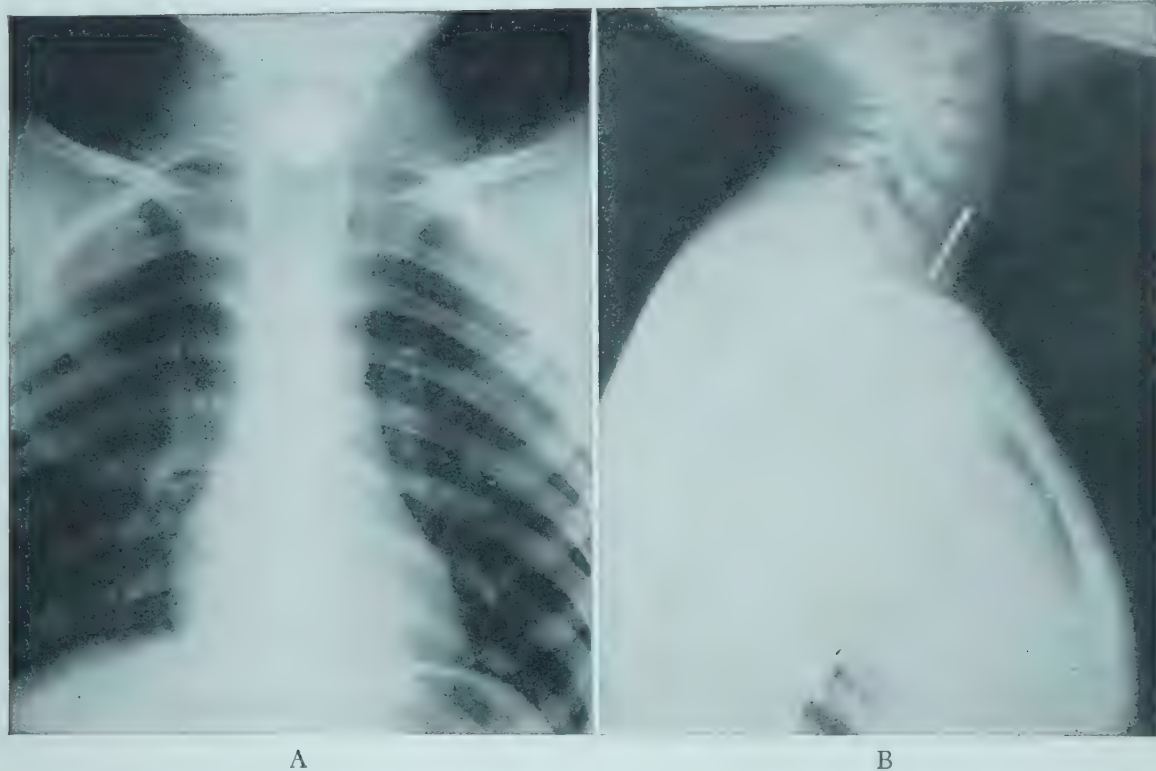


FIG. 188. Foreign body (penny) in the cervical esophagus. A, Anteroposterior and, B, lateral views show the penny in the location in which 75 per cent of foreign bodies in the esophagus are found.

follow. Once a foreign body becomes fixed, there is frequently a symptomless interval until edema around the foreign body produces evidence of obstruction, or until signs of infection resulting from esophageal perforation become evident.

Laryngeal symptoms may be produced by foreign bodies in the cervical esophagus. Dyspnea resulting from compression of the trachea may be severe enough to require a tracheotomy before the foreign body can be removed. This is especially true of marbles or jackstones. Cough and hoarseness follow obstruction of the cervical esophagus because of the irritation from secretions overflowing into the larynx. Similar symptoms occur if the foreign body erodes through the party wall.

**Diagnosis.** The diagnosis of a foreign body in the esophagus is most frequently made from the history. The child, if old enough, may state that he swallowed a button or coin, or the mother may state that the child placed some object in his mouth and choked on it. A history of difficulty in swallowing or the refusal of a child to take solid or liquid food suggests an esophageal foreign body.

When the history or symptoms suggest the possibility of a foreign body, a complete search of the gastrointestinal tract as well

as of the respiratory system must be made in an effort to locate the object. Fluoroscopic examinations and roentgenograms of the cervical esophagus, with the introduction of radiopaque media, if necessary, and of the chest and the abdomen in the anteroposterior and lateral projections are indicated.

**Treatment.** Only one type of treatment of foreign bodies in the esophagus should be considered: removal under direct vision through the esophagoscope. The use of blind instrumentation with attempts to force the foreign body into the stomach or attempted extraction by means other than by direct vision is liable to lead to esophageal perforation, mediastinitis and death. Attempts to force the foreign body into the stomach with dry bread, cabbage, cotton or roughage diets are irrational and not infrequently necessitate the removal of this material as well as of the foreign body. Such procedures may also wedge the foreign body more firmly into the esophageal mucosa.

PAUL H. HOLINGER

#### REFERENCES

- Berenberg, W., and Neuhauser, E. B. D.: Cardioesophageal Relaxation (Chalasia). *Pediatrics*. 5: 414, 1950.
- Carré, I. J., Astley, R., and Smellie, J. M.: *Minor De-*



- grees of Partial Thoracic Stomach in Childhood. *Lancet*, 2:1150, 1952.
- Herweg, J. C., and Ogura, J. H.: Congenital Tracheo-esophageal Fistula with Esophageal Atresia. *J. Pediat.*, 47:293, 1955.
- Holinger, P. H., Johnston, K. C., and Potts, W. J.: Congenital Anomalies of the Esophagus. *Acta Oto-Lar.*, Suppl. 100 (1952).
- Holinger, P. H., Johnston, K. C., Potts, W. J., and da Cunha, F.: The Conservative and Surgical Management of Benign Strictures of the Esophagus. *J. Thoracic Surg.*, 28:(Oct.) 1954.
- Ray, S. R., and Morgan, D. L.: Cortisone Therapy of Lye Burns of the Esophagus. *J. Pediat.*, 49:394, 1956.
- Sieber, W. K., and Girdany, B. R.: Tracheo-esophageal Fistula without Esophageal Atresia—Congenital and Recurrent. *Pediatrics*, 18:935, 1956.

## THE GASTROINTESTINAL TRACT

### DIGESTIVE DISTURBANCES

Gastrointestinal disturbances may have their origin from lesions in the digestive system or may reflect disturbances of other systems of the body. Since such symptoms as anorexia, vomiting, diarrhea, are frequent complaints in pediatric practice, they are considered separately.

#### ANOREXIA

At all ages anorexia is an accompaniment of acute febrile diseases and is frequently present in chronic diseases. Allergy to specific foods is an occasional factor, although children may be fond of foods to which they are allergic. Long-continued undernutrition may be a result of anorexia and in turn may become a cause of it; in such instances the anorexia is difficult to overcome. Anorexia is also a symptom of specific nutritional deficiencies.

**Feeding Habits.** As a persistent symptom, anorexia arises frequently from faulty feeding habits. In the first year of life this condition results from a number of factors, including attempts at forced feeding and too frequent feeding. It is common in children in the age range of three to five years. Too great supervision of the child's eating habits may result in antagonism and detract from the pleasure of eating to such a degree that anorexia becomes persistent. The failure of parents and even of physicians to recognize that the growth rate decelerates rapidly in late infancy and early childhood is often responsible for attempts to force eating in order to maintain the rapid gain in weight of early infancy.

Failure to recognize that children's appetites may vary from meal to meal or from day to day is also frequently responsible for antagonism toward eating. Moreover, the gastric capacities of children of the same age

vary, as do their caloric needs, and parents may err in attempting to make all children conform to a single pattern. Refusal to eat, in some instances, is the child's means of attracting attention or maintaining a position of authority within the family group. Poor feeding habits of other members of the family are also frequently reflected in children. This applies not only to special food dislikes, but also to total intake.

**Nervous Excitement.** Anorexia resulting from nervous excitement or tension is as frequent among children as among adults. When this condition is persistent, the term "anorexia nervosa" (see p. 89) is used to describe it. It is important to recognize that temporary aversion to food is common to practically all children during periods of great excitement or emotional stress and varies only in degree. Emotionally unstable children frequently reflect behavior patterns of their parents, and in other instances emotional disturbances are accentuated and prolonged by the interference of adults. Tension at mealtimes between other members of the family or tense situations which directly involve the child are frequent causes of poor eating habits. In older children worries and anxieties which have their origin outside the home must be considered in the evaluation of persistently poor eating habits. Insufficient time for meals, fatigue resulting from too great activity or too little rest, and unattractive meals are other factors which must be considered.

#### VOMITING

Vomiting is such a common symptom in children that it often excites little concern. The "spitting up" or regurgitation by infants after feeding, or the occasional vomiting of infants and children, may not have serious conse-

quence, but persistent vomiting has. Not only may it reflect some serious underlying disturbance, but also it may be responsible for sufficient loss of body fluids and electrolytes to produce dehydration and alkalosis. Failure to retain food may be responsible for the ketosis of starvation. In all instances an attempt should be made to understand the cause of vomiting so that proper remedial measures may be instituted.

**Vomiting by the Newborn Infant** (pp. 330, 665). If vomiting is persistent, one should think especially of congenital obstructive anomalies of the alimentary canal, irritation of the stomach from swallowed amniotic contents, and intracranial birth injuries.

**Faulty Feeding of Infants.** Vomiting resulting from improper feeding techniques or improper diets is discussed on page 130. The vomiting of overfeeding usually occurs shortly after feeding, as does that of failure to eruct swallowed air. This type of vomiting is more properly termed "regurgitation" and is principally a nuisance. Other factors which must be considered in regurgitation are too tight clothing, especially about the abdomen, and the placement of the infant on his back or left side immediately after feeding instead of on his abdomen or right side.

**Acute Infectious Diseases.** Vomiting is a common initial symptom.

**Acute Gastric Indigestion.** This type of vomiting is frequent among children. It results from overeating, especially of foods whose digestion is naturally prolonged, and from eating during nervous excitement.

**Acute Gastrointestinal Diseases.** These diseases include the various diarrheal disturbances. Vomiting is a serious symptom, owing to the additional loss of water and electrolytes and because oral administration of fluids is not possible.

**Pyloric Obstruction.** Vomiting from this cause has a characteristic pattern (p. 658).

**Intestinal Obstruction** (p. 665). The vomiting of intestinal obstruction is persistent. Unless the obstruction is relieved, the vomitus contains intestinal contents, the nature depending upon the level of the obstruction.

**Acute Peritonitis.** In contrast to chronic peritonitis, vomiting is practically a constant accompaniment of acute peritonitis and in the late stage is due to paralytic ileus.

**Appendicitis.** Vomiting is an early symptom in acute appendicitis; it becomes manifest again when the appendix ruptures. It is

greater with generalized peritonitis than with a localized abscess.

**Organic Nervous Disease.** Vomiting is an early symptom of acute meningeal disturbances and may be persistent when the infection is not controlled. Space-taking intracranial lesions such as neoplasms, abscesses and hemorrhages frequently are responsible for vomiting, which characteristically is projectile in type, aggravated by change in position as in arising in the morning and unassociated with nausea. It may, however, be nonprojectile and associated with nausea.

**Toxic Vomiting.** This is an unsatisfactory designation, which is used for vomiting from such causes as uremia, diabetic acidosis and certain poisons, such as apomorphine, tartar emetic and digitalis, which presumably stimulate the vomiting center. The vomiting that often occurs in the initial stages of acute infectious diseases and in the late stages of diphtheria and typhoid fever is also probably of this order. A similar mechanism may explain the vomiting.

**Reflex Vomiting.** Vomiting may be initiated by conditions which stimulate the gag reflex, such as a copious postnasal drip, enlargement of the uvula, persistent or spasmodic cough such as that of pertussis, and gagging on food. This last is common in infants who have been started too early on solid food or whose introduction to it has been too long delayed. Some children have exceptionally sensitive gag reflexes, and vomiting may be induced by slight provocation.

**Nervous or Habit Vomiting.** Nervous or habit vomiting is seen in neurotic children and is excited by emotional disturbances of all sorts. Carsickness, seasickness and the vomiting following swinging may in many instances be placed in this category, although the possibility of a relationship to visual and aural disturbances must not be disregarded.

**Other Causes of Vomiting.** Gastrointestinal allergy, anesthesia, especially that induced by ether, operative manipulation of the abdominal organs, the swallowing of caustic poisons (esophageal stricture) and adrenal insufficiency in early infancy may all be causes of vomiting.

When vomiting occurs before breakfast and is associated with nausea and a sense of faintness, the possibility of *hypoglycemia* should be considered.

**Treatment of Vomiting.** Vomiting should in all instances be considered a symptom, and principal attention should be directed to



determination and then correction of the cause. When considerable amounts of water and electrolytes have been lost and there is ketosis, parenteral fluid therapy (p. 186) may be necessary. Occasionally, when vomiting is persistent, an attempt to control it by drug therapy may be justified. At present, principal interest in this respect is centered in the phenothiazine group of drugs, such as chlorpromazine (Thorazine, p. 226), promazine (Sparine) and promethazine (Phenergan, p. 223), all of which can be given in rectal suppositories.

## RUMINATION

### (MERYCISMUS)

**Etiology.** Infants occasionally expel gastric contents by a series of movements analogous to those made in rumination by cattle. Rumination usually occurs in young infants, but is rare at any age. The cause is not understood; perhaps in most instances it is due to a disturbed parent-infant relationship, and particularly to a lack of affectionate care.

**Clinical Manifestations.** The symptoms are repeated regurgitations of small amounts of food, which usually begin a half-hour or so after feeding. Rumination may be observed after all or only some of the feedings. Some of the regurgitated food may be promptly swallowed again, some may be lost from the mouth, and some may be held in the mouth or pharynx for a time. The return of food from the stomach is preceded by peculiar but characteristic chewing movements, with the tongue pushed forward within the oral cavity. Sometimes the infant starts the procedure by putting his fingers or other objects into his mouth. Both breast-fed and artificially fed infants are affected, and the kind of food seems to have little influence, although some infants will retain solid food, such as thick cereal, but ruminate liquids.

**Diagnosis and Prognosis.** The diagnosis is usually obvious from the nature of the act, and rumination is not likely to be confused with cardiospasm, pylorospasm, esophageal stricture or achalasia, although such conditions might be associated with it. The prognosis depends on the severity of the condition and on the possibility of establishing satisfactory environmental conditions for the infant. Death has occurred from extreme emaciation.

**Treatment.** Many therapeutic techniques have been used, but one may doubt whether any of them have been really successful.

These have included the use of thickened feedings and restraining devices such as a tightly fitting cap with a strap which passes under the jaw and prohibits opening of the mouth. The suggestion of Richmond to provide psychotherapy for the mother and an abundance of affectionate care for the infant would seem to be much more appropriate.

## RECURRENT VOMITING

### (CYCLIC, PERIODIC OR ACETONEMIC VOMITING)

**Etiology.** This condition, characterized by irregularly recurring attacks of vomiting of several days' duration associated with ketosis, is a syndrome and not a disease entity. There is no adequate explanation for the attacks, although they seem to be more frequent in emotionally unstable children than in phlegmatic ones. The incidence is higher in private than in clinic practice, with a relatively large percentage of the cases among the so-called intelligentsia. There is frequently a family history of migraine. Attacks usually begin early in childhood, rarely in infancy, and recur at intervals ranging from a month or two to two or three attacks a year. There is often some initiating factor such as fatigue, emotional excitement or onset of an acute infection, but at times there is no apparent "trigger mechanism." Millichap suggests that cyclic vomiting may be a form of epilepsy.

There is no evidence that these children have any inability to burn sugar. The greater readiness in all children in comparison with adults to develop ketosis during periods of glycogen depletion explains the rapidity with which ketosis develops with persistent vomiting. The fact that the vomiting can usually be controlled by sedation favors a neurogenic basis rather than a metabolic defect.

**Clinical Manifestations.** The onset of an attack may be sudden, with vomiting from the first, or there may be a prodromal period of hours or a day during which there is malaise, irritability, anorexia, abdominal discomfort, coated tongue, and constipation. The initial vomitus consists of ingested food, but it soon becomes mucoid, then bile-stained, and often blood-stained or brownish. Vomiting is often forceful, with much retching, and occurs whenever anything is swallowed and even when no food or liquid is taken. There is little or no fever unless the attack has been initiated by an acute infection. Thirst is great, headache and abdominal pain are frequent, and obstinate constipation is the rule.

The abdomen is usually retracted, rarely distended, and at times there is tenderness. As the attack continues, prostration may become extreme, there is an anxious expression of the face, the eyes are sunken, there is an odor of acetone on the breath, and the urine, which is scanty, contains ketones and often albumin. Hemoconcentration may be responsible for an apparent increase in nonprotein nitrogenous constituents.

**Diagnosis.** Diagnosis is based on a history of previous attacks and the onset of persistent vomiting without apparent cause. The vomiting may be responsible for an alkalosis, but in protracted cases this may be counterbalanced by the ketosis and by retention of other acid metabolites, when hemoconcentration is sufficient to be responsible for a decrease in renal function. Appendicitis, intestinal obstruction and other organic causes of vomiting must be eliminated in the differential diagnosis. Occasionally a child with recurrent spontaneous hypoglycemia may be incorrectly thought to have recurrent vomiting.

Every effort should be made to determine the underlying cause or "trigger mechanism" for the individual attacks; the child should have an electroencephalogram to test the possibility of epilepsy as the etiologic factor. There should also be a psychologic evaluation of the child and his family.

**Prognosis.** In spite of the extreme prostration frequently present, the convalescent period is short. As a rule, attacks become less frequent during the latter part of childhood and disappear at or before puberty. Migraine may be a sequel during later life.

**Treatment.** Treatment is directed toward control of the vomiting and correction of the ketosis. Food and liquid by mouth should be discontinued in severe cases, and only cracked ice given to alleviate the dryness of the mouth. In milder cases, sips of glucose water or ginger ale may be permitted if they do not increase the vomiting. The two most important measures are parenteral administration of glucose and saline solution, and sedation. The vomiting can be controlled in the majority of instances by hypodermic injection of sodium phenobarbital. Chlorpromazine or one of the other phenothiazines might also be administered in a rectal suppository. Neither should be administered until the possibility of a surgical lesion has been eliminated.

Specific physical defects should be corrected, the nutritional status should be im-

proved, and, when necessary, psychiatric treatment should be provided.

### EPIDEMIC NAUSEA AND VOMITING

**Etiology.** The occurrence of mild respiratory infection in association with nausea, vomiting and, at times, diarrhea in epidemic outbreaks has suggested to some that this clinical pattern may represent a disease entity. The infection is presumed to be a viral one, but it would be surprising should there prove to be a single etiologic viral agent. Varying degrees of gastrointestinal symptoms are not uncommon in epidemic viral infections of the upper respiratory tract. Such manifestations are as a rule more common and more pronounced in infants and children than in adults.

**Clinical Manifestations.** Vomiting is a more constant symptom among children than among adults, who often complain only of severe nausea. The onset is abrupt, and the vomiting is often projectile. The urgency may be so great that a child who has been otherwise well is unable to leave the room before vomiting occurs. Nausea is usually a consistent manifestation. There is often a sense of dizziness, and even a feeling of faintness. Frontal headache and abdominal discomfort are common symptoms. Diarrhea is not invariably present and is usually a minor manifestation.

There is usually slight fever, the pharynx is moderately infected, and the tongue is usually coated and its papillae enlarged.

**Treatment.** Treatment is symptomatic and consists in mild sedation and the avoidance of food other than liquids until the vomiting is controlled. The phenothiazines may be effective in these cases.

### NORMAL AND ABNORMAL STOOLS

The pediatrician should be familiar with the characteristics of the normal stools of infants and children as well as of the various types of abnormal stools. Though the information gleaned from examination of the stools has limitations, it may contribute to a better understanding of a particular disturbance.

**Normal Stools.** The characteristics of the meconium stools of the first few days of life and of the transitional stools are described on page 290. When breast-milk feeding is well established and the infant's intake is composed entirely of it, the stools are yellow to golden, of salvelike consistency and faintly acid in reaction.



When cow's milk is ingested, the stools tend to be paler yellow, or they may assume more of a brownish color, are firmer in consistency, less acid in reaction and may even be slightly alkaline; there is a more decided odor, owing to decomposition of protein. A ratio of 3:1 between the fat and protein produces an acid stool, whereas a ratio of 1:1 causes the stool to become alkaline. The pH of the stools of normal breast-fed infants varies from 4.7 to 5.1, greater acidity being encountered as a rule only in diarrheal conditions. Infants fed on protein milk, cow's milk formulas or whole acid milk with carbohydrate added generally have stools which approach a pH of 7 or higher. Oral administration of acids or alkalis has little effect on the reaction of the stools.

The number of stools varies considerably, breast-fed infants tending to have more frequent movements than artificially fed ones. Breast-fed infants average from two to four stools a day during the first three or four months of life, whereas artificially fed infants average about only one or two stools. By the end of the first year of life the majority of infants have only one stool a day, although more or less than one is not incompatible with a normal regimen. The character of the stool is more important than the number in the estimation of whether the infant has diarrhea or constipation.

A normal stool contains approximately 80 per cent water. The greater part of the residue consists of cellular elements, mucus and bacteria. Fat is present in the form of neutral fat, fatty acids and soaps. The fat is largely a residue from unabsorbed foods; some comes from bile, bacteria and cellular detritus, and some from lipids excreted from the blood through the intestinal wall. The fat content of infants' stools varies tremendously and may be as much as 35 per cent of the weight of the dried stool of artificially fed infants and as much as 50 per cent in breast-fed infants. The sugar of the infant's diet is entirely absorbed. Starch is not completely digested and may be demonstrated in the stool by the iodine test. Only about 8 per cent of the protein ingested is lost in normal stools. The greater part of the nitrogen and phosphorus recoverable from the stools of breast-fed infants is derived from the digestive secretions and not from the milk. From 8 to 10 per cent of the dried stool consists of mineral matter, chiefly calcium, which is partly derived from food and partly secreted into the intestine from the blood.

Curds may be found in the stools of both breast-fed and artificially fed infants and in small number are of no particular significance. They are whitish, but the outer coating is yellow or brown; they are composed of a casein coagulum; those of breast milk stools are much smaller and less firm in consistency than those of cow's milk. The small white curds which appear in diarrheal stools represent undigested neutral fat.

Various ferments are present in the stools, such as diastase, lactase, invertin, trypsin, rennin and a fat-splitting ferment.

Microscopically, the stools of an infant exhibit fat globules of various sizes, needles of fatty acids, innumerable bacteria, cholesterolin plates, epithelial cells, small round cells, calcium salts in crystalline form, granular detritus, and occasionally bilirubin crystals, yeast fungi and protein matter.

As the infant grows older the stools become a darker yellow, and, when the diet is more varied and especially when the amount of milk is relatively diminished, they acquire more of the characteristics of the stools of adults in both color and odor. By the time the child is about two years of age stools become formed, although even young infants may pass fully formed stools, especially when they are ingesting a diet with a high protein content.

**Mucous Stools.** Mucus is often present in the stools of infants and in small amounts may have no significance. During starvation the stools consist of thin mucoid secretions of the intestine which are stained a brownish tint (*starvation stool*). Mucus is generally present in considerable quantity after administration of a purgative such as castor oil. In older children it may represent a functional disturbance and be associated with emotional or neurotic disturbances. It is present in large quantity in inflammatory conditions. Stools composed almost entirely of blood-stained mucus occur in dysenteric conditions and in intussusception. Undigested starch may resemble mucus in appearance, but can be distinguished by the iodine reaction.

**Protein Stools.** The odor of putrefaction may be present in the stools of infants who ingest large amounts of protein or whose digestion of protein is impaired. The color is brownish-yellow or sometimes a greenish-black, and mucus may be present. Tough, yellowish, beanlike protein curds are often present after ingestion of unboiled milk.

**Fat Stools. Soap stool.** This depends upon an excess of fatty acids combined with cal-

cium or magnesium to form a soap. The stool is white or gray, shiny, fairly firm, homogeneous, crumbly or salvelike and of acid reaction, and has a rancid or sour odor.

**Fatty stool.** The stool is yellow to gray and soft and bulky, has a greasy appearance, and will produce a grease spot when placed upon paper. If protein is also present in large amount, the odor is cheesy and offensive; when there is also undigested carbohydrate, the stool is frothy. Such stools are seen in the celiac disturbances.

**Curdy stool.** Fat curds occur most often in loose or diarrheal stools, and the stool has an acid reaction. The curds are generally small and white. (See also Normal and Protein Stools.)

**Carbohydrate Stools.** Stools from diets exceptionally high in carbohydrate content are of normal consistency, smooth, brown or yellowish-brown, and have an acid reaction. Starch present in excess may be demonstrated by the iodine test. When there is indigestion of carbohydrate and decomposition of it in the intestinal tract, the stools become thin, frothy, light yellow or often green, the odor is suggestive of acetic acid, and there is an acid reaction.

**Green Stools.** A faint pea-green color when the stool is passed or developing shortly thereafter is not abnormal; it results from oxidation of bilirubin (responsible for the yellow color) to biliverdin. Green watery stools are common in diarrhea.

**Blood in the Stools.** Occult blood in the stools of newborn infants who have no other evidences of hemorrhage is not uncommon and may be of no particular significance. Gross evidence of fresh or digested blood, however, requires explanation. Streaks of fresh blood in the stool may result from bleeding hemorrhoids, anal fissures, rectal polyps or the passage of a large hard stool. Blood in combination with large amounts of mucus occurs in intussusception and, with mucus and pus, in colitis. Among the acute infectious diarrheal conditions, blood is especially likely to be present in amebic or bacillary dysentery. When there is extensive bleeding in the stomach or high in the intestinal tract, or when large amounts of blood have been swallowed, the stools are reddish-black. Under these circumstances the various blood dyscrasias and ulceration of the stomach or duodenum should be considered in the differential diagnosis. Ingested iron causes the stools to become black, and bismuth causes them to be greenish-black. When the blood

in the stool is midway between that of the fresh state and that characteristic of bleeding high in the stomach or duodenum, the possibility of a Meckel's diverticulitis, intestinal polyps and the blood dyscrasias should be considered.

## CONSTIPATION

The term "constipation" indicates that intestinal evacuations are too infrequent, too small in amount or too firm and dry. There are, however, individual variations in frequency which must be considered within the normal range. Some infants, for example, of an age when two or three stools usually occur daily may not average a stool a day, but they are not to be considered constipated if the evacuation is of sufficient size and is normal. In older children, in whom but one movement daily is to be expected, there may be two or three, but they may be hard and small, and the child is actually constipated. There is, in fact, no absolute rule for the number of evacuations which should occur daily, nor is it necessary that there be a stool every day. The quality of the stool is a better measure of constipation than is the frequency of evacuation. The causes of constipation are shown in Table 87.

**Clinical Manifestations.** The symptoms accompanying constipation depend mainly upon its cause. In chronic constipation general symptoms may be entirely lacking, and the child may appear to be in good health. There may be abdominal discomfort, flatulence and anorexia, and, infrequently, fever, malaise and vomiting. Such nervous symptoms as headache and disturbed sleep are rare. Apparently some of the nervous manifestations which occur in constipation are reflex and are caused by mechanical distention of the lower bowel; they can hardly be due to absorption of toxic substances, as is sometimes claimed, since they almost immediately disappear when the rectum is evacuated. Local disturbances, such as fissures, rectal prolapse or hemorrhoids, may at times be the cause of or may be secondary to constipation. The retained fecal masses at times may be palpated as hard nodules through the abdominal wall, occasionally attaining tumor-like size and hardness.

**Diagnosis.** The decision whether an infant or child actually has constipation should be determined from a description or preferably from an examination of the stool. Small ribbon stools or small inspissated, ball-shaped



fecal masses are likely to be associated with a spastic or irritable colon; hard, dry, small stools with atony of the gut or improper dietary habits; and normal stools with anal or rectal stenosis in infants.

In every instance a visual and digital examination of the anus should be made. Anal stenosis in infants is not rare and should be considered in the differential diagnosis of every constipated infant. When the anus of an infant does not admit the examiner's little finger easily, the diagnosis is established (p. 680). Proctoscopic and roentgenologic examinations are rarely necessary, but should be made when the cause is not apparent from an evaluation of the history and from examination of the stool, anus and rectum (digital examination). Roentgenologic examination is an important aid in the diagnosis of spastic colitis, a rare condition in children.

**Treatment.** It should be proved that constipation actually exists before treatment is instituted.

**Acute constipation.** A simple enema may be all that is necessary in acute constipation. If the feces are hard or if there is impaction, 2 to 4 ounces (60 to 120 cc.) of mineral oil may first be injected and allowed to remain for a few hours. When indigestion accompanies the constipation, a cathartic such as milk of magnesia in infants and citrate of magnesia in older children may be prescribed.

**Chronic constipation. DIET.** In the treatment of chronic constipation attention should be given to the cause, which is usually a faulty diet or faulty bowel habits. It should be remembered that a high or even average casein content of a milk mixture tends to produce hard, firm stools. An increase in the quantity of sugar in the formula of infants or a change in the type of sugar may at times be helpful. In some instances the use of oatmeal water as a diluent is of benefit. The quantity of fat in the diet should not be increased beyond the usual requirement. The quantity of milk should be diminished if it has been excessive and that of solid food increased; water should be given freely. Butter-milk and acidophilus milk may sometimes be used with advantage instead of plain milk.

Fruit juices and, later, fruits themselves are excellent, especially prune pulp and applesauce. For older children, figs, prunes, apricots and dates in moderate quantities are likely to be helpful. Such green vegetables as spinach, beet tops, lettuce, asparagus tips and string beans, and such flours as oatmeal,

whole wheat and graham should be included in the diet. Bran biscuits or crumbled bran is frequently of value. Broth may exert a laxative action through the salts contained in it. In general, foods which are largely digested and absorbed, such as the protein of milk and foods consisting chiefly of starch, should be restricted in amount; those containing considerable residue, such as green vegetables, many of the fruits, and the outer coating of grain, should be increased.

**TRAINING.** This is of great importance; too early training and coercive methods should be avoided (p. 136). Older children should attempt to establish a time for defecation when the inclination is most strongly felt and there is nothing to cause hurry. Shortly after eating is generally a suitable time, since ingestion of food increases intestinal peristalsis. Though straining is not to be encouraged, a sufficient time (fifteen minutes or so during the period of habit formation) allowed on the toilet will often be followed by a stool, even though at first

Table 87. Causes of Constipation

<i>Insufficient or Improper Food</i>
In both breast-fed and bottle-fed infants there may be a deficiency of food in total quantity, and in artificially fed ones of an ingredient such as carbohydrate or fat. High protein mixtures tend to cause hard, firm stools, and high fat mixtures may cause dry soapy stools. There may be too much milk and too little residue from other foods. Boiling the milk has little effect in producing constipation
<i>Spasticity of Intestine</i>
Irritation by cathartics or too much residue; spasm of rectal sphincter from fissure or hemorrhoids
<i>Lack of Muscular Tone</i>
Lack of tone of intestinal and abdominal muscles may occur in malnutrition, rickets, anemia, any protracted illness, lack of exercise, and after continued use of laxatives, enemas and suppositories
<i>Anatomic Abnormalities</i>
Unduly long or tortuous sigmoid; megacolon; various forms of intestinal obstruction; enteroptosis; anal stenosis
<i>Faulty Habit</i>
Irregular habits of evacuation; injudicious use of suppositories, enemas and laxatives

no inclination is felt. Prolonged periods on the toilet should be avoided. A low seat may help when evacuation is difficult with a higher one.

**LOCAL ANAL MEASURES.** Stretching of the anal sphincter is occasionally serviceable for spasm of the muscle or stenosis. The mother should be instructed to perform daily dilatation, wearing a lubricated finger cot. The finger should remain in the anus for five minutes or so. For anal fissures see page 682.

**SUPPOSITORY AND ENEMA.** These should be used only as temporary measures. Suppositories may be made of soap, glycerin and soap or gluten. Sometimes the introduction of an oiled thermometer gives all the local stimulus that an infant requires. Suppositories may be used for several days in training to a daily habit, but no longer. Small enemas are useful in emptying the bowel in chronic constipation, but should not be used as a routine measure.

**DRUG THERAPY.** Drugs should be avoided so far as possible. In infancy milk of magnesia (2 to 8 cc.) added to the bottle may be helpful. Dioctyl sodium sulfosuccinate (p. 216) has proved to be effective. The use of any drug should be eliminated by gradually decreasing doses as improvement in bowel habit is attained from dietary and regulatory measures. Liquid petrolatum absorbs vitamin A, and vitamin A should be abundantly supplied if this substance is used.

**Spastic constipation.** This is rare in children and requires special consideration. Laxatives and purgatives should be discontinued, and a lubricant or dioctyl sodium sulfosuccinate (p. 216) substituted until satisfactory bowel habits are established. Roughage in the diet should be avoided. Tincture of belladonna, atropine or Syntropan in conjunction, when necessary, with phenobarbital for its sedative effect, constitute the medicinal therapy. Most important is correction of the underlying psychologic difficulties. Every effort should be made to establish normal bowel habits without dietary restrictions and without medicinal therapy.

### ENCOPRESIS

Encopresis, or fecal incontinence unassociated with organic lesion or disease, is not a rarity in pediatric practice. It occurs most often in the postinfancy and preschool years, but may persist into later childhood. Most often it takes the form of frequent fecal soiling, with severe constipation; less often there are intermittent larger evacuations. Encopresis may be considered to exist when children beyond three years of age do not have bowel control and have no organic explanation for the incontinence. Enuresis is frequently associated. The principal causes are mental retardation and emotional disturbances.

Many of the children with average intelli-

Table 88. Differentiating Features of Psychogenic and Aganglionic Megacolon

Psychogenic Megacolon	Aganglionic Megacolon (Neurogenic)
Admitting complaint: Fecal soiling	Admitting complaint: Constipation without fecal soiling
Age at onset: 2nd year or later	Age at onset: Birth or first weeks of life
History: Coercive bowel training Toilet training successful at some time or always unsuccessful Infrequent use of toilet after onset Defecation in standing or supine position Inhibition of stool Colicky abdominal pain Periodic voluminous stools	History: Lack of coercive bowel training (enemas only for true constipation) Toilet training usually successful Use of toilet for defecation Defecation in sitting position Rarely abdominal pain Pellet-like or ribbon-like stools
Past history: No episodes of intestinal obstruction	Past history: Frequent episodes of intestinal obstruction
Physical examination: Feces-packed rectum	Physical examination: Empty rectum
Fluoroscopy (Neuhauser's technique): Absence of spastic segment of rectum or rectosigmoid	Fluoroscopy (Neuhauser's technique): Presence of spastic segment of rectum or rectosigmoid
Course: Negligible mortality	Course: High mortality if untreated

Adapted from Garrard and Richmond: Pediatrics, Vol. 10.



gence who have encopresis have been toilet-trained at least for defecation. Any type of emotional disturbance may be the underlying factor for the development of encopresis. In many instances these children have had early, coercive toilet training and a distinct lack of parental affection. The parents often make a fetish of daily bowel movements, and the use of enemas, suppositories and laxatives is common. Some time later, perhaps with any of a variety of emotional "trigger mechanisms," the child refuses to use the toilet, and obstipation and then encopresis follow. In some instances the clinical pattern may be that of megacolon (see Table 88 and p. 673). Treatment is psychiatric for both parents and child.

## DIARRHEAL DISORDERS

### DIARRHEA IN INFANTS AND CHILDREN

Diarrhea is a major clinical manifestation of a variety of disorders which collectively constitute one of the principal causes of illness and of mortality among infants and children throughout the world. The problem is a much more serious one during infancy than in later childhood. This difference is due in part to the infant's greater susceptibility to infection and to his lesser ability to combat it, but mainly it is due to the relatively greater disruption of the water and electrolyte balances within the infant than in the older child. Although infection itself may be the cause of death, more often death can be attributed to the effects of dehydration and acid-base imbalance, usually acidosis.

Among people of high socio-economic standards the decrease in the incidence of diarrhea has been tremendous and has been principally responsible for the great decrease in infant mortality rates since 1900. In countries in which standards of living continue at a low level among a large portion of the population, infant deaths from diarrheal disorders continue at a high rate. This difference is due almost entirely to the effective use of methods for the preparation, sterilization and storage of milk or formulas and the handling of other foods for infant feeding so that bacterial contamination is avoided. Such diarrheal disorders have been termed "filth diarrhea" and occur mainly in hot, humid climates, where bacteria can grow luxuriantly in milk or other foods intended for infant feeding.

In most areas in the United States the distinct seasonal variation in the incidence of diarrhea among infants has largely disap-

peared, and the incidence in the winter months now approximates that of the summer ones.

**Etiology.** In the majority of instances the etiologic agent of acute diarrheal disturbances is not determined. From an epidemiologic standpoint the diarrheal problem among infants and children can be approached on the basis of age groups: the newborn period, infancy and childhood.

Any of the known intestinal pathogens can presumably infect a person of any age, but there are differences in susceptibility at various ages and, as noted, differences in the clinical patterns. The clinical disturbances of the recognized enteral infectious diseases in which diarrhea is a significant manifestation are described elsewhere. These are bacillary dysentery, amebiasis, typhoid fever, salmonella infections and food poisoning. Diarrheal disorders in the newborn infant are discussed on pages 344 and 346.

*Diarrhea in the newborn* presents its biggest problem as an epidemic in the nursery (p. 346). Most of the intestinal pathogens have either been incriminated or suspected in individual epidemics. In addition, for a number of organisms which are commonly found in the intestinal tract during health, there is presumptive evidence that they may act as pathogens under certain circumstances, and presumably more often in early infancy than later. These include the paracolon, *Proteus*, *Pseudomonas*, staphylococcal and streptococcal groups in particular. In the 1940's rather strong presumptive evidence was presented in support of viral agents as the principal etiologic factor in the epidemic form of diarrheal disease in the newborn (Hodes and Light, and Buddingh and Dodd). Subsequently attention has been directed to pathogenic strains of *Escherichia coli* which are identified by agglutination. A number of strains or serotypes have now been identified as unquestioned pathogens (p. 344). Although these strains may presumably cause diarrheal disorders at any age, it would appear that they are more likely to cause intestinal disease in the first year or so of life, especially in the newborn period, when perhaps they may be the most frequent cause of nursery epidemics. Likewise they appear to be a common cause of nosocomial infections on infant wards. Epidemiologic studies are now under way which it may be hoped will clarify the situation. It would be a mistake, however, at this time to oversimplify the problem, and it must be assumed that a number of viral

and bacteriologic pathogens can cause diarrheal disease in the infant. As an example, recent evidence incriminates certain strains of the ECHO viruses (p. 531).

The problem in *infants* subsequent to the newborn period varies greatly in different socio-economic groups. In those of the lowest order contamination of milk formulas and other foods is still the most important source of infection. In the higher socio-economic groups infections of this sort are now comparatively rare, and most infections would seem to be transmitted by infected persons or "carriers." Perhaps the most frequent causes at present are the pathogenic serotypes of *E. coli* mentioned above and various viral agents. In addition to enteric viruses, it is possible that some of the respiratory viruses may be responsible for mild diarrheal disturbances in conjunction with the respiratory infection. It is not uncommon to observe diarrhea in an infant of a family of which older members have an epidemic respiratory infection.

In *childhood*, diarrheal disturbances become much less frequent and relatively less severe. Many of the mild diarrheal disorders would seem to be due simply to overeating and perhaps in some instances to a combination of this with nervous excitement and exhaustion. Emotional disturbances must always be recognized as a possible cause. It is also possible that food contamination of a slight degree which has little or no effect on adults may be responsible for mild diarrhea (food poisoning, p. 1374) in children. In all instances of severe diarrhea a careful history of possible sources of infection and bacterial cultures of the stools should be obtained.

At present it is necessary to pay special attention to the *Staphylococcus aureus* as a cause of diarrheal disease. Its association with acute food poisoning has been described (p. 1374). A similar type of clinical pattern may also result from enteric staphylococcal infections which are permitted to become established as a result of alterations in the intestinal flora during prolonged antibiotic therapy, especially with the tetracyclines. Diarrhea which is presumably due to direct enteric infection by the *Staphylococcus* in association with staphylococcal infections elsewhere in the body such as skin lesions and pneumonia is not uncommon. Such infections are seen principally in infants. In addition, primary staphylococcal enteritis has been reported as a cause of an epidemic of diarrhea in the newborn (Smith).

Antibiotic-induced diarrhea may not be as frequent in infants and children as in adults, but it does exist. In addition to staphylococcal enteritis mentioned above, other infectious agents may overgrow in the intestinal tract or be permitted colonization as a result of disruption of the usual intestinal flora by therapy with the various antibiotic agents as well as the sulfonamides. Staphylococcal and fungal (*Candida albicans*) infections would appear to be the more frequent ones, but infections with *Proteus*, *Pseudomonas* and perhaps certain other bacteria may be significant.

Parenteral infections have been accorded a high place as a cause of diarrhea, especially in infants, but it is doubtful whether they are as frequently a cause as was previously supposed. With the more universal sterilization of infants' formulas and the increasing practice of avoiding overfeeding during acute infectious diseases, intercurrent diarrheal disturbances during parenteral infections have become relatively uncommon. The majority of diarrheal disturbances attributed to parenteral infection would seem more likely to be secondary intestinal infections in infants whose natural resistance was temporarily lowered. Grippelike infections which tend to occur in epidemic form and have in their clinical patterns varying degrees of upper respiratory tract infection and of diarrhea are not considered parenteral infections.

A number of noninfectious conditions may be responsible for diarrheal disorders. These include allergy to certain foods (p. 1326); metabolic disorders such as those associated with hyperthyroidism, uremia and acidosis; emotional excitement and fatigue; direct irritation of the intestinal tract by such food-stuffs as unripe fruits or vegetables, or those which contain large proportions of undigestible material or have an especially high fat content. Excessive ingestion of ordinary foods, especially by infants, may also be a factor. The persistent or injudicious use of laxatives and purgatives is also a cause. So-called starvation diarrhea, in which the stools contain an excessive amount of mucus and a little fecal material, is not, strictly speaking, a diarrheal disturbance. Diarrhea may be a prominent symptom of congenital aganglionic megacolon in early infancy.

**Clinical Manifestations.** See page 346 for description of diarrhea in the newborn; for clinical manifestations in older children, see descriptions under bacillary dysentery, salmonella infections, amebiasis and food poison-



ing. The descriptions here apply principally to infants and very young children.

**Mild diarrheal disturbances.** Occasionally there are such prodromal symptoms as slight fever, some irritability and a disinclination to eat. Severe vomiting is not a common symptom. The frequency of stools varies; there may be only two or three a day or as many as ten or twelve. Temporary reduction in oral feeding usually results in abatement of the diarrhea, and there is little or no evidence of dehydration.

**Severe diarrheal disturbances.** The severe cases vary widely; in general they can be placed in two groups: (1) cases in which the onset is only moderately severe and toxic manifestations are greatly accentuated when dehydration and electrolytic disturbances have become a factor; (2) cases in which the onset is abrupt with high fever and extreme toxicity.

In the first group there may or may not be fever. There is often vomiting at the onset, but it is usually not persistent. It may return in the later stages if dehydration and acidosis develop. Diarrhea appears within twenty-four hours of the onset; the stools are at first chiefly fecal, often with the presence of small white curds, and are usually strongly acid in reaction. They quickly become liquid and greenish or greenish-yellow, contain increasingly larger amounts of mucus, and at times are blood-tinged. Initially there are evidences of irritability and, at times, stupor and convulsions. These symptoms frequently disappear after the first day or so, but the irritability and restlessness return if dehydration and acidosis develop. The number of stools varies from a few to twenty or more a day. The evacuation is often preceded by pain, and the stools may be expelled with force.

The extent of dehydration and the rapidity of its development depend upon the amount of fluid lost in the stools, the presence or absence of vomiting, and the extent to which fluids are replaced parenterally. In untreated cases there is loss of subcutaneous tissues and elasticity of the skin. The pulse is rapid and weak, and the prostration becomes greater. The output of urine is progressively decreased; the urine has a high specific gravity and often contains albumin and casts. There is invariably some hemoconcentration, which in severe cases becomes marked. Owing to the decrease in renal function and to the hemoconcentration, nonprotein nitrogen levels of the blood are increased, at times to as much

as 100 mg. per 100 ml. or more. Acidosis is usually a prominent manifestation; in untreated cases plasma carbon dioxide levels may be less than 10 volumes per milliliter, and the pH may approach 7. Hypertonic dehydration may be a significant factor, especially when milk feedings have been continued or hypertonic saline solutions are given (p. 187).

Cases which fall in the second category have been variously termed "acute toxic diarrhea" and "alimentary intoxication." They are characterized by an abrupt onset with high fever, often 104° to 106° F., and extreme prostration. Vomiting is frequently severe. An infant who otherwise has been well suddenly becomes extremely prostrated. In some instances there is evidence of irritability, restlessness and even convulsions, but symptoms of collapse are more frequent. The infant in this latter instance is flaccid, and pallor is usually noticed. Respirations are rapid and may be hyperpneic. Diarrhea may not appear for some hours or even a day and, as a rule, is not striking in contrast to the extreme severity of the general symptoms. The fatality rate is extremely high, and death often occurs within the first twenty-four hours. This clinical condition may be the infantile pattern of severe food poisoning. Though acidosis and hemoconcentration are likely to be extreme, such peripheral manifestations of dehydration as loss of subcutaneous tissue and inelasticity of the skin are not prominent in the infants who die in the first day or two of the disease.

**Diagnosis.** Clinical evaluation of the infant with diarrhea is essential for planning treatment. There is no differential diagnosis beyond that of establishing the etiology. Occasionally a lead may be had from the history, indicating the source and nature of the infection or the possibility of food poisoning, but in most instances the etiology can be determined, if at all, only by bacteriologic cultures of the stool and, in infections with the pathogenic strains of *E. coli*, agglutinative studies (p. 344). Cases suspected of being viral in origin can be studied serologically by determinations of antibody levels in acute and convalescent stage serums (p. 388). Samples of several stools of those passed in the first twenty-four hours of observation or, preferably, several rectal swabs at intervals of eight to twelve hours should be plated immediately for culture.

Since the metabolic disturbances of diarrhea in infants are an important part of the

clinical situation, no severe case may be adequately appraised without the assistance of laboratory data (see p. 184).

**Prevention.** Diarrheal disturbances are much more frequent in artificially fed infants than in breast-fed ones. Thus every effort should be made to secure breast feeding for all newborn infants. When artificial feeding is a necessity, the mother should be properly instructed in the sterilization of formulas and in their storage until the time of feeding, so that contamination is prevented. Weaning of breast-fed infants should be avoided during hot weather. During periods of unusually high environmental temperature and humidity or during any febrile disturbance infants should be supplied with adequate amounts of fluid,

and the intake of food should be temporarily reduced. Excessive clothing should be avoided, and the infant should be kept at home and away from visitors.

**Treatment.** This is discussed under the various diarrheal entities. See under Mild diarrhea (p. 189), Acute severe Diarrhea (p. 187), Diarrhea in the Newborn (p. 347), Bacillary Dysentery (p. 437), Amebiasis (p. 613), Salmonella Infections (p. 444), Botulism (p. 1374), Chronic Diarrhea (p. 189), Celiac disturbances (p. 724), Gastrointestinal Allergy (p. 1328,) Congenital Alkalosis of Gastrointestinal Origin (p. 189) and antibiotic and sulfonamide dosages (p. 210).

WALDO E. NELSON

## THE STOMACH AND INTESTINES

### DISORDERS OF THE STOMACH

#### MALFORMATIONS AND MALPOSITIONS OF THE STOMACH

*Malformations*, with the exception of pyloric stenosis, are rare. The stomach may be unusually small and remain so; in such instances there is often increased thickness of the walls. There may be complete atresia at either orifice, or the stomach may be partly divided by a constriction somewhere in its midportion (hourglass stomach). Duplication of the stomach is a rare anomaly; one or both portions may be partially or totally intrathoracic. See page 663 for defects in gastric musculature.

*Malpositions*, though not common, occur somewhat more frequently than malformations. In association with transposition of other viscera, the stomach may be situated on the right side of the abdomen and empty to the left. In diaphragmatic hernia the stomach may be situated partly or completely within the thoracic cavity; with congenitally short esophagus the stomach may be partly in the thoracic cavity. In the latter instance or in the case of abdominal adhesions the stomach may be maintained, as in fetal life, in a vertical or nearly vertical position.

#### CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

Congenital hypertrophic pyloric stenosis is characterized by vomiting beginning as a rule

in the second or third week of life and becoming increasingly projectile, by gastric peristaltic waves, often by a palpable tumor mass at the pylorus, by constipation and by loss of weight. Pathologically, there is hypertrophy and hyperplasia of the pyloric musculature resulting in a tumor mass which constricts the lumen of the pyloric canal and impedes gastric emptying.

The *pathogenesis* of this condition is not understood. In favor of congenital origin is the high incidence of involvement of both of monovular twins, in contrast to the relative infrequency in both of binovular twins.

**Incidence.** By far the majority of cases occur in male infants and usually in the first-born. It has been estimated that the incidence in Sweden is one in 150 male infants and one in 775 female infants. Familial incidence has been observed. Pyloric stenosis has been reported in both of eleven sets of identical twins, whereas there are only two sets recorded in which only one of them had pyloric stenosis. Breast-fed as well as artificially fed infants are affected. Pyloric stenosis is apparently rare in Negro infants.

**Pathology.** The pylorus is elongated, thickened to as much as twice its usual size, and almost cartilaginous in consistency. There is thickening of the muscular coat, principally of the circular fibers, and severe narrowing of the lumen, which explains the difficulty in



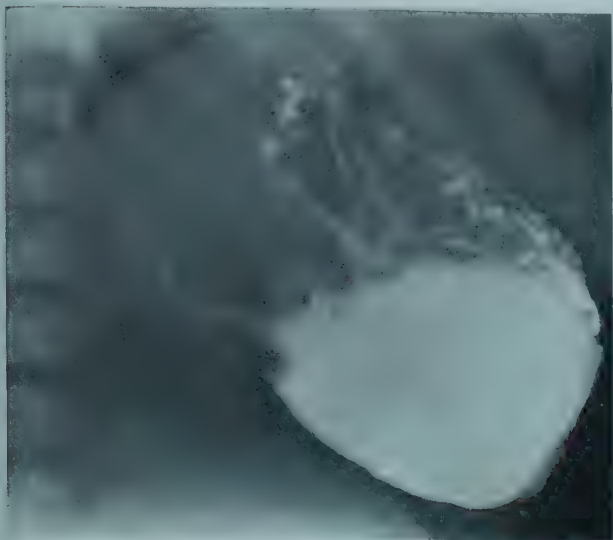


FIG. 189. Hypertrophic pyloric stenosis. Elongated pyloric canal in an infant with hypertrophic pyloric stenosis, showing the so-called string sign, the blunt antrum and evidence of retained gastric contents. Hyperactive peristalsis was observed fluoroscopically.

the passage of food (Fig. 189). The stomach is usually dilated, and in long-standing cases there may be hypertrophy of its muscular coat.

**Clinical Manifestations.** Initially there is only occasional vomiting, which may begin within a week or so after birth, more often not until the second or third week. The onset is rarely delayed until the second or third month of life. After a few days the typical manifestations rapidly make their appearance. When fully developed, perhaps no other clinical condition has a more characteristic pattern. The principal manifestations are projectile vomiting, loss of weight, constipation, visible gastric peristaltic waves and a palpable pyloric tumor.

**Vomiting.** Within several days or at most a week after the onset, vomiting becomes projectile. Perhaps in no other conditions is there such forceful vomiting. At times the vomitus may be propelled 3 or 4 feet when the child is lying on his side, and for a foot or more when lying on his back. Vomiting characteristically occurs during or shortly after feeding, but at times as much as several hours later. The frequency varies; in some instances it may be after each feeding, whereas in others it may occur only after two or three feedings. There is apparently no nausea, and the infant will take another feeding immediately. The vomitus consists only of gastric contents, but may be blood-tinged; it is not bile-stained. When the vomitus is blood-streaked, the

possibility of impending massive hemorrhage should be recognized.

**Dehydration.** When vomiting has been persistent for some days, there is dehydration, and loss of hydrochloric acid may be responsible for severe metabolic alkalosis. At such times there is an increase in plasma carbon dioxide content, increase in pH and decrease in serum chloride. There is also a loss of potassium, which is usually reflected by a low serum potassium level. When dehydration is extreme, however, the hemoconcentration may be responsible for sufficient decrease in renal function so that the retention of acid metabolites compensates for the loss of hydrochloric acid, and there is little or no shift to the alkaline side.

**Constipation.** This is a striking feature. At times no fecal matter is passed for days. The stools are characteristically small; occasionally a starvation type of diarrhea develops.

**Loss of weight.** This may be extensive, and the weight may decrease to a level below the birth weight. At such times there is inelasticity of the skin and loss of subcutaneous tissues, and in extreme cases even the fat pads of the cheeks are lost. In such instances the infant has a withered, "old man" appearance.

**Gastric peristaltic waves.** These waves, visible through the thin abdominal wall, are most prominent immediately after ingestion of food or just before vomiting. Occasionally they may be stimulated by deep palpation or friction of the abdominal wall. They are initiated at the left side near the costal margin and pass toward the pylorus, one or two being visible at a time, suggesting the rolling of balls under the abdominal wall; they become smaller as they approach the pylorus (Fig. 190). The waves are usually best observed from the right side with the eyes on



FIG. 190. Gastric peristaltic waves of pyloric stenosis in an infant 3 weeks of age. (Courtesy of Dr. Carl Wagner, Cincinnati.)

a level with the abdomen, and with the light, which should not be too bright, coming from the left side. At times the infant appears to be uncomfortable, but pain is not a prominent feature.

**Pyloric tumor.** The tumor may be palpated in the majority of instances. It is usually situated about midway between the umbilicus and the costal margin, just lateral to the right rectus muscle. It may be situated underneath the lower margin of the liver. The mass is cylindrical and a centimeter or so in diameter. Palpation with the tip of the finger (which should be warm) should at first be superficial, with a rotary motion over the pyloric area (the angle formed by the right rectus muscle with the costal border). If the mass is not located, the fingers are then pressed deeply but gently into the abdomen in this area with a to-and-fro motion while pressure is exerted on the stomach from the left side by the examiner's left hand in order to push the pylorus toward the right and to help to immobilize it. In this maneuver the infant is rolled to his right side. Relaxation of the abdomen is usually best secured just after vomiting and while the infant is being fed. The mass is more likely to be located before the stomach has become distended with food.

**Diagnosis.** In typical cases there is little difficulty in diagnosis, which is established by the characteristic clinical pattern. The rare instances of *congenital atresia of the pylorus* are distinguished by the development of symptoms within a few hours after birth. *Congenital obstructions of the duodenum* may be responsible for projectile vomiting and visible peristaltic waves. When the obstruction is complete, it is apparent a few hours after birth; but if it is incomplete, as, for example, because of external bands or stenosis, it may not become evident for days or weeks after birth. The vomitus contains bile if the constriction is below the ampulla of Vater. Colonic peristaltic waves may at times be mistaken for gastric waves, and gastric waves are occasionally visible in small emaciated infants who do not have pyloric stenosis. *Adrenal insufficiency* in infants (p. 1182) may simulate hypertrophic pyloric stenosis; the absence of a palpable tumor mass and changes in the chemical constituents of the blood aid in differentiating them. *Chalasia* and *achalasia* of the esophagus may be responsible for vomiting in the first few weeks of life, but should be differentiated by roentgenographic studies.

The principal diagnostic difficulty is with

hyperactive infants who vomit frequently and often explosively in the first few weeks after birth. In some instances the vomiting is sufficiently persistent and projectile so that a differential diagnosis is made only after roentgenologic studies. The vomiting often disappears completely, however, when the feedings are given by a different and experienced attendant. In such instances the cause of the vomiting appears to be due to errors of feeding technique, especially to failure to eructate swallowed air. Some infants are easily excited and overactive and vomit readily, frequently with considerable force. It is especially in this latter group that the term "*pylorospasm*" has been used. Since this type of vomiting is controlled by an antispasmodic such as atropine or by prefeeding sedation with phenobarbital, there is justification for the medical treatment of cases in which the diagnosis of pyloric stenosis is not definitely established.

A roentgenologic examination is not necessary in patients with a characteristic clinical pattern, but it may be in early or questionable cases. The examination should be more inclusive than a simple determination of the gastric emptying time, since on occasion little or no gastric contents may pass through the pyloric canal for three or four hours, and total emptying may be delayed much longer in nonstenotic cases. Determination of the prepyloric opening time is of value. Normally this is observed within five minutes after barium has been swallowed. Demonstration of the narrowed pyloric canal (Fig. 190) is the most important roentgenologic sign. It is diagnostic in conjunction with a delayed prepyloric opening time and a delayed emptying time.

**Prognosis.** When the diagnosis is made early in the course of the disease and the infant is properly prepared for operation, the operative fatality rate is less than 1 per cent. There have been no comparable results with medical therapy. That an occasional patient with true pyloric stenosis survives without surgical treatment is apparent from the reports of finding pyloric tumors at autopsy in infants who died of other causes some months after symptoms of pyloric stenosis had disappeared. At best, medical therapy can be expected to require two or three months. With surgery the infant is usually well within two or three weeks. Gastric disturbances in older children and adults have been attributed to the after-effects of pyloric stenosis in infancy, but the data are not convincing. Complete recovery is the rule.



**Treatment.** Relief of the pyloric obstruction by operation as soon as the diagnosis is established and metabolic imbalances are corrected is the treatment of choice. The better results with early rather than late surgical correction, the long duration and frequent unsatisfactoriness of medical therapy, and the dangers of cross infections in infants' wards of hospitals support such a policy.

**Nonsurgical treatment.** Since some clinicians prefer to give medical therapy a trial, and since it is justified for cases of so-called pylorospasm, the procedure is outlined here. Under no circumstances should it be used for the infant with pyloric stenosis who has marked loss of weight or severe alkalosis.

**THICKENED FEEDINGS.** The advantages of thickened feedings are not such as to justify discontinuance of breast feeding. When the infant is artificially fed, cereal or barley flour has been traditionally added to thicken the milk formula. For this purpose a precooked cereal is satisfactory. Feedings may be made of such a thickness that they will pass through nipple holes which have been enlarged to about 2 mm. in diameter. When vomiting occurs shortly after feeding, the feeding should be repeated. Some clinicians believe that vomiting is less frequent after a "small curd formula" than with the thickened feedings. Emptying of the stomach by gastric lavage before a feeding when there is epigastric distention may decrease the chance of vomiting after the succeeding feeding.

**HYDRATION.** Adequate hydration must be maintained and parenteral administration of fluids is often required. The carbon dioxide content of the blood should be measured from time to time in order to avoid development of severe alkalosis.

**DRUGS.** Atropine has been a standard remedy for years, but satisfactory results from its use are rare. Other atropine derivatives have also been used; European clinicians in particular have reported good results with Eumydrin. Wallgren recommends a 0.6 per cent alcoholic solution of Eumydrine which contains approximately 0.1 mg. in each drop of the solution. The initial dose is 1 drop, about twenty minutes before each feeding, the medication being placed directly on the infant's tongue. The dose is then gradually increased until vomiting is controlled or flushing of the face appears, when the dose is decreased. Doses exceeding 3 to 5 drops are rarely administered.

If atropine is given, a freshly prepared

solution should be used. Although infants appear to have a high tolerance for atropine, there are occasional instances of idiosyncrasy. Since these reactions may be lethal, initial doses should always be small, 1 drop of a 1:1000 solution or, preferably, 10 drops of a 1:10,000 solution. The dose is gradually increased until the vomiting is controlled or until flushing of the face, dilatation of the pupils or fever occurs, when the dose should be decreased. When the dose is equal to 10 drops of the 1:1000 solution, this concentration should be used rather than the weaker one.

Some clinicians prefer phenobarbital to atropine, and others give them together. The good results obtained with phenobarbital in so-called *pylorospasm* may be due to a sedative effect in hyperactive infants. In such infants administration of phenobarbital twenty minutes or so before feeding has been effective in controlling vomiting and in facilitating adjustment to a more satisfactory regimen. An initial dose of 10 or 15 drops of the elixir may be prescribed with instructions to increase it gradually to 30 to 40 drops if necessary, unless too heavy sedation results. When vomiting is controlled, the dose should be gradually reduced until administration of the drug is discontinued.

Medical therapy should not be continued for more than a week or two unless there are evidences of benefit from it, and not for this long when the infant continues to lose weight or otherwise does poorly.

**Surgical treatment.** **PREOPERATIVE MANAGEMENT.** No infant should be operated upon without satisfactory preoperative preparation. This consists in adequate hydration, the correction of any anemia by blood transfusions, and the correction of metabolic deficits (see p. 189 and Table 34 for details). Determination of the optimum time for operation is based on clinical judgment and laboratory data. Thiamine chloride, ascorbic acid and vitamin K should be given parenterally prior to operation. It is good practice to empty the stomach by lavage before operation; leaving the tube in the stomach during the operation seems to reduce postoperative vomiting by removal of stomach secretions and swallowed air.

**OPERATION.** The hypertrophied muscles of the pylorus are split without incising the mucous membrane (Fredet-Ramstedt method).

**POSTOPERATIVE MANAGEMENT.** Details of postoperative feeding vary in different clinics mainly in the time of offering the first

feeding. It is general practice to give a non-milk liquid such as a solution of 5 per cent glucose in saline for the first one to three feedings. In our clinic the first feeding of one ounce of 5 per cent glucose in a balanced saline solution is offered to the infant eight to twelve hours after operation, with repetition of it once or twice at intervals of two to three hours, and then a milk formula is substituted (the initial one 10 to 12 calories per ounce, with subsequent ones of an isocaloric mixture, if tolerated) with gradual increase in the amount and in the intervals between feedings until the infant is on an average schedule after four to six days. An occasional infant requires one or two subcutaneous infusions postoperatively, but the majority do satisfactorily without parenteral administration of fluids. Vomiting other than of occasional small amounts of mucus after the first glucose water feeding is unusual. Adequacy of preoperative preparation and gastric aspiration during operation may be factors lessening postoperative vomiting.

## INFLAMMATION OF THE GASTRIC MUCOSA

For gastric ulcer, see Peptic Ulcer (p. 671).

### ACUTE GASTRITIS

This condition is relatively uncommon. It is difficult of diagnosis and is most often demonstrated at autopsy. In general, lesions which come under this heading are associated with infectious diseases or are caused by corrosive agents.

**Infectious Gastritis.** Acute catarrhal gastritis is infrequently demonstrated at autopsy, but may occur in association with a number of infectious conditions such as acute gastroenteritis, thrush and a variety of parenteral infectious diseases. Multiple, small, nonindurated superficial ulcers are occasionally observed in newborn infants dying of a variety of causes or in infants dying of enteritis. Erosive lesions may result at points where an indwelling gastric tube rests against the gastric mucosa. Pseudomembranous gastritis is rare; it is usually seen with diphtheria, but has been observed with smallpox, scarlet fever, sepsis of the newborn infant, and other infectious diseases. Gastric lesions in these conditions are often unsuspected during life, since vomiting and anorexia are frequent symptoms in all of them. Occasionally there is bleeding, and the vomitus contains either fresh or digested blood.

**Corrosive Gastritis.** This form of gastritis is produced by strong acids or alkalis or by other irritants. There are accompanying lesions of the mouth, pharynx and esophagus. When sufficient quantities of an irritant are swallowed to produce an extensive gastritis, the prognosis is grave. Collapse occurs quickly, and death is likely within a few hours, or life may be prolonged for two or three days and then death results from exhaustion. If the child survives, there may be symptoms of chronic gastritis. In most instances the esophageal lesion is the one of most importance.

**Treatment.** The general treatment of burns from acids and alkalis is discussed on page 1380, and of esophageal lesions on page 644. There is no special treatment for acute catarrhal gastritis, except that of the infection responsible for it. Coarse foods should be avoided; when there is persistent vomiting, parenteral administration of fluids and nutrients is required.

## GASTRIC DILATATION

**Acute Dilatation.** Acute dilatation of the stomach, and of the intestine as well, may occur during the acute stages of pneumonia and other severe infections, after abdominal and thoracic operations, during peritonitis, with diabetic acidosis and intestinal obstruction, and occasionally without discoverable cause. Dilatation is a serious condition, especially when it occurs with pneumonia and peritonitis. Temporary relief can be provided by deflation through a stomach tube or, when there are accumulated gastric contents, by lavage. The use of the Wangenstein suction apparatus in postoperative conditions has been helpful in avoiding and in treating gastric dilatation. Prostigmin, subcutaneously, may be of some benefit.

**Chronic Dilatation.** Chronic dilatation may follow a mechanical obstruction such as stenosis of the pylorus, or one from external traction by adhesions or by pressure of a tumor in the pyloric area. It may also be a manifestation of chronic gastritis. During infancy the most frequent cause is atony of the muscular wall in such conditions as rickets and extreme malnutrition.

The treatment depends upon the cause. A mechanical obstruction should be relieved. Chronic nutritional disturbances should be corrected. Overfeeding should be avoided, but an adequate intake of calories, vitamins and minerals must be maintained.



## GASTRIC HEMORRHAGE

Bleeding from the stomach may occur in association with purpura, hemophilia, hypoplastic anemias, leukemia, scurvy, cirrhosis of the liver, peptic ulcer, esophageal varices associated with obstruction of the portal or splenic vein, polypoid adenoma of the stomach or congenitally short esophagus. Traumatic rupture of the stomach, injury from a swallowed foreign body, generalized infections, diabetic acidosis and persistent vomiting as in pyloric stenosis may also be responsible for gastric hemorrhage.

**Differential Diagnosis.** Blood which is vomited may originate elsewhere than in the stomach; it may come from the nose, mouth, esophagus, lungs or the fissured nipple of the nursing mother. Blood expectorated from the lungs without swallowing is frothy. When hemorrhage from the stomach is copious, the blood is usually bright red, but when bleeding has taken place slowly and the blood has remained for some time in the stomach, the color will be dark brown or black (coffee ground vomitus).

**Prognosis and Treatment.** The prognosis depends upon the cause, but extensive gastric hemorrhage is usually serious.

In extensive hemorrhage immediate steps should be directed toward its control, treatment of shock and replacement of lost blood. The child should be put at absolute rest, an ice bag should be placed over the epigastrium, and morphine given hypodermically. When the hemorrhage is extensive, blood transfusions should be given as soon as possible to replace the lost blood. When the bleeding is continuous, gentle but constant aspiration through a Levin tube may aid in putting the stomach at rest, remove the irritation from gastric secretions and provide an index of the extent of the bleeding. Every effort should be made to determine the cause.

## NEOPLASMS OF THE STOMACH

Neoplasms of the stomach are extremely rare in early life; primary carcinoma, sarcoma, lymphosarcoma, lipomas, polypoid adenomas and teratomas have been observed.

## FOREIGN BODIES IN THE STOMACH AND INTESTINES

An object which reaches the stomach will in most instances pass through the gastrointestinal tract. Certain types of foreign bodies,

however, are potentially dangerous. Needles, hairpins or bobby pins pass easily through the esophagus on their long axis, but may be unable to round the turns of the duodenum, where they become fixed and eventually perforate the intestine. Such potentially dangerous foreign bodies can usually be removed gastroscopically. Special attention should be paid to safety pins in the stomach. If they are small, they will probably pass without difficulty, whether open or closed. If they are large, either closed or open, peroral removal is safe and is indicated.

If the foreign body has passed through the pylorus into the intestine, its progress should be observed daily by means of roentgenograms, and every stool should be examined for its presence. The stool can be placed in a fine-meshed sieve and disintegrated by allowing water to run through the sieve with some force. If the roentgenogram shows the foreign body to move progressively down the intestinal tract, perforation is not likely. If it remains stationary for a week, surgery is indicated because of the dangers of ulceration and perforation of the bowel. If at any time such signs of perforation as tenderness, rigidity, pain, nausea or vomiting develop, surgery is indicated immediately. The diet should be normal, with no change from that to which the child has been accustomed. The bizarre roughage and wool or cotton diets sometimes recommended are valueless and may be extremely dangerous. Laxatives are contraindicated, since the accelerated activity of the intestine increases the danger of perforation.

## GASTRIC PERFORATION

Perforation of the stomach or adjacent portions of the esophagus or duodenum is relatively uncommon in infants and children; it is more often recognized at autopsy than during life. Recently there have been a number of reports of spontaneous rupture of the stomach in newborn infants, some of which were recognized during life and repaired surgically with recovery of the infant.

Among the causes, perforation of ulcers is the most readily explained; these include ulcers secondary to an indwelling lavage tube, those associated with systemic diseases, usually acute ones, Rokitansky-Cushing ulcers and chronic gastric and duodenal ulcers (p. 671). Of particular interest are the cases of spontaneous perforation in apparently healthy newborn infants. Some of these have not

been explained at autopsy by any lesion other than the rent; rarely some have been associated with obstructive lesions, such as atresia of the pylorus, but a significant number have occurred in infants with defects of the gastric musculature. The perforation has occurred through these defects, usually along the greater curvature.

Initial *symptoms* are not characteristic. Vomiting is usually the first one; both the vomitus and the stool may contain blood. Abdominal distention occurring suddenly in an infant should always suggest the possibility of perforation at some site in the gastrointestinal tract, especially if there is obliteration of liver dullness. Cyanosis may appear if the distention is sufficient to interfere with respiration. Manifestations of shock can appear rapidly. A roentgenogram of the abdomen taken in an upright position revealing a pneumoperitoneum is diagnostic of perforation.

*Treatment* consists in surgical repair as quickly as the infant can be prepared. Post-operatively, Wangensteen suction may be useful for two or three days, and fluids, and blood if necessary, should be given parenterally (see p. 191).

## BEZOARS

Occasionally infants and children acquire the habit of swallowing hair from their head or from dolls, brushes, hair pillows or the like, or they may swallow fur, wool or cotton from wearing apparel or blankets. Though some of this material may be passed through the intestines, when the habit is persistent, there is an accumulation in the stomach with formation of the so-called *hairball* or *trichobezoar*. The *symptoms* are indefinite, but indigestion and gastric distress are often present. The tumor mass is often palpable, and may give a soft crackling sensation on palpation. A roentgenogram taken after administration of barium may disclose a characteristic



Fig. 191. Hairball (trichobezoar) in the fundus of the stomach of a girl 5 years of age; it is outlined by barium. The child was admitted to the hospital for intestinal obstruction resulting from a portion of the trichobezoar which had detached from the gastric mass and become impacted in the ileum.

picture (Fig. 191). A portion of the bezoar may be dislodged and subsequently become impacted in the intestine and cause obstruction. The *diagnosis* may be suspected from observation of the child in the act of swallowing these materials, and hair may occasionally be observed in the mouth or the stools. The tumor mass should be removed surgically. The child's mental and psychologic status should be evaluated, and treatment provided as indicated.

*Phytobezoars* are accumulations of fibrous or mucilaginous materials such as that in persimmons and various tar products. The accumulation is usually rapid in comparison with that of the hairball.

## INTESTINAL DISORDERS

### MALFORMATIONS AND MALPOSITIONS OF THE INTESTINES

A variety of congenital anomalies of the intestinal tract are responsible for partial or complete obstruction. The majority of these malformations involve the rectum and the

anus (p. 680), with the duodenum next in order of involvement: the jejunum, the ileum and the colon are less often affected. The principal anomalies may be grouped under the following headings: (1) intrinsic obstruction of the lumen by stenosis, atresia, aplasia or absence of a segment of the gut; (2)



anomalies of position which include (a) variations in mesenteric attachments resulting at times in volvulus or in bands of tissue constricting the intestine, (b) malrotation of the intestine with or without associated volvulus and constricting bands (*malrotation may be responsible for intestinal obstruction at any age, for recurrent abdominal pain throughout childhood or for the clinical manifestations of the celiac syndrome*); (c) transposition of the intestines in conjunction with transposition of other viscera; (3) diverticula, of which the principal one is Meckel's; (4) anomalies of size such as microcolon; (5) anomalies of innervation, as manifest by aganglionic segments (megacolon); (6) duplications, which may occur in practically any portion of the digestive tract, viz., esophagus, stomach and small and large intestines; (7) intra-abdominal hernias through omental and mesenteric defects, through rings formed by remnants of the omphalomesenteric duct, and through diaphragmatic defects; and (8) external hernias, which include those into an omphalocele, through the inguinal canal, and through various external muscular defects.

## INTESTINAL OBSTRUCTION

### CONGENITAL INTESTINAL OBSTRUCTION

Obstruction of the intestinal tract at birth may be complete or partial. A completely obstructive lesion is most likely to be either an atresia or an aplasia of a segment of the intestine, although complete obstruction may occur from some of the lesions which characteristically produce only partial obstruction. From an anatomic standpoint congenital obstructive lesions of the intestines can be divided on the basis of whether the obstructing factor is intrinsic or extrinsic.

#### *Intrinsic Obstructions*

Aplasia  
Atresia  
Stenosis  
Aganglionic segments  
Meconium ileus

#### *Extrinsic Obstructions*

Volvulus of the midgut, usually with malrotation of the cecum  
Extrinsic duodenal bands, commonly with malrotation of the cecum and its fixation in the right upper quadrant  
Constricting bands in the region of the ligament of Treitz  
Duodenal compression by the mesenteric artery  
Herniations  
Intra-abdominal through

#### *Extrinsic Obstructions*

Omental and mesenteric defects  
Rings formed by remnants of omphalomesenteric duct  
Diaphragm  
Extra-abdominal  
Annular pancreas  
Duplications of segments of small or large intestine

**Clinical Manifestations.** Clinically, the anatomic feature of a congenital intestinal obstruction is often not definable and is of secondary importance, since operation is *always* indicated. An attempt to locate the lesion, however, is of considerable importance, since it may determine the surgical approach. The differences in operative techniques for a duodenal atresia and in imperforate rectum are readily appreciated.

When the obstruction is *complete*, there should be no difficulty in clinical recognition, but when incomplete, there may at times be considerable difficulty. With complete obstruction symptoms appear shortly after birth. If the obstruction is in the duodenum, the symptoms may become manifest within a few hours; if it is in the large intestine, the symptoms may be delayed for a day or so. They consist characteristically in vomiting, abdominal distention and an absence of feces. Meconium stools may be passed, but, on microscopic examination, absence of lanugo hairs and cornified epithelial cells, which are swallowed with the amniotic fluid, is suggestive evidence of a complete obstruction (*Farber test*). This test is a valuable one, but care should be taken to obtain the specimen for examination from the center of the meconial mass. Epithelial cells from the rectum and perianal area may adhere to the outside of the stool and be misinterpreted as swallowed epithelial cells.

When the obstruction is *incomplete*, symptoms may appear shortly after birth or be delayed, depending on the degree of obstruction. Enough food may pass the constriction to permit fecal discharge.

Obstruction in the duodenal area is responsible for epigastric distention and, at times, for gastric waves similar to those of pyloric stenosis. The distention may not be persistent, however, since it may be relieved by vomiting. The vomiting may be projectile, and the vomitus will contain bile if the obstruction is below the ampulla of Vater.

Obstructions in the lower ileum, colon or rectum will be responsible for more generalized distention, often with bulging of the flanks. When the liver dullness is obliterated,

there is a strong possibility that intestinal perforation has occurred. Vomiting with lower bowel obstruction may be delayed a day or so, but eventually may become fecal in type. Meconium ileus is described on page 331, aganglionic megacolon on page 674, and anal and rectal obstructions on page 680.

**Differential Diagnosis.** This is principally from other causes of persistent vomiting, abdominal distention and obstipation. In *atresia of the esophagus* swallowed food is vomited immediately; when there is a *fistula* between the trachea and lower esophageal segment, there is air in the stomach. The esophageal obstruction can be demonstrated by inability to pass a catheter or by roentgenologic examination with the use of iodized oil. If the obstruction is in the duodenum, pyloric stenosis may be suspected because of the gastric peristalsis and because the distended duodenum may simulate a pyloric tumor. The symptoms of *pyloric stenosis* are rarely manifest, however, until the second or third week of life, and the vomitus does not contain bile, as it does when the duodenal obstruction is below the ampulla of Vater.

In stenosis of the lower ileum or colon the vomiting appears later and is eventually fecal. In newborn infants a paralytic ileus may develop within a few days after birth in association with general sepsis or peritonitis and simulate lower intestinal obstruction.

Valuable information on the location of congenital obstructive lesions in the intestine may be obtained by roentgenograms of the abdomen without ingestion of contrast material, since in completely obstructive lesions there will be distention of the bowel above the obstruction and there may be a series of fluid levels with superimposed gas in the distended loops. When the use of contrast material is considered necessary either by mouth or by enema, some material other than barium should be used.

Insufflation of air into the stomach under fluoroscopic control may localize duodenal and other obstructive lesions. Under usual circumstances air is demonstrable roentgenographically in the stomach of the normal infant immediately after birth. Within an hour the proximal portion of the small intestine is outlined, and, between the first and third hours, the entire small intestine and segments of the colon are demonstrable. The distal parts of the colon may be visualized as early as the third hour. Up to the time of the first feeding there is a progressive increase in the amount of air in both the small and

large intestines. After the first feeding there is a relative decrease in the amount of air in the small intestine and an increase of it in the colon.

**Prognosis.** When a complete obstruction is not relieved promptly, the clinical course is rapid. Vomiting is persistent, dehydration, loss of weight, and prostration become marked, and the infant dies within a few days. When the obstruction is not complete, the infant may survive for weeks; minor obstructions may be compatible with life even without treatment. Recovery from both complete and incomplete obstructions can be expected in the majority of instances with early diagnosis and appropriate management.

**Treatment.** Not every obstructive lesion is amenable to surgery, but every patient is entitled to the opportunity for surgical repair. Infants can even withstand massive resection of the small intestine when the lesion or lesions necessitate it.

Preoperative preparation, including constant gastric aspiration, and postoperative care are of the greatest importance, especially in relation to the correction of dehydration and electrolyte deficits and to the maintenance of fluid balance and nutrition by parenteral means (p. 195).

#### ACQUIRED INTESTINAL OBSTRUCTION

There are a number of causes of acquired intestinal obstruction. Paralytic ileus, which is secondary to acute infections, especially pneumonia and peritonitis, and to uremia and electrolyte imbalance of any origin, is a frequent cause. Pneumonia is probably the most frequent cause of paralytic ileus in infants; peritonitis, the most frequent cause in older children. Incarcerated inguinal hernias and intussusception are the most frequent mechanical causes of intestinal obstruction in infants. Intestinal obstruction may also result from adhesions produced during the course of an acute peritonitis from which recovery occurred, or the adhesions may result from a chronic peritonitis such as a tuberculous one. Other causes are foreign bodies in the intestine, including fecal concretions and inspissated meconium in the newborn infant (p. 331); tumors of the bowel or those pressing on it, such as mesenteric cysts, and masses of roundworms. Rectal stricture from lymphogranuloma venereum rarely occurs in children.

Certain congenital anomalies responsible for intestinal obstruction may not manifest themselves until some time after birth. These



include intra-abdominal herniations, volvulus resulting from malrotation of the intestine, and duplications of the bowel.

### INTUSSUSCEPTION

Intussusception or invagination of a portion of the intestine into an adjacent part competes with incarcerated inguinal hernia as the most frequent acquired mechanical cause of intestinal obstruction in infancy. Though rare in the first month of life, over half of the cases occur in the first year and most of the remainder in the second. It is two to three times more common in males than in females.

**Etiology.** In most instances intussusception develops in healthy infants, its production supposedly being favored by the unusual mobility of the cecum and ileum and by the hyperperistalsis present in early life. *Agonal intussusception* is presumably caused by the loss of muscular tone which precedes death.

**Predisposing factors.** Infrequently there are demonstrable predisposing factors such as drastic purgation, diarrhea, constipation, abnormalities such as Meckel's diverticulum, invagination of the appendix, abdominal injuries, hemorrhage or ulceration of the gut, foreign bodies, large fecal masses or parasites in the lumen of the intestine, polyps, cysts, papillomas or other intestinal tumors, and swelling of the lymphatic tissue of the intestinal wall.

**Pathology.** The invagination is almost invariably from above downward. The upper portion, the intussusceptum, slips into the lower, the intussusciens, pulling the mesentery with it (Fig. 192). The dragging upon the mesentery causes the intestine to assume a curved, sausage-shaped form, with the concavity toward the mesenteric attachment at the spinal column. The bowel can remain patulous, the circulation of blood in it be preserved, and occasionally the intussusception is spontaneously reduced. Usually, however, swelling begins promptly as a result of edema and hemorrhage secondary to venous engorgement, with resultant complete intestinal obstruction. Incarceration of the intussusceptum occurs, which becomes irreducible through adhesive inflammation between the adjacent serous surfaces, and finally strangulation takes place, with necrosis of the part. The strangulated portion may perforate or rarely become entirely separated by gangrene and be discharged through the anus, the lumen of the gut thus becoming re-established. Agonal intussusception shows little

evidence of inflammation or swelling and is without clinical significance.

**Clinical Forms.** Intussusceptions are classified according to their situation as enteric, colic, ileocolic and ileocecal. Mixed forms may occasionally occur; a double intussusception is observed in less than 10 per cent of cases. Ileocecal intussusception is the most frequent form; the cecum with the ileum behind it passes into the colon.

**Clinical Manifestations.** In typical cases there is a sudden onset, with severe paroxysmal pain, vomiting, and restlessness. In between the initial paroxysms of pain the infant may be quite comfortable. These symptoms are usually followed within twelve to twenty-four hours by the rectal passage of bloody mucus and by a rapidly developing and increasingly severe prostration. The abdomen is at first soft, later distended, and often tender. The fecal matter in the colon and rectum may be evacuated during the first several hours. After this time fecal excretions are small, or more often they do not occur, and little if any flatus is passed.

**Pain.** Characteristically, pain is paroxysmal, occurring at frequent intervals and attended by straining efforts if the intussusception reaches the rectum. Early the pain is usually intense and causes loud outcries; later it may be evidenced only by grunting sounds.

**Blood and mucus in the stools.** Blood generally appears in the first twelve hours, but at times not for one or two days or even not at all. Stools containing blood and mucus are often described as currant jelly stools. Failure of evacuation of fecal matter and of flatus is most common in enteric invagination, in which, too, hemorrhage may be delayed or entirely absent.

**Vomiting.** This is usually more frequent at the beginning. Stercoraceous vomiting is uncommon and generally not until late in the course.

**Tumor.** The elongated, sausage-shaped tumor may often be found early in the course,

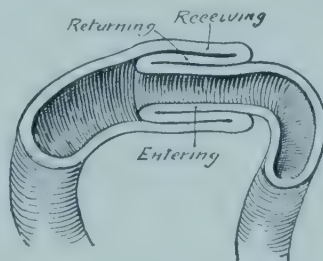


FIG. 192. Diagrammatic representation of the production of intussusception. (Kemp: Diseases of the Stomach, Intestines and Pancreas.)



FIG. 193. Intussusception in an infant. The obstruction is evident in the proximal transverse colon. Contrast material between the intussuseptum and the intussusciens is responsible for the coil-spring appearance.

even in the first few hours, and rarely may reach the anus by the second day. It is usually possible to palpate it rectally by bimanual examination; during a paroxysm of pain the tumor temporarily increases in size and approaches nearer to the anus. When protruding from the anus, the intussusception may have the appearance of a rectal prolapse or a polyp. The presence of bloody mucus on the finger as it is withdrawn after rectal examination is supportive evidence.

**Prostration.** The initial restlessness is rapidly replaced by exhaustion and prostration. In the untreated case prostration is likely to be extreme by the second day, and the temperature may reach  $106^{\circ}$  to  $108^{\circ}$  F.

**Atypical forms.** Intussusception rarely may exist for a number of days (*chronic form*) without the usual acute symptoms. Such cases are more likely to occur in infants during a severe diarrheal disturbance or in older children, when intussusception is a rarity. The obstruction is not complete, and the circulation in the mesentery is not entirely obliterated. Pain and vomiting may not be severe, and there may not be bloody mucous stools. Diarrhea may be present instead of constipation. The symptoms in these chronic cases may come on in separate attacks and suggest recurrent ileocolitis. There is always the danger of sudden complete strangulation.

*Chronic recurrent intussusception* is rare;

instances have been observed, especially in older children, in which repeated intussusceptions are spontaneously reduced.

**Differential Diagnosis.** The diagnosis is not difficult in the average case when there are sudden developments of abdominal pain, vomiting, tenesmus, bloody stools without fecal matter, prostration and an abdominal tumor. The mass may be obscured after several hours by abdominal distention or rigidity unless examination is made under an anesthetic. Enteric intussusception seldom presents a discoverable tumor, there is no tenesmus, and these cases cannot be distinguished with certainty from intestinal obstruction of other causes. The bloody, mucous movements of intussusception may suggest *colitis*; conversely, *colitis* may be supposed to be intussusception. In *nonthrombocytopenic purpura* hemorrhage into the lumen and walls of the intestine may simulate intussusception, but evidences of purpura elsewhere aid in distinguishing it. Intussusception may, however, be a complication of purpura. With *Meckel's diverticulum* there may be blood in the stool without other symptoms, or, if there is a diverticulitis, it may simulate appendicitis.

Contrast roentgenograms, after a barium enema, may demonstrate the intussusception (Fig. 193).

**Prognosis.** Untreated cases in infants are nearly always fatal; the chances of recovery are directly related to the duration of the intussusception before reduction. The majority of infants will recover if the intussusception is reduced within the first twenty-four hours, but the mortality rate rises rapidly after this time, and recoveries are unusual when reduction is deferred to the third day. In the uncommon less acute cases the course, if untreated, may be as long as two or three weeks. In such instances death usually results from exhaustion and rarely from peritonitis. Spontaneous reduction may occur; the incidence, of course, is not known. The rate of recurrent attacks in infants is apparently not more than 2 or 3 per cent.

**Treatment.** The intussusception should be reduced as soon as the patient can be prepared for operation by treatment for shock and correction of water and electrolyte imbalances (p. 186). Experience in our clinic in reduction of the intussusception has been limited to the direct surgical approach. Ravitch and others use a nonoperative technique in selected cases. An adequate comparative evaluation of the operative and non-



operative methods is not available; in each the skill and experience of the operator are important factors.

The advantages of the operative method are (1) certainty of reduction, (2) demonstration of any "lead points" (Meckel's diverticulum, polyp, and the like, which occur in 5 to 8 per cent), (3) avoidance of delay when the initial nonoperative method is not effective, and (4) possibly a lower recurrence rate.

When the nonoperative technique is to be used, Ravitch stresses that the operating room must be in readiness for immediate surgery should the nonoperative attempt be unsuccessful and that the reduction by barium enema should be performed by the surgeon under fluoroscopic observation. His technique for reduction by hydrostatic pressure is as follows:

The stomach is aspirated, intravenous administration of fluids is started, and a nonlubricated Foley bag catheter is placed in the rectum and inflated. The buttocks are compressed tightly and taped with adhesive plaster. A barium solution is then allowed to flow by gravity into the colon from a height of not more than 3 to 3½ feet above the fluoroscopic table. The abdomen is *not touched* during the procedure. If the intussusception is reduced, it is manifest by free filling of the small intestine, disappearance of the mass, passage of flatus or feces and improvement in the infant's condition. Charcoal is then administered by mouth, and its recovery in an enema six hours later is further evidence of intestinal patency. If there is any doubt about the completeness of the reduction, an exploratory operation is performed immediately through a McBurney's incision.

## DIVERTICULOSIS AND DIVERTICULITIS

Diverticulosis refers to the presence of multiple outpouchings of the intestinal tract, usually in the colon, but occasionally in the small intestine. With the exception of Meckel's diverticulum, most diverticula are of the false type, i.e., saccular pouches, the walls of which are largely devoid of the muscular coat of the intestine. Their etiology is unknown, but they seem to result from weakness of the intestinal wall. The condition is usually benign, often being unproductive of symptoms. Occasionally there is general abdominal discomfort such as that associated with spastic colitis, but in the majority of instances one may doubt whether the diverticula are responsible for the symptoms. The condition, though more common in adults, may occur in children.

*Diverticulitis*, or inflammation of the diver-

ticula, may take place, giving rise to nausea and vomiting, fever, leukocytosis, and abdominal tenderness and rigidity usually in the lower left quadrant. Perforation occasionally occurs with resulting peritonitis. Treatment is symptomatic; if perforation occurs, it is that of peritonitis.

## DISORDERS ASSOCIATED WITH MECKEL'S DIVERTICULUM

The omphalomesenteric duct, which connects the ileum to the umbilical vesicle or yolk sac and ordinarily atrophies and disappears by the fifth or sixth month of fetal life, may persist in all or part of its course and be responsible for a variety of anomalies (Fig. 194). Of these, the most frequent is Meckel's diverticulum, which is estimated to occur in 2 to 3 per cent of all persons, more frequently in males than in females.

**Pathology.** Meckel's diverticulum is located on the ileum. The wall of the diverticulum is similar to that of the adjacent intestine, as is its lining membrane, although cells of other tissues may make up a part of the membrane. The most frequent type of aberrant tissue is identical with gastric mucosa. Less frequently there are pancreatic cells, including those of the islets of Langerhans, or cells of duodenal or colonic mucosa.

**Clinical Forms.** The diverticulum is usually not responsible for any symptoms, but perhaps the most common one is hemorrhage from the bowel with or without other manifestations. It may, however, be responsible for a variety of clinical conditions, the principal ones being diverticulitis, intestinal obstruction and umbilical lesions.

**Diverticulitis.** This condition is relatively infrequent; about one third of the cases occur in children, the incidence being higher in males than in females. The pathogenesis and the pathologic changes may be similar to those of appendicitis. The course may be acute or chronic. When the onset is abrupt and is accompanied by abdominal pain, nausea, vomiting, often constipation, fever, leukocytosis, abdominal tenderness and muscular resistance, the differential diagnosis from appendicitis may be impossible except by operation. In some instances there is blood in the stools, which may provide a clue to the diagnosis. Hemorrhage may also occur into the peritoneal cavity. Perforation with secondary peritonitis is an occasional complication, as is intestinal obstruction, which may be produced by compression of the intestine by the inflammatory mass or by intussusception.

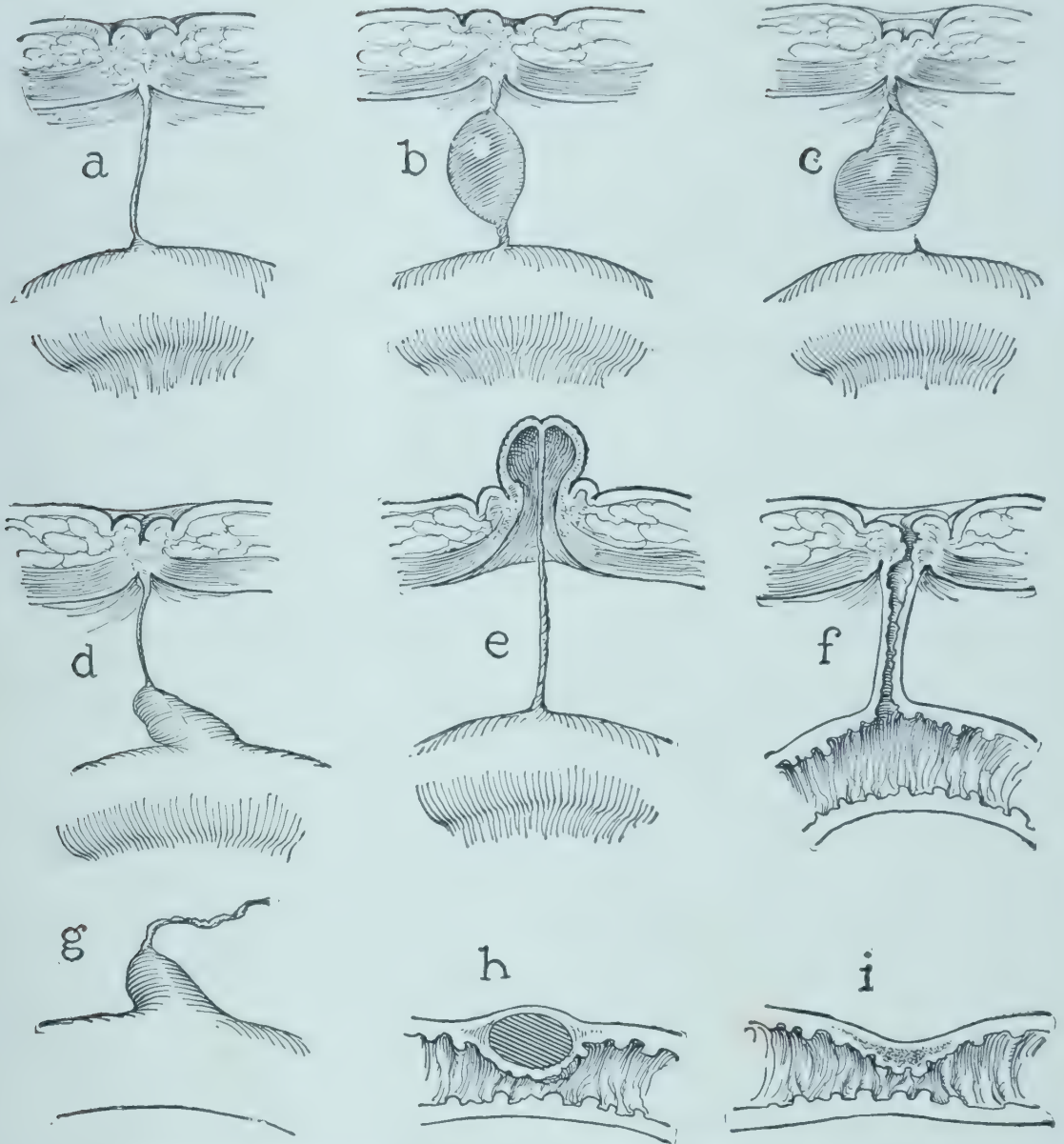


FIG. 194. Diagrammatic representation of structures derived from remnants of the omphalomesenteric duct. *a*, Cord extending between umbilicus and ileum; *b*, cyst suspended between umbilicus and ileum; *c*, cyst suspended from umbilicus; *d*, Meckel's diverticulum with cord extending to umbilicus; *e*, everted mucocoele attached by cord to ileum; *f*, fecal fistula between ileum and umbilicus; *g*, Meckel's diverticulum with free intraperitoneal cord; *h*, enterocystoma; *i*, stenosis from excessive evolution. (Brennemann: Practice of Pediatrics. W. F. Prior Co., Vol. 3.)

A *peptic ulcer* situated in aberrant gastric mucosa is occasionally observed in, or in the vicinity of, a Meckel's diverticulum. The method of production of the ulcer, its course and the symptoms produced are similar to those of gastric and duodenal ulcers. Hemorrhage from the bowel is the most frequent symptom; it may be intermittent and present over long periods of time or may be abrupt and extensive. Perforation of the ulcer may be responsible for peritoneal bleeding or peritonitis. Rarely a Meckel's diverticulum

can be identified roentgenographically after a barium meal.

**Intestinal obstruction.** Meckel's diverticulum may be responsible for intestinal obstruction in several ways. Strangulation of the intestine may result from herniation of a loop of intestine through a ring formed by the atrophied cord of the diverticulum. Volvulus of the intestine may be secondary to anomalies associated with Meckel's diverticulum, or the diverticulum may invaginate itself into the intestine and be responsible for a true



enteric intussusception. Littre's hernia is a rare condition in which a Meckel's diverticulum protrudes, along with the adjacent portion of the intestine, into a hernial sac, such as that of an inguinal, femoral or umbilical hernia. If the diverticulum becomes inflamed, as is likely, it becomes adherent to the hernial sac and is thus responsible for incarceration.

**Umbilical lesions.** A variety of lesions may occur (Fig. 194). If the omphalomesenteric duct remains patent, the fistulous tract from the intestine may discharge intestinal contents through the umbilicus. If the intestinal terminus is closed, there is only a mucoid secretion. A cystic mass may be formed in the tract when both ends of the duct are closed, and at times it may protrude through the umbilicus.

**Treatment.** In practically all disturbances of Meckel's diverticulum, operation is indicated. The kind of operation obviously depends upon the type of anomaly and its complications. If, during an abdominal operation for other conditions, a diverticulum is discovered, it should be removed if the situation otherwise permits.

## PEPTIC ULCER

### (GASTRIC AND DUODENAL ULCERS)

Gastric and duodenal ulcers occur at all ages of infancy and childhood, including the neonatal period. Although usually recognized only at autopsy, in a fairly large number the diagnosis has been established during life (see Gastric Perforation, p. 663). There is no good approximation of their incidence, but they are generally considered to be infrequent.

The *symptoms* related to the ulcer may dominate the clinical picture, but often the symptoms are obscured by some other serious disease, e.g., meningitis, gastroenteritis, sepsis or extensive burns (Curling's ulcer); ulcers associated with cerebral lesions of various types (Rokitansky-Cushing ulcers) are commonly diffuse areas of digestion of the esophagus or fundus of the stomach, but typical crater-like peptic ulcers may also be associated with cerebral lesions.

Duodenal ulcers are more frequent than gastric ones and are usually located on the posterior wall of the duodenum. Ulcers in infants are more likely to be acute than chronic, and signs and symptoms are often limited to the occurrence of melena and hematemesis or to those of perforation and peritonitis; vomiting may be projectile, owing to severe pylorospasm.

*Chronic primary peptic ulcers* occur more frequently after infancy, the incidence being higher in late childhood. The symptomatology is varied. In some instances there are only vague digestive complaints such as abdominal discomfort with or without localization or relation to eating. In some instances the pain is more characteristic of that in adults, being relieved by eating in most instances, but occasionally aggravated by it. Paraumbilical pain would appear to be more frequent in young children, and epigastric pain in older ones. Vomiting is less frequent than pain; in a few instances cyclic vomiting has been a manifestation. Blood may be present in the vomitus or stools. The frequency with which children with peptic ulcers are reported as being tense, compulsive and maladjusted speaks strongly for a psychogenic disturbance as a contributing etiologic factor.

In the *differential diagnosis* it must be ascertained that blood has not entered the stomach and intestine from outside sources, as from the nose or mouth or, in nursing infants, from the nipple of the mother (see p. 337 for laboratory test), and other causes for melena must be sought. Pyloric stenosis, Meckel's diverticulum, appendicitis, intestinal polyposis, gastrointestinal allergy, parasitic diseases and the various blood dyscrasias must all be considered diagnostic possibilities. Roentgenograms may show a characteristic appearance of the duodenum. Sometimes duodenitis occurs without ulceration, and the roentgenogram shows poor filling and rapid emptying of the duodenal cap.

**Treatment.** Extensive hemorrhages require transfusions and continuous but gentle gastric aspiration when there are no signs of perforation (see Gastric Hemorrhage). Immediate laparotomy is indicated when perforation has occurred. Treatment of the chronic peptic ulcer is similar to that recommended for adults and consists of a bland diet with frequent small feedings with or without antacids and antispasmodics. Banthine has been used extensively in adults. Psychologic evaluation and appropriate therapy are considerations of first importance. Surgical repair should be reserved for those children whose lesions cannot be controlled by other means.

## REGIONAL ENTERITIS

Regional enteritis is a localized chronic lesion of the lower intestinal tract which may eventually be controlled spontaneously or may be slowly progressive. In the latter event in-

testinal obstruction may be produced, or there may be discharging sinuses which open through the abdominal wall into any of the hollow viscera of the abdominal cavity or into the vagina. Occasionally there are perirectal, rectal or rectovaginal fistulas. The incidence is highest in young adults, but cases have been observed in children.

**Etiology.** The cause is unknown; low grade infection and allergy have been suggested as possible causes.

**Pathology.** The lesion is usually limited to the terminal ileum, but may extend into the jejunum or even into the cecum and colon. Occasionally, multiple involved areas may be separated by relatively intact bowel. The wall of the bowel is thickened, hyperemic and indurated, and extensions of mesenteric fat partially encircle the serosa. The lumen is narrowed and the mucosa ulcerated; fistulas may extend from the ulcers into the abdominal wall, the mesentery or adjoining loops of bowel. Histologically, there is severe edema of the submucosa, with fibrosis in the chronic stages. The lymphoid tissue of the involved bowel is hyperplastic, as are the mesenteric lymph nodes. Granulomatous foci or isolated giant cells are often present.

**Clinical Manifestations.** The onset is occasionally acute, with symptoms suggestive of acute appendicitis. More often, however, the onset is insidious, and the course is that of a low grade chronic infection without specific complaints. There may be abdominal pain, failure to gain or loss of weight. Though there may be mild diarrhea, there are often intermittent periods of constipation. During the periods of diarrhea the stools contain mucus and pus and, at times, blood. Vomiting is not common. There is frequently a low grade fever and anemia. Abdominal examination may not reveal any evidence suggestive of the lesion unless there is a tender fixed mass in the lower part of the abdomen. The mass is more often situated on the right than in the midline or on the left side. The presence of an external fistula should always suggest the possibility of regional enteritis. Complete or partial intestinal obstruction may be the presenting symptom.

**Differential Diagnosis.** When the onset has been abrupt, appendicitis may be suspected. In the chronic stage, chronic colitis, tuberculosis and abdominal actinomycosis should be considered. On occasion Hodgkin's disease or lymphosarcoma may be responsible for symptoms suggestive of regional enteritis. The possibility of chronic colitis can usually be

eliminated by proctoscopic examination or by means of a barium enema. The characteristic "string sign" of regional enteritis may be demonstrated by this method.

**Prognosis.** The prognosis for life is usually good, but the course of the disease is persistently chronic, and spontaneous cures are infrequent; this is especially true when fistulous tracts have developed.

**Treatment.** No treatment is entirely satisfactory. Initially elimination diets may be tried with the possibility that the lesion is an allergic one. There are differences of opinion concerning surgical treatment, but it should be reserved for cases which do not respond to medical therapy. One of the broad-spectrum antibiotics may be given a trial and is recommended for the immediate preoperative and postoperative periods if radical surgery is undertaken. Corticosteroids have been used, but their value is not established.

### PNEUMATOSIS INTESTINALIS

This is a rare condition characterized by multiple gas-filled cysts in the wall of the bowel. The cysts may be located in the small intestine, the colon, or both; in infants they



FIG. 195. Lateral roentgenogram of the abdomen of an infant with aganglionic megacolon involving the entire colon. Pneumatosis of the colon was demonstrated ante mortem and post mortem in the walls of the rectum and sigmoid; note the apparent double contour of the intestinal walls (arrows).



are predominantly submucosal. The condition may occur at any age. In infants it is often associated with intrinsic disease of the gastrointestinal tract, e.g., enterocolitis, pyloric stenosis or congenital abnormalities. No symptoms directly related to pneumatosis in infancy are recognized. The diagnosis has been established roentgenographically (Fig. 195) or at laparotomy, but more frequently at autopsy. The pathogenesis of the cysts is not known, but may be related to mucosal defects with escape of intestinal gases into the lymphatics and wall of the bowel. Death appears to result from some cause other than the pneumatosis.

WALDO E. NELSON

## REFERENCES

### *Vomiting and Recurrent Vomiting*

Millichap, J. G., Lombroso, C. T., and Lennox, W. G.: Cyclic Vomiting as a Form of Epilepsy in Children. *Pediatrics*, 15:705, 1955.

Richmond, J. B., Eddy, E., and Green, M.: Rumination, a Psychosomatic Syndrome of Infancy. *Pediatrics*, 22:49, 1958.

Smith, C. H.: Recurrent Vomiting in Children; Its Etiology and Treatment. *J. Pediat.*, 10:719, 1937.

### *Epidemic Nausea and Vomiting*

Reimann, H. A., Hodges, J. H., and Price, A. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause. *J.A.M.A.*, 127:1, 1945.

Zahorsky, J.: Winter Vomiting Disease. *Arch. Pediat.*, 57:666, 1940.

### *Diarrhea*

Colgan, M. T.: The Bacterial Flora of the Intestinal Tract: Changes in Diarrheal Disease and Following Antimicrobial Therapy. *J. Pediat.*, 49:214, 1956.

Eichenwald, H. F., Abadio, A., Arky, A. M., and Hartman, A. F.: Epidemic Diarrhea in Premature and Older Infants Caused by ECHO Virus Type 18. *J.A.M.A.*, 166:1563, 1958.

Hodes, H. L.: The Etiology of Infantile Diarrhea; in Levine, S. Z., ed.: *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1956, Vol. 8.

Morgan, H. R., Breese, B. B., and Greendyke, R. M.: Primary Staphylococcal Enterocolitis. *A.M.A. Am. J. Dis. Child.*, 93:526, 1957.

Smith, R. T.: Epidemic Staphylococcal Gastroenteritis in a Newborn Nursery. *A.M.A. Am. J. Dis. Child.*, 92:45, 1956.

Wheeler, W. E., and Wainerman, B.: The Treatment and Prevention of Epidemic Infantile Diarrhea. *Pediatrics*, 14:357, 1954.

### *Pyloric Stenosis*

Meeker, C. S., and DeNicola, R. R.: Hypertrophic Pyloric Stenosis in a Newborn Infant. *J. Pediat.*, 33:94, 1948.

Wallgren, A.: Lingual Application of Eumydrin in Treatment of Congenital Pyloric Stenosis. *Arch. Dis. Child.*, 15:103, 1940.

———: Preclinical Stage of Infantile Hypertrophic

Pyloric Stenosis. *Am. J. Dis. Child.*, 72:371, 1946.

### *Gastric Perforation*

Meyer, J. L., II: Congenital Defect in the Musculature of the Stomach Resulting in Spontaneous Gastric Perforation in the Neonatal Period. *J. Pediat.*, 51:416, 1957.

### *Malformations and Malpositions, Intestinal Obstruction*

Gross, R. E.: *The Surgery of Infancy and Childhood*. Philadelphia, W. B. Saunders Company, 1953.

Manson, G.: Anomalies of Intestinal Rotation and Mesenteric Fixation. *J. Pediat.*, 45:214, 1954.

Mellins, H. Z., and Milman, D. H.: Congenital Duodenal Obstruction: Roentgen Diagnosis by Insufflation of Air. *Am. J. Dis. Child.*, 72:81, 1946.

Pilling, G. P., and Cresson, S. L.: Massive Resection of the Small Intestine in the Neonatal Period. *Pediatrics*, 19:940, 1957.

Ravitch, M. M.: The Nonoperative Treatment of Intussusception. *S. Clin. North America*, 36:1495, 1956.

Santulli, T. V.: Intestinal Obstruction in the Newborn Infant. *J. Pediat.*, 44:317, 1954.

Wasch, M. G., and Marck, A.: The Radiographic Appearance of the Gastrointestinal Tract during the First Day of Life. *J. Pediat.*, 32:479, 1948.

### *Diverticulosis and Diverticulitis*

Howell, L. M.: Meckel's Diverticulum: A Consideration of the Anomaly, with a Review of Sixty-One Cases. *Am. J. Dis. Child.*, 71:365, 1946.

Potts, W. J.: Diseases of the Small Intestine, Cecum, Peritoneum and Omentum; in McQuarrie, I., ed.; *Brennemann's Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Co., Inc., 1957, Vol. 3, Chap. 6.

### *Peptic Ulcer*

Cole, A. R. C.: Gastric Ulcer of the Pylorus Stimulating Hypertrophic Pyloric Stenosis. *Pediatrics*, 6:897, 1950.

Girdany, B. R.: Peptic Ulcer in Childhood. *Pediatrics*, 12:56, 1953.

### *Regional Enteritis*

Crohn, B. B.: Regional Ileitis. *Surg., Gynec. & Obst.*, 68:314, 1939.

Rowe, A. H., Rowe, A. H., Jr., and Uyeyama, K.: Regional Enteritis—Its Allergic Aspects. *Gastroenterology*, 23:554, 1953.

### *Pneumatosis Intestinalis*

MacKenzie, E. P.: Pneumatosis Intestinalis. Review of the Literature with Report of 13 Cases. *Pediatrics*, 7:537, 1951.

## MEGACOLON

The terms "megacolon" and "Hirschsprung's disease" have been used interchangeably to include most enlargements of the colon except those resulting from partial obstruction by obvious anatomic lesions in the anorectal area, such as anorectal stenosis (p. 680). The demonstration that many examples of megacolon are secondary to an absence of

myenteric ganglion cells in the distal, constricted segment of the colon has created a separate clinical entity, designated neurogenic or congenital aganglionic megacolon. Psychogenic factors resulting in obstipation, at times with encopresis (p. 654), may also be responsible for enlargement of the colon. The classification of megacolon by Garrard and Richmond is a useful one:

- Megacolon due to gross anatomic lesion
  - Stricture secondary to surgical repair of imperforate anus
  - Anorectal stenosis
  - Intrinsic or extrinsic obstructing tumors
- Aganglionic megacolon (neurogenic)
- Psychogenic megacolon

Since patients with megacolon of either the first or second category can expect improvement from surgical or other mechanical therapy, and since those with psychogenic megacolon not only would be harmed by such treatment, but also might be helped by psychotherapy, the importance of differentiation is obvious.

#### CONGENITAL AGANGLIONIC MEGACOLON

##### (HIRSCHSPRUNG'S DISEASE)

Congenital absence of parasympathetic ganglion cells from the intramural plexus of a portion of the intestinal tract, usually the distal end of the colon, is responsible for the entity described here. The involved section of the gut is narrowed and devoid of peristaltic activity, and is thus responsible for accumulation of fecal material above it. As a result the uninvolved portion of the intestine (usually colon) becomes greatly dilated and hypertrophied and is responsible for abdominal distention, which with the obstinate constipation creates the typical clinical pattern.

Congenital megacolon is more common in males than in females. In a series of 200 cases Swenson has observed three families with more than one child with aganglionic megacolon.

**Pathology.** A narrowing of a portion of the rectum or rectosigmoid is usually demonstrated. Proximal to the narrowed segment, the colon is tremendously dilated and filled with feces and gas, and the muscular coat is hypertrophied. In long-standing cases this dilated portion of the intestinal wall may become thin. Ulceration of the mucosa is an infrequent complication in older children, but it is not rare in infants; perforation is unusual.

Histologic examination of the constricted portion of the rectosigmoid colon reveals an absence of the parasympathetic ganglion cells

of the intramural plexus, whereas they are present in the proximal dilated portion.

In the majority of instances (90 per cent) the aganglionic segment of the bowel is located in the rectum or rectosigmoid for a length of 4 to 25 cm. Instances of involvement of the entire colon, of portions of the small bowel and rarely of variously situated segments with absence of ganglion cells have been reported.

**Clinical Manifestations.** In newborn infants the symptoms of congenital megacolon may present a variety of patterns. The symptoms may be present at birth with failure to pass meconium, or may appear during the first week of life and be those of partial or even apparently complete intestinal obstruction with vomiting, constipation and abdominal distention. Roentgenograms of the abdomen will reveal fluid levels indicative of intestinal obstruction. Relief of symptoms may occur after a rectal examination or an enema with the appearance of normal stools for a short time. Bile-stained and even fecal vomiting may occur. In such cases the infant becomes dehydrated, and there is loss of weight. In some instances diarrhea may be the predominant symptom in the neonatal period and may occur in association with such symptoms of obstruction as vomiting (often fecal) and abdominal distention.

When the symptoms during early infancy are not prominent, the subsequent course is marked by increasingly obstinate constipation. Eventually the child presents the typical appearance of congenital megacolon with a distended abdomen. Laxatives may be effective initially in producing evacuations, but this is true for only a short time. Stools may not be passed for days and when passed may consist of small pellets, be ribbon-like or have a fluid consistency. Enemas are frequently necessary to produce evacuations. Progressive abdominal enlargement results, owing to the dilatation of the colon with feces and gas. The abdominal wall becomes thin, the superficial veins are prominent, peristaltic patterns of the colon are frequently visible and audible, and large, soft fecal masses may be readily palpated. Rectal examination usually reveals an absence of fecal material despite a large impaction of the colon. In mild cases the nutrition may not be greatly disturbed, but in the more severe ones there is likely to be loss of subcutaneous tissue and failure to grow. In such instances the combination of wasted extremities and a large protruding abdomen creates a typical appearance. A hypochromic anemia



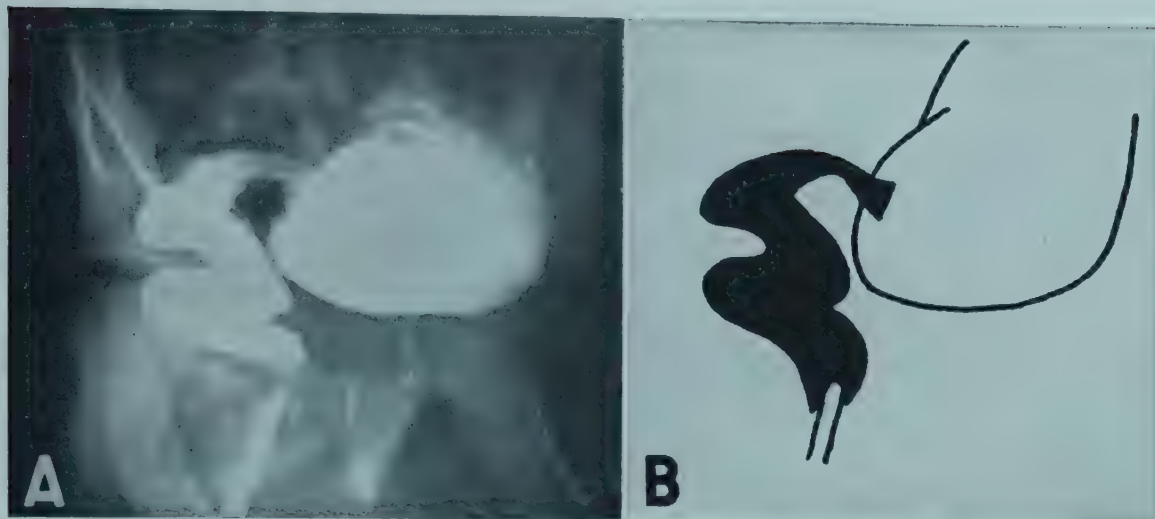


FIG. 196. A, Roentgenogram with barium in the distal colon shows narrowed segment in the rectosigmoid area with a relatively normal-appearing rectum. Note the dilatation of the colon proximal to the narrowed segment. B, Represents a tracing of A, and shows the approximate extent of aganglia in black; actually, the area of aganglia does not stop abruptly and usually extends into the dilated portion for a short distance. (From Keefer and Mokrohisky, Radiology, Vol. 63.)

is often a complicating factor. Intermittent attacks of intestinal obstruction resulting from impaction of feces may be associated with pain and fever.

**Diagnosis.** Anorexia, constipation, abdominal distention and vomiting in the absence of a readily demonstrable organic obstruction are suggestive of congenital megacolon in a newborn infant. The symptoms may appear soon after birth, but in some instances an "overflow type" of diarrhea may develop to confuse the picture. Differentiation of megacolon from *cystic fibrosis of the pancreas* can be accomplished by examination of the duodenal secretions for trypsin and by the "sweat test." Demonstration (see below) by appropriate roentgenographic studies of the narrowed segment of the rectosigmoid, which is characteristic of congenital megacolon, is possible at all ages, but is likely to be less definitive in infants less than six months of age than in older ones.

In children the diagnosis is suggested by a history of constipation and abdominal distention existing from infancy. Spontaneous bowel movements are infrequent, and response to laxatives and enemas is characteristically unsatisfactory. Rectal examination reveals an absence of fecal material despite a large impaction of the colon.

Roentgen examination of the colon with barium according to the technique of Neuhäuser reveals in the most common type a narrowed segment just proximal to the anus and distal to the dilated colon. Only a small amount of barium should be injected slowly

through a small catheter whose tip is inserted barely beyond the anal sphincter while the patient in an oblique position is being observed under the fluoroscope (Figs. 196 and 197). The characteristic narrowing of the rectosigmoid portion will be missed if the lower colon is flooded with too much barium. The possible existence of mechanical obstructions such as stenosis or stricture of the anus and membranous valvelike lesions in the rectum or sigmoid should be eliminated by

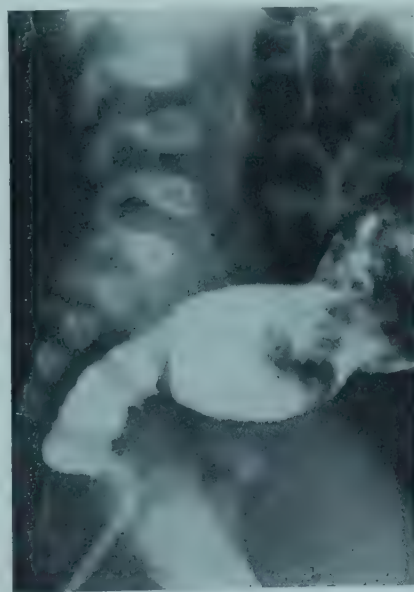


FIG. 197. Aganglionic megacolon in infant 3 weeks of age. The extent of the aganglionic segment is evident, as is the dilatation of the sigmoid above it. Such clear-cut demarcation of the aganglionic section is not always demonstrable in infants of this age.

proctoscopic and sigmoidoscopic examinations.

Megacolon may at times be confused with the *celiac syndrome*, which may be differentiated by the more severe degree of malnutrition, by the fatty, diarrheal stools and by roentgenographic examination. Differentiation must also be made in children with chronic constipation, and particularly in those described earlier with psychogenic megacolon. Roentgen examination of the urinary tract should also be obtained, since megaloureters have been demonstrated in some instances in conjunction with congenital megacolon.

Swenson has described a technique of rectal biopsy as an aid in the diagnosis of difficult or unusual cases, especially in newborn infants in whom the constricted portion of the colon may not be demonstrated by roentgenographic studies.

**Treatment.** Cleansing of the bowel is usually a difficult task, but retention enemas of 3 to 4 ounces of mineral or olive oil followed by repeated colonic irrigations with an isotonic saline solution will usually remove most of the fecal accumulation. The rectal catheter should be inserted beyond the constricted segment. Attacks of syncope, shock and even death have been attributed to water intoxication following the use of tap water and soap suds enemas. Magnesium poisoning has been reported following retention of enemas of magnesium sulfate in patients with congenital megacolon. Thus the use of solutions other than isotonic saline solution for rectal irrigation should be avoided.

Removal of the narrowed segment of bowel by the "pull-through" surgical technique devised by Swenson results in relief of symptoms and a return to normal bowel habits in the majority of instances. During operation it is essential to ascertain from biopsies of the bowel that ganglion cells are present in the proximal portion of the resected bowel before the final anastomosis is made.

If an infant's condition does not warrant the extensive procedure of a "pull-through" operation, a colostomy should be performed. It is desirable to make the colostomy in the distal portion of the colon containing normal ganglia. Preoperative preparation, with correction of any water and electrolyte deficits and anemia, and adequate maintenance postoperatively are essential for success. Later, when the infant is in good nutritional state and has been gaining weight, the "pull-through" form of resection of the bowel can be performed.

NORMAN KENDALL

## REFERENCES

- Bodian, M., Carter, C. O., and Ward, B. C. H.: Hirschsprung's Disease. *Lancet*, 1:302, 1951.  
 Garrard, S. D., and Richmond, J. B.: Psychogenic Megacolon Manifested by Fecal Soiling. *Pediatrics*, 10:476, 1952.  
 Hirschsprung, H.: Stuhltrugherb Neugeborener in Folge von Dilatation und Hypertrophie des Colons. *Jahrb. f. Kinderk.*, 27:1, 1887.  
 Keefer, G. P., and Mokrohisky, J. F.: Congenital Megacolon (Hirschsprung's Disease). *Radiology*, 63:157, 1954.  
 Richards, M. R., and Hiatt, R. B.: Untoward Effects of Enemata in Congenital Megacolon. *Pediatrics*, 12:253, 1953.  
 Swenson, O.: A New Concept of the Pathology of Megaloureters. *Surgery*, 32:367, 1952.  
 Swenson, O., Fisher, J. H., and MacMahon, H. E.: Rectal Biopsy as an Aid in the Diagnosis of Hirschsprung's Disease. *New England J. Med.*, 253:632, 1955.  
 Swenson, O., Neuhauser, E. B. D., and Pickett, L. K.: New Concepts of Congenital Megacolon. *Pediatrics*, 4:201, 1949.

## APPENDICITIS

**Incidence.** Appendicitis is rare in the first two years of life, but has been observed as early as three days. There is a slowly increasing incidence up to twelve years of age; the greatest incidence is between fifteen and thirty years. Boys appear to be somewhat more susceptible than girls.

**Etiology.** Obstruction seems to be the principal predisposing factor. Fecal concretions are a recognized form of obstruction; other forms are not so easily demonstrated, but are thought to result from swelling in response to acute respiratory infection or, less commonly, to systemic infections such as rheumatic fever, measles, varicella or scarlet fever, or to allergy. The small lumen of the appendix makes it vulnerable to obstruction from such causes as kinking, scarring from previous inflammation and the anatomic narrowing near the base. On occasion appendicitis occurs in association with enteric infections which fail to subside completely. Streptococci and, less commonly, *Staphylococcus aureus*, either alone or mixed with coliform bacilli, are the organisms most frequently isolated from infected appendices. Pinworms occasionally cause inflammation.

**Pathology.** Inflammation begins in the mucosa, which may ulcerate; the wall is edematous and infiltrated with neutrophils; the lumen is distended, often enough to impair the blood supply and produce gangrene and perforation. In milder types there may be mucosal ulceration without obstruction.



Bacteria may escape through a perforation or even the gangrenous wall to produce diffuse peritonitis or an abscess confined by adherence of adjacent omentum and intestines.

**Clinical Manifestations.** The classic triad of abdominal pain, vomiting and constipation is diagnostic when associated with localized tenderness, increased muscular resistance in the right lower quadrant and the absence of peristalsis. In children, however, the clinical manifestations are often not so typical; when the child is unable to relate in detail the type and location of his discomfort, the diagnosis may be difficult. The pain varies greatly in intensity and may be paroxysmal or more or less constant. It may be, and often is, generalized, but there is usually some localization, most often in the right lower quadrant or the umbilical region, less often in the epigastrium or the pelvic region.

Slight to moderate increases in temperature and pulse rate are commonly present.

The appendix may lie below, behind or on either side of the cecum, behind the small intestine or omentum, over the brim of the pelvis or even deeply in the pelvis adjacent to the rectum or bladder, and, on rare occasions, may extend to or be located on the left side. In those positions in which other viscera are interposed between the appendix and the anterior abdominal wall, physical findings are often slight. When the appendix lies in the pelvis, even as high as the promontory of the sacrum, a gentle rectal examination in a moderately cooperative child will often reveal a definite difference in pain response on the right and left sides, and bimanual palpation may reveal the actual indurated area. Gentleness and explanation are of particular importance in this part of the examination.

Infrequently the onset may be with diarrhea, vomiting and abdominal pain. Diarrhea is more likely to be a manifestation when the appendix is located in the pelvis or when gastroenteritis is a precursor.

The most reliable diagnostic features are (1) persistent abdominal pain of more than twelve hours' duration associated with vomiting—the latter is rarely absent in children; (2) localized or "point" tenderness in the right lower quadrant or umbilical region; (3) absence of peristalsis, unless diarrhea is present or food or laxatives have been given; (4) leukocytosis of 12,000 to 15,000 with a relative increase of immature polymorphonuclear cells; and (5) absence of acute intrathoracic or urinary tract disease. The pres-

ence of acute nasopharyngitis should cause one to be cautious in attributing abdominal findings to appendicitis.

**Differential Diagnosis.** The diagnosis of appendicitis is frequently difficult in infants and children, because atypical cases are common, and because other conditions may simulate acute appendicitis. When there is any reasonable diagnostic doubt, and there frequently is, it is safer to err on the side of laparotomy, except in the presence of pneumonia. Though many conditions may simulate appendicitis, only a few are common. During early infancy these include so-called colic, gastroenteritis, pyelitis and intussusception. Later there are the common acute digestive upsets of children, food poisoning, gastroenteritis, pyelitis, acute mesenteric adenitis, pneumonia, rheumatic fever, certain of the acute contagious diseases and acute nasopharyngitis.

Pneumonia involving the right lung may be responsible for referred pain and tenderness and even muscular spasm in the right lower quadrant, and abdominal symptoms may be present before the pulmonary ones are clearly evident. Rapid shallow breathing, grunting expirations, movement of the alae nasi with respiration and, when present, cyanosis, of course, favor pneumonia. The pain on pressure over the abdomen is frequently cephalic of the cecal region, and tenderness is diffuse, being present on superficial palpation and frequently disappearing on deep pressure. The roentgenogram of the chest may reveal pulmonary consolidation.

Less frequent diagnostic possibilities are tuberculous mesenteric adenitis or peritonitis, Henoch's purpura, inflammation of a Meckel's diverticulum, and a twisted pedicle of an ovarian cyst.

**Complications.** Whether localized abscess formation (p. 688) and diffuse secondary peritonitis (p. 687) are to be considered complications or part of the natural course of acute appendicitis may be debatable, but they are the only common sequels. Perforation occurs earlier and more frequently in children than in adults, and there is less tendency for the infection to become localized. This failure to localize has been attributed to the relatively small size of the omentum in young children. A pelvic abscess occasionally occurs, but subphrenic abscess is rare. Less common complications are paralytic ileus and thrombophlebitis.

**Prognosis.** There is great danger in postponing operation for appendicitis, since local

or diffuse peritonitis consistently follows perforation, and almost negligible risk attends operation before perforation. Even when perforation has occurred, the mortality rate may be less than 1 per cent. This low rate is probably due to several factors, including improvements in preoperative preparation, operative technique, anesthesia, parenteral fluid therapy and antibacterial therapy.

**Treatment.** The appendix should be removed as soon as the diagnosis is established and the child has been placed in as good condition as possible for surgery. Preoperative preparation includes hydration (see p. 195), reduction of temperature below 102° (rectal) even if mild hypothermia is required, and of the pulse rate below 120, and the use of antibiotics and analgesics. As much as six to eight hours can be spent advantageously to decrease the risk of anesthesia. When perforation has occurred, the treatment of peritonitis must be instituted. Even if the diagnosis is disproved by operation, it is usually best to remove the appendix.

A small muscle-splitting incision in the region of the appendix is the preferred procedure. After this type of operation children are usually out of the hospital within four or five days, return to school in two weeks, and are allowed athletic privileges after six weeks.

During observation, when there is some uncertainty about the diagnosis, an enema may be helpful, but food or laxatives should be scrupulously avoided, owing to the danger of hastening perforation.

W. EMORY BURNETT

## REFERENCES

- Brayton, D.: Acute Perforated Appendicitis in Childhood; Analysis of Management, Including the Use of Hypothermia. *California Med.*, 85:89, 1956.
- Dutz, W., and Hanson, S.: Appendicitis in Infancy. *Canad. M.A.J.*, 75:10, 832, 1956.
- McLaughlin, C. W., Jr., and Organ, C.: Acute Appendicitis in Infancy and Childhood; A Critical Review of Seven Years' Experience in a Children's Hospital. *Am. J. Surg.*, 92:558, 1956.

## MESENTERIC LYMPHADENITIS

### ACUTE MESENTERIC LYMPHADENITIS

Acute mesenteric lymphadenitis is frequently associated with an acute infection of the upper respiratory tract, especially of the pharynx. So much attention has been directed

to this combination of inflammatory lesions, and the possibility that it may simulate acute appendicitis, that the physician may fail to recall that both acute and chronic involvement of the mesenteric lymph nodes may also be associated with infections of the appendix and the intestines.

**Clinical Manifestations.** There is fever, abdominal pain, vomiting and at times constipation or diarrhea. The pain may be spasmodic, is often in the right lower quadrant, but may be in any part of the abdomen.

**Differential Diagnosis.** When the pain is in the right lower quadrant and there is localized tenderness and muscular resistance, the possibility of appendicitis cannot be eliminated except by laparotomy. Certain diagnostic differences have been suggested, such as a tendency in adenitis for the area of tenderness to shift when the patient is moved from side to side in contrast to a fixation of the area of tenderness in appendicitis, and the presence of tenderness along the route of the mesentery on a line extending from McBurney's point upward to the left of the umbilicus in mesenteric adenitis. However, the diagnosis of mesenteric lymphadenitis can be made only by exclusion of other causes, and, unless the child is operated upon, only a presumptive diagnosis can be made at the termination of the illness.

**Complications.** Suppuration of the lymph nodes is rare, but it may be responsible for localized or generalized peritonitis.

**Treatment.** Whenever appendicitis is a reasonable possibility, operation is indicated, since the danger of operation in mesenteric adenitis is much less than is the danger of rupture of an inflamed appendix.

### CHRONIC MESENTERIC LYMPHADENITIS

Chronic infections of the lymph nodes may be sequels to an acute infection, or the involvement may be low grade from the onset. In addition to the conditions which may be responsible for acute adenitis, tuberculosis and histoplasmosis are etiologic possibilities. Involvement of the lymph nodes is practically a constant accompaniment of all chronic intestinal infections, but is usually overshadowed by the clinical manifestations of the primary disease. Noninfectious lymph node involvement is seen in association with Hodgkin's disease, lymphosarcoma and with neoplasms of any of the abdominal or pelvic organs.

WALDO E. NELSON



## REFERENCES

- Brennemann, J.: The Abdominal Pain of Throat Infections in Children and Appendicitis. *J.A.M.A.*, 89:2183, 1927.
- Ochsner, A., and Murray, S. D.: Pitfalls in Diagnosis of Acute Abdominal Conditions. *Am. J. Surg.*, 41: 343, 1938.

## CHRONIC COLITIS

If the cases of chronic colitis caused by known etiologic agents, such as those of chronic amebic and bacillary dysentery, are eliminated, most of the remaining cases can be placed in two groups: (1) the so-called irritable colon (chronic spastic colitis or chronic mucous colitis) and (2) chronic ulcerative colitis of unknown etiology. The irritable colon or chronic spastic colitis is not a common condition in children (p. 654).

## CHRONIC ULCERATIVE COLITIS

**Etiology.** This is a chronic inflammatory condition of unknown etiology in which, as the term implies, there is a tendency to the production of chronic indolent ulcerations. Possibly a number of different organisms may be responsible for this condition, but proof of any one is lacking. Occasionally, amebic or bacillary dysentery may become chronic; it has been suggested that many cases of chronic ulcerative colitis may begin as an acute infection caused by one of these etiologic agents with the chronic phase caused by some other organism. Food allergy has been considered to be the primary cause in some cases. Deficiency of vitamins and minerals is a secondary rather than a primary factor. It has been estimated that about 10 per cent of all cases occur in children under fifteen years of age. There appears to be little doubt but that psychogenic factors have a big role in the maintenance of the chronic course and in causing acute exacerbations; it may also be that they are an etiologic factor.

**Pathology.** Any part or all of the colon may be involved, and the ileum is involved in approximately one third of the cases. The mucosa may be largely denuded, only a few irregular patches of epithelium remaining, or multiple longitudinal ulcers may be joined to each other at irregular intervals as a network of ulcers. The remaining mucosa often contains soft, edematous pseudopolypoid nodules. The ulcers are commonly superficial, extending into the submucosa, but they may penetrate the muscularis. In long-standing cases there is extensive fibrosis of the submucosa, and both the internal diameter and the length of the colon are decreased.

**Clinical Manifestations.** The characteristic symptom is the frequent passage of small stools which fairly consistently contain considerable amounts of mucus, pus and blood. At times true diarrhea may intervene and the bowel movements be large. Extensive hemorrhage from the bowel is an occasional complication. There may be no pain and no abdominal tenderness, but in some instances there are tenderness, cramps and tenesmus. Prolapse of the rectum is an occasional complication, vomiting is not particularly common, and fever is absent or occurs only irregularly. The appetite may be unaffected, but in some instances there is anorexia. The emaciation is often extreme. The skin may be dry and rough. There is almost invariably an anemia; though there may be little change in the total white blood cell count, there is likely to be a preponderance of immature granular forms. The erythrocyte sedimentation rate is usually increased. Nutritional edema may be due to a low serum protein level.

**Diagnosis.** Diagnosis of the lesion is established by the clinical pattern, by failure to isolate a specific etiologic agent, by direct visualization of the rectum and sigmoid through the sigmoidoscope and by roentgenographic examination after barium enemas. Though the roentgenographic appearance varies somewhat, there are frequently areas of localized spasm, and in well advanced cases there is loss of haustral markings with the production of the so-called lead pipe appearance. The possibilities of chronic amebic or bacillary dysentery, tuberculous enteritis, gonococcal proctitis and lymphogranuloma venereum should be considered.

Evaluation of the psychosomatic problem should be made by a competent child psychiatrist. The child is rarely, if ever, well adjusted. There is a variety of behavior patterns, including disturbed parent-child relationships in the majority of instances. In the average situation the psychosomatic aspect appears to be the most important one.

**Course and Prognosis.** The course is chronic with periods of transitory improvement and exacerbations and is usually measured in years. A period of six months or so without symptoms should elapse before it is assumed that recovery has taken place. In occasional instances, however, relapses have occurred even after two or three years. Death usually results from exhaustion, rarely from perforation of the colon.

**Treatment.** There is no specific therapy,

but considerable relief can usually be provided. The diet should be a soft bland one with a low residue. Owing to the poor absorption of minerals and vitamins, these should be provided in concentrated form in several times the usual daily requirements. Purgatives and drastic cathartics should be avoided. Kaolin or Kaopectate may provide some relief from the tenesmus, but the effect is not great; bismuth appears to be of little benefit. Small retention enemas of oil or of a mixture of 3 per cent aluminum hydroxide and 15 per cent kaolin may provide some symptomatic relief. Blood transfusions should be given for the anemia. The results of sulfonamide and antibiotic therapy have not been impressive. Vaccines, either autogenous ones or those prepared from the diplostrep-tococcus described by Bargen, have been used, but it is doubtful whether they have been effective. Ileostomy may be justified in persistent cases, but once established, it is usually permanent. There is lack of unanimity of opinion about colectomy, but the results are such as to justify it only as a last resort. During acute exacerbations medical colectomy

may be achieved by using a double-lumen tube of the Miller-Abbott type passed to the ileocecal region. This permits liquid feeding and aspiration to prevent the entrance of material into the colon. Temporary relief is often achieved with one of the corticosteroids; such therapy may be a valuable adjunct, but must be individualized. Perhaps the most encouraging results are to be expected from a well balanced program based on joint pediatric and psychiatric management of the child and his total situation, which includes the family group.

## NEOPLASMS OF THE SMALL INTESTINE AND COLON

See pages 684 and 1351.

WALDO E. NELSON

### REFERENCES

- Holowach, J., and Thurston, D. L.: Chronic Ulcerative Colitis in Childhood. *J. Pediat.*, 48:279, 1956.  
Kirsner, J. B., Raskin, H. F., and Palmer, W. L.: Ulcerative Colitis in Children. *A.M.A. Am. J. Dis. Child.*, 90:141, 1955.

## ANUS, RECTUM AND SIGMOID

Anomalies of the anus and rectum are comparatively uncommon. They occur approximately once in every 5000 births and comprise about 1 per cent of all congenital anomalies. They are somewhat more common among males than females and are commonly associated with other anomalies. The following classification of anal and rectal anomalies has been found useful:

### Anus

1. Absence of orifice (imperforate anus)
  - Membranous occlusion
  - Mural occlusion
2. Stenosis of the anal canal
  - Membranous
  - Mural
3. Abnormal location

### Rectum

1. Nonfistulous
  - Absence of ampulla
  - Absence of supra-ampullary segment
2. Fistulous
  - Rectovesical fistula
  - Recto-urethral fistula
  - Rectovaginal fistula
  - Rectoperineal fistula

## MALFORMATIONS OF THE ANUS

**Pathogenesis.** Absence of the anal orifice or stenosis of the canal (types 1 and 2) results from improper absorption of the anal plate during the eighth week of gestation. Abnormal location of the anus (type 3) occurs with undevelopment or overdevelopment of the urorectal septum. The usual malformation is that of anterior malposition of the anal canal, occurring when the perineal body is inadequately formed by the continued down-growth of the urorectal septum.

**Diagnosis.** *Imperforate anus* is obvious by inspection at birth. Complete membranous occlusion of the anus can be detected by palpation of the rather thin anal membrane which gives a sensation of resiliency, suggesting that the rectal pouch is slightly cephalad. If means are not taken to open the anus, signs of bowel obstruction become manifest.

*Stenosis* (anorectal) may be present in any part of the anal canal, or it may extend its entire length. The constriction may be crescentic or annular in shape and centrally or laterally placed. The symptoms are propor-



tionate to the degree of narrowing and may include dribbling of meconium, ribbon-like stools, constipation, mucoid or bloody discharge in association with straining, abdominal distention owing to enlargement of the colon (megacolon) and restlessness. Occasionally there may be only slight straining at stool and constipation, and the child may even reach adolescence before the condition is detected. The diagnosis is established by digital examination and endoscopically.

*Fistulas* occurring with anal malformations may be detected by inspection or probing or by the injection of a radiopaque substance. Most fistulas associated with anal anomalies are recognized by passage of stool or flatus through them.

*Abnormal location of the anus* usually occurs anterior to its normal position; it may not be detected for some time after birth. In the female fecal contamination of the vagina is the usual sign.

**Treatment.** A partially persistent anal membrane may be excised completely or incised and the free margin sutured to the fibers of the sphincter ani muscle. It is advisable to perform a posterior sphincterotomy, a partial incision of the sphincter muscle bundle in the posterior commissure, when any residual stenosis exists. Mural stenosis of the anal canal usually is best treated with some form of anoplasty. These are all minor operative procedures which result in better function than do simple incision and repeated dilatation.

Completely imperforate anal plates may be incised with cruciate incision, and the skin edges trimmed, or the tip of each quadrant may be sutured lightly to the sphincter muscle.

An abnormally located anal canal and rectum can be transplanted to their normal location by means of a modified Rizzoli procedure. An adequate perineum or rectosigmoid septum must be constructed with the levator ani muscles, or the rectum will tend to resume its misplaced position in later years.

## MALFORMATIONS OF THE RECTUM

**Pathogenesis.** Absence of the distal portion of the rectum (type 1) would seem to be the result of persistence of the solid stage of either the ampulla or the supra-ampullary portion rather than destruction of the rectum by a resorptive process as has been postulated.

The fistulous malformations of the rectum (type 2) usually occur in conjunction with absence of the ampullary segment (anomalies of type 1), but may also occur with anal malformations. It has not been established whether the incomplete downward extension of the mesenchymal urorectal septum or a primary failure of the cloacal duct to disappear is responsible for anomalous connections between the rectum and the genitourinary tract in the male. In the female, connections between the rectum and the genital tract are formed during the descent of the region of attachment of the müllerian ducts to the posterior wall of the urogenital sinus. Such fistulas may connect the rectum with the vagina or the uterus; the latter connection is rare.

**Diagnosis.** In anomalies with absence of the ampullary segment it is obvious that there is an imperforate anus, but the level of the rectal pouch and the amount of intervening tissue are the points in question. Palpation of the anal area indicates that there is a greater barrier than mere persistence of the anal plate. The amount of intervening tissue is determined by the inversion roentgenographic technique (Fig. 199).

Absence of the supra-ampullary segment may not be suspected until signs of bowel obstruction are apparent. Digital and proctoscopic examination should confirm the existence of the blind distal pouch; the inversion roentgenographic technique is also helpful here.

When the blind rectal pouch is fairly high and cannot be easily mobilized from the perineum, and when signs of bowel obstruction are present, a transverse colostomy is indicated immediately. Definitive reconstructive procedures are then usually deferred until the child is at least three years of age.

In the reconstruction of rectovaginal fistulous malformations the Rizzoli procedure is used. When possible, the fistulous tract and a small portion of the distal rectum are exteriorized over a large mushroom catheter for the anticipated retraction which frequently results, rather than suturing the rectal mucosa to the skin margins primarily. Usually the redundant bowel can be excised and the anal canal reconstructed as a minor operative procedure seven to eight days after the initial operation. If the perineal body is carefully reconstructed during this procedure, the likelihood of anterior recession of the rectum is minimal.

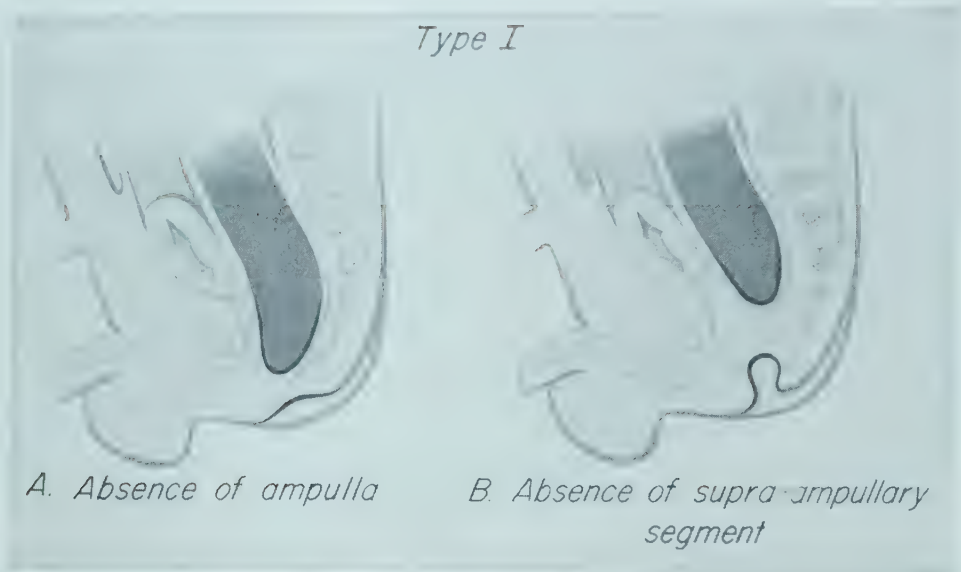


FIG. 198. Rectal malformations. (Bacon and Sherman: Arch. Surg., Vol. 64.)

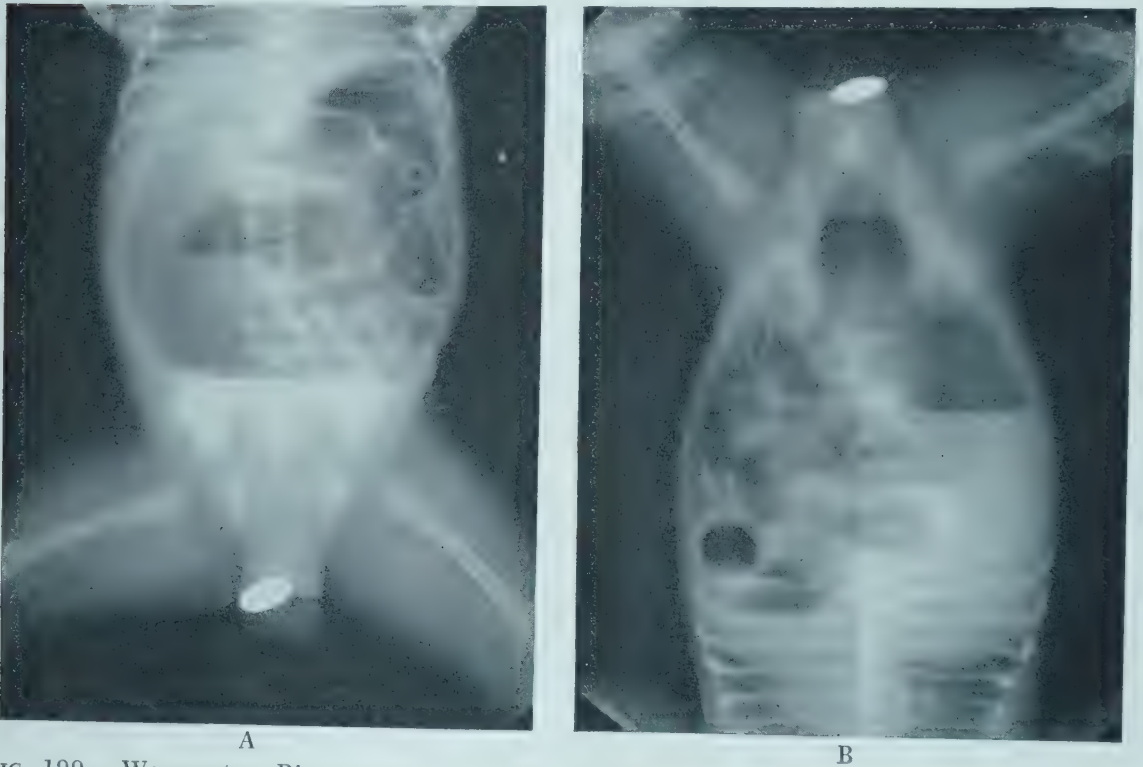


FIG. 199. Wangenstein-Rice roentgenologic technique for demonstration of the position of the blind colonic pouch in the case of an imperforate or absent rectum. The infant is held head downward, causing the intestinal gas to rise to the blind end of the gut. A, Roentgenogram of child in upright position, showing transverse level of gas. The level of the obstruction is not demonstrated. B, The level of the obstruction is apparent when the roentgenogram is taken with the child in the inverted position. The site of the anus is marked by a lead disk.

### FISSURE IN ANO

Fissure in ano, or anal ulcer, is a slitlike tear in the anal canal. It is usually associated with cryptitis and is one of the most common proctologic disorders in infancy and childhood. Predisposing factors are anal stenosis, trauma, irritation by *Oxyuris vermicularis*,

perianal eczema and passage of large scybalous masses. The possibility of a tuberculous, syphilitic or lymphogranuloma venereal lesion should be considered when multiple lesions are present.

**Clinical Manifestations.** Difficulty in defecation and crying associated with it are the usual symptoms. Sparse, bright red bleeding



may be observed. Occasionally there may be a limp suggestive of a lesion in the hip joint.

**Treatment.** Mineral oil by mouth, instillations of warm olive oil into the rectum before defecation with a small rubber-tipped syringe and a dietary regulation to soften the stools tend to diminish irritation of the fissure. Gentle introduction of the lubricated, gloved finger twice daily lessens sphincter spasm. Hot sitz baths, three times daily, especially after defecation, are also helpful. If the sphincter is not spastic, topical applications of 5 per cent silver nitrate twice weekly may be beneficial. Chronic lesions with undermined edges and associated crypts should be excised under anesthesia. Postoperatively, hot sitz baths and 1 per cent gentian violet applications should be given until healing is complete.

## PRURITUS ANI

Irritation from coarse, moist or unclean undergarments is the most common cause of anal itching, but anal fissures and oxyuriasis (p. 579) are also frequent causes. Other causes include gastrointestinal allergy, uncontrolled diabetes, constipation, diarrhea, procidentia or prolapse of the rectum, and foreign bodies. Nocturnally accentuated itching is the salient feature; it results in scratching, restlessness and irritability.

**Treatment** consists in proper cleanliness, dry, nonirritating garments and removal of the predisposing cause. The anal area should be cleansed by washing or with soft cotton rather than with toilet paper. As an aid in keeping the parts dry, the following powder is useful:

Phenol ..... 0.2 gm. (3 grains)  
Starch powder ..... 15.0 gm. (½ ounce)  
Zinc oxide powder, to make . . . 30.0 gm. (1 ounce)  
Sig: Powder anus several times daily

## PROLAPSE AND PROCIDENTIA OF THE RECTUM AND SIGMOID

*Prolapse* is abnormal descent of the mucous membrane of the rectum with or without protrusion through the anal orifice; *procidentia* is abnormal descent of all the coats of the rectum and/or sigmoid with or without protrusion through the anus. These conditions are most common between the ages of three and five years. The infantile rectum lies on a lower plane than the other pelvic organs, which exert downward pressure on the rectum. This anatomic arrangement, com-

bined with the effect of the nearly vertical infantile sacrum, predisposes to prolapse. Any factor causing suddenly increased intra-abdominal pressure may precipitate abnormal descent of the bowel wall. Malnutrition with consequent absorption of ischiorectal fat is a contributory factor. Protrusion at stool initially recedes spontaneously, but later necessitates manual replacement. Bleeding and the passage of mucus may occur. The protruding mass varies from bright to dark red; it may be as much as 6 inches in length, and may be spherical or sausage-shaped. In prolapse the striations or furrows radiate from the center of the anal aperture, in contrast to the circular, concentrically arranged rosette of procidentia.

**Treatment** of the underlying cause is essential; attention should be directed to dietary correction of constipation and proper toilet training as well as to the treatment of any existing disturbance, such as parasitic infection, diarrhea or polyps. Oral administration of mineral oil, rectal instillations of olive oil and strapping the buttocks together with adhesive tape, having first placed a cotton ball over the anal area, may be helpful. Local inflammation of the mucosa may be treated with 25 per cent aqueous instillations of Ichthyol or 10 per cent krameria solution twice daily.

**Reduction of protrusion** is aided by pressure with hot compresses. Cold packs are contraindicated. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, gently push it into the rectum and then immediately withdraw it. The toilet paper adheres to the mucous membrane, thus permitting release of the finger; the paper, when softened, is later expelled. Maintenance of the child in an inverted (head-low) position during the reduction may be useful, especially in procidentia. In prolapse of the mucous membrane, but not in procidentia, injection of sclerosing substances into the submucosa is of value. One-half cubic centimeter of 3 per cent quinine and urea hydrochloride or 1 per cent sodium morrhuate solutions may be injected circumferentially at weekly intervals. For intractable cases perineal operation is indicated. In procidentia of the rectum and sigmoid abdominal sigmoidopexy is required.

## ANORECTAL ABSCESES

The most common type of anorectal abscess occurs in the ischiorectal fossa. Infection

usually gains entrance through the anal crypts and the preformed spaces. The symptoms are pain and swelling. Defecation is painful, and the child is unable to sit on the affected part. The temperature is not markedly elevated unless the perirectal space is invaded. Diagnosis is based on presence of a painful swelling overlying the ischiorectal fossa, with redness, heat, induration and fluctuation. Treatment consists in immediate incision and drainage under anesthesia. Hot sitz baths, three times daily, are helpful in the post-operative period.

## FISTULA

An anorectal fistula is an abnormal communication between the anorectum and some adjacent tissue, viscus or skin surface. All noncongenital fistulas are preceded by abscess formation, usually originating from an infected crypt of Morgagni situated at the anorectal line. In infants and children there is usually a single communicating tract. There is frequently a history of one or more incisions into the abscess.

The *symptoms* are those of a painful swelling which recurs intermittently, followed by a purulent discharge. Diagnosis is based on the presence of an opening into the skin beside the anal orifice into which a probe may be introduced (Fig. 200).

*Treatment* is by complete excision of the tract. Care must be taken to incise rather than excise the sphincter in order to prevent incontinence. The operative wound should



FIG. 200. Complete anorectal fistula in a child 15 weeks of age; probe demonstrating external and internal openings. (Bacon: Anus, Rectum and Sigmoid Colon. J. B. Lippincott Company.)

not be sutured or packed. The results, with proper technique, are excellent.

## HEMORRHOIDS

Hemorrhoids are rare in infancy and only infrequently encountered in children. The most common cause is increased abdominal pressure from straining, crying and coughing associated with repeated fecal impactions, constipation and diarrhea. Hemorrhoids in children are usually single, but may be multiple, and they may be of the external or internal variety. Pain, protrusion and bleeding are the usual symptoms. Associated conditions such as constipation and diarrhea should be corrected. When there is protrusion, hot compresses are usually effective. Operation is seldom indicated except for an acute external thrombosis.

## NEOPLASMS

### BENIGN TUMORS

With development of proctosigmoidoscopy, growths of the rectum and sigmoid colon have been more readily demonstrated in infants and children. The majority of these prove to be adenomatous polyps. The presence of numerous eosinophils, dilated cystic mucosal glands and a more diffuse infiltrate of leukocytes tends to distinguish the adenoma of childhood from the adenoma of the adult. Rectal bleeding in children in the absence of a blood dyscrasia is strongly suggestive of an adenomatous polyp. Rectal bleeding in infants is more apt to result from other causes. Bleeding usually is not extensive and tends to occur at the time of defecation; the blood is bright red. Pain is uncommon. Polyps which are situated low in the rectum and have a long pedicle may protrude through the anus. Other benign tumors such as hemangioma and lymphoid hyperplasia may be encountered. Adenomas in the rectum or sigmoid colon can be identified through the sigmoidoscope and/or by double air-contrast, barium enema roentgenograms.

*Treatment* consists in removal of the adenoma. If it is the sessile type located in the rectum, and satisfactory evidence of benignity is established, the growth may be electrodesiccated. Sufficiently pedunculated polyps of the rectum may be removed by an electric snare. Polypoid lesions above the peritoneal reflexion in the sigmoid require excision by abdominal colotomy. Sessile processes, which are usually detected by umbilication of the bowel wall, are best removed by segmental resection.



**MALIGNANT TUMORS**

Malignant neoplasms of the rectum and colon are extremely rare in children, less than forty authentic cases of primary sarcoma and carcinoma in children under twelve years of age having been reported. Malignant tumors occur more often in the rectum than in the sigmoid or anus. The symptoms in order of frequency are abdominal pain, bleeding, constipation, rectal pain, diarrhea, lumbar pain and loss of weight. Digital examination, proctosigmoidoscopy and roentgenographic studies will establish the diagnosis. All tissue removed should be examined microscopically. Radical extirpation is the treatment of choice.

## **CONGENITAL DIMPLES, SINUSES, CYSTS AND TUMORS OF THE SACROCCYGEAL REGION**

**PILONIDAL SINUS AND CYST**

*Pilonidal sinus* is a congenital defect which probably results from faulty coalescence or invagination of the skin ectoderm in the midline over the sacrococcygeal region during early embryonic development. It is characterized by formation of a tract in which are collected the products of dermal activity. Infection enters through the original site of invagination or through aberrant tracts which are manifest after puberty. A *pilonidal dimple* is commonly encountered, but is asymptomatic. Pilonidal cysts and sinuses do not cause symptoms unless infection has occurred. The presence of swelling, heat, redness, tenderness and fluctuation over the sacrococcygeal region is characteristic of an infected sinus. Purulent material may be discharged from one or more openings. If infection occurs, total excision should be performed. (See page 1106 for complications within the spinal canal.)

**DERMOIDS AND TERATOMAS**

Dermoid tumors, or teratomas, are the most common sacrococcygeal tumors in infants and children and are trigeminal in origin. They are classified as congenital tumors. Dermoid cysts do not usually become manifest until adult life, when by increased size, pressure or suppuration they produce symptoms. Teratomas are usually manifest at birth, forming a large skin-covered mass posterior to the rectum. They are more common in females than in males. It is important to differentiate teratomas from meningoceles; the meningocele is usually smaller and does not

increase in size in proportion to the infant's growth as does the teratoma. The teratoma usually displaces the rectum anteriorly. The meningocele is apt to expand with crying or coughing because of its communication with the spinal canal, and pressure on it may cause bulging of the anterior fontanel. The rare anterior spina bifida associated with an anterior sacral meningocele must also be differentiated from a teratoma. Dermoid cysts usually have cavities lined with squamous epithelium and contain associated ectodermal structures such as hair and sebaceous glands. Teratomas are more complex, containing teeth, bone, fat, cartilage, muscle and nerve tissue in many instances. The signs are usually those of a visible mass, pressure, inflammation or purulent discharge. Spontaneous rupture and discharge of the teratoid contents into the rectum may occur. Though the prognosis has been poor, recovery can be expected in most instances when the tumor is removed early in the newborn period.

Sacroccygeal chordomas or chordoblastomas arise from remnants of the primitive notochord and are ectodermal in origin; they are more commonly noted in later life. They are classified as bone tumors, owing to the commonly associated pain from destruction of bone. Pain, sphincter impairment, paralysis and paresthesia are common symptoms. The tumor is usually palpable through the rectum. Destruction of bone as revealed on the roentgenogram is a diagnostic feature. The tumor extends by infiltration, rarely by metastases, but cures are rare.

The neurogenic group includes ependymomas, neurofibromas, neuroblastomas and ganglioneuromas, all of which may occur in the presacral area; lipomas, fibrosarcomas and lymphangiomas are rarely found in this area.

HARRY E. BACON

**REFERENCES***General*

- Bacon, H. E., Ross, S. T., and Recio, P. M.: *Proctology*. Philadelphia, J. B. Lippincott Company, 1956.  
 Delano, P. J., Ronayne, F. J., and Boland, T. B.: Rectal Dyschezia. *Radiology*, 37:730, 1941.  
 Gross, R. E., Clatworthy, H. W., Jr., and Meeker, I. A., Jr.: Sacrococcygeal Teratomas in Infants and Children. *Surg., Gynec., & Obst.*, 92:341, 1951.

*Anomalies of Anus and Rectum*

- Bacon, H. E., and Sherman, L. F.: Surgical Management of Congenital Malformations of the Anus and Rectum. Report of One Hundred and Eleven Cases. *Arch. Surg.*, 64:331, 1952.

Moore, T. C., and Lawrence, E. A.: Congenital Malformations of the Rectum and Anus. I. Clinical Features and Surgical Management in 120 Cases. *Surgery*, 32:352, 1952; II. Associated Anomalies Encountered in a Series of 120 Cases. *Surg., Gynec., & Obst.*, 95:281, 1952.

Rhoads, J. E., Pipes, R. L., and Randall, J. P.: A

Simultaneous Abdominal and Perineal Approach in Operations for Imperforate Anus with Atresia of the Rectum and Rectosigmoid. *Ann. Surg.*, 127:552, 1948.

Wangensteen, O. H., and Rice, C. O.: Imperforate Anus. *Ann. Surg.*, 92:77, 1930.

## PERITONEUM AND ALLIED STRUCTURES

### MALFORMATIONS OF THE PERITONEUM

Congenital peritoneal bands at times may be responsible for intestinal obstruction (p. 664); numerous other anomalies may occur in the course of the development of the peritoneum, but are rarely of clinical importance. Intra-abdominal herniations infrequently occur through ringlike formations produced by anomalous peritoneal bands. Absence of the omentum or duplications of it are rare anomalies.

### ASCITES

**Etiology.** The term "ascites" indicates an accumulation of fluid in the peritoneal cavity, but it is usually applied to accumulations of serous fluid. Renal, especially nephrotic, and cardiac conditions are most often responsible for ascites. It may represent a localized and extensive accumulation of fluid in chronic adhesive pericarditis, or it may be part of a polyserositis in so-called Pick's syndrome. Other causes include obstruction of the portal circulation as in hepatic cirrhosis or by enlarged lymph nodes, tumors, thrombosis, chronic tuberculous peritonitis, rheumatic peritonitis or obstruction of the splenic vein.

**Clinical Manifestations.** The abdomen is distended; when the distention is marked, there is flattening or pouting of the umbilicus. Fluctuation can be detected on palpation; a distinct wavelike impulse is obtained by sharp tapping on one side of the abdominal wall while the other hand is placed on the opposite side of the abdomen and an attendant's hand compresses it in the midline; shifting percussion dullness can often be demonstrated.

Ascites must be differentiated from other conditions which cause distention of the abdomen. These include gaseous distention of the intestines, fecal distention as in megacolon, tumor masses, as well as cysts of the mesentery, acute or chronic peritonitis, per-

itoneal hemorrhage from trauma or other causes, extreme distention of the bladder and simple obesity.

**Prognosis and Treatment.** The course, prognosis and treatment depend entirely upon the cause.

### CHYLOUS ASCITES

Chylous ascites is an uncommon form of ascites which may occur at any age of childhood and is occasionally congenital in origin. True chylous ascites is caused by some anomaly, injury or obstruction of the thoracic duct. In the case of anomalies the condition is present at birth or shortly thereafter. At times in traumatic cases there is an associated chylothorax. Obstructions may be produced by enlarged lymph nodes or neoplasms.

The fluid has the appearance of milk, owing to its high fat content. In chronic tuberculous or nontuberculous peritonitis, peritoneal fluid may have a somewhat similar color from degeneration of inflammatory products. The prognosis in chylous ascites is unfavorable, but recovery has followed surgical therapy. The amount of chyle formation can apparently be reduced by decreasing the dietary intake of fat. Since there is a loss of considerable protein in this fluid, high protein diets should be prescribed.

WALDO E. NELSON

### REFERENCE

Wegner, E. S.: Congenital Chylous Ascites; Apparently Cured by Ruotte's Operation (Venous Peritoneal Anastomosis). *Am. J. Dis. Child.*, 47:586, 1934.

### PERITONITIS

Acute infections of the peritoneum are arbitrarily designated as primary when the focus is outside the abdominal cavity and the infection is blood-borne or lymph-borne. The infection is termed secondary when it is disseminated by extension from or rupture of



an intra-abdominal viscus or of an abscess of one of the solid organs.

Peritonitis in the neonatal period (p. 344) may arise from a transplacental infection in utero; more frequently it is the result of infection acquired during or shortly after birth. It may be a manifestation of septicemia, a direct extension from an umbilical infection, perforation of the intestine or, rarely, the sequel of a ruptured appendix. Meconium peritonitis is described on page 332. After the neonatal period, peritonitis is uncommon until later childhood, when appendicitis becomes relatively frequent.

#### ACUTE PRIMARY PERITONITIS

**Etiology.** Primary peritonitis, which is now relatively uncommon, is most often caused by the *Pneumococcus* and beta hemolytic *Streptococcus*. Streptococcal peritonitis is especially likely to be associated with acute throat infections, scarlet fever and erysipelas; pneumococcal, with throat infections, pneumonia or empyema. Primary peritonitis is more common in girls than in boys, and in some instances a preceding nongonorrheal vaginitis appears to be a portal of entry. Pneumococcal peritonitis is a relatively frequent complication of nephrosis (p. 1046); in such instances the same strain of *Pneumococcus* is frequently isolated from the nose and throat as from the peritoneal exudate. Gonococcal peritonitis is a rare complication of gonorrheal vaginitis.

**Pathology.** The infection is usually widely distributed, although occasionally it is localized in one or more areas. The exudate, which is initially serous or serofibrinous, may become purulent; large amounts of fibrin are formed, especially in pneumococcal infections, and adhesions mat the intestines and other organs together, so that single or multiple localized abscesses may form.

**Clinical Manifestations.** The onset is usually rapid with extreme prostration, some abdominal pain and vomiting. Paradoxically, intestinal activity is usually continued, and diarrhea is common. Evidences of active or subsiding infection elsewhere are often present. The facial expression is likely to be anxious; there is often cyanosis, and the child appears toxic and weak. The temperature is usually septic in type, and may be as high as 104° to 105° F., although in very ill patients, and especially in young infants, it may be normal or subnormal. The pulse is rapid, small and compressible, and the respirations are rapid and shallow because of the pain which abdominal respiration produces.

There is usually distention of the abdomen, moderate diffuse tenderness and a doughy resistance, the latter two being much less than might be expected. Peristalsis is usually active until late in the disease. Evidences of free fluid may be present. Rectal examination reveals tenderness. The white blood cell count is high, ranging from 20,000 to 35,000 with 90 to 95 per cent polymorphonuclear cells with an increase in immature forms. Pus obtained by abdominal aspiration establishes the diagnosis; the procedure is not without risk.

**Prognosis.** Before sulfonamides and antibiotics were available the mortality rate was 80 to 90 per cent; with early treatment recovery is now the rule. Infrequently there is a residual chronic peritonitis.

**Treatment.** Early pelvic drainage with peritoneal lavage with saline solution and antibiotics should be instituted through an abdominal muscle-splitting incision made under local anesthesia. Drainage is facilitated by use of the Babcock type of metal "sump" drain. The general treatment is a modification of the Ochsner method (see treatment of secondary peritonitis, p. 688). Appropriate antibacterial therapy determined by bacterial culture and susceptibility tests should be administered in full dosage and continued for five or six days after apparent recovery. Careful attention to water and electrolyte balance is essential.

#### ACUTE SECONDARY DIFFUSE PERITONITIS

**Etiology.** This type of peritonitis results from perforation of an abdominal viscus or from an abscess of an intra-abdominal organ. Since peptic ulcer, cholecystitis, diverticulitis and pancreatitis are extremely rare in childhood, perforation of the appendix and traumatic rupture of viscera are responsible for the majority of infections. Thus the invading bacteria are largely coliform bacilli with varying numbers of other organisms which, in the main, belong to the streptococcal and staphylococcal groups. Rarely an empyema perforates the diaphragm and is responsible for peritonitis. Strangulation of the intestine as in a hernia or in intussusception is an occasional cause.

**Pathology.** The peritoneal surfaces are lusterless and hyperemic, and the cavity contains cloudy fluid or purulent exudate. Fibrinous adhesions are present between the abdominal viscera, and one or more localized abscesses may result. The larger abscesses, in order of frequency, are located in the pelvic,

the subhepatic and subphrenic areas. Such abscesses may rarely burrow through the abdominal wall, through the diaphragm into the pleura or, more commonly, into a loop of intestine. More often they spread to other peritoneal areas, producing extension of the infection. By lymphatic transmission the subphrenic infections may pass through the diaphragm without actual perforation and produce first a sterile effusion and later an empyema. Pelvic collections of pus irritate the bladder or rectum or both, producing symptoms referable to them.

**Clinical Manifestations.** The manifestations of shock from a ruptured viscus or the early symptoms of acute appendicitis are superseded by an increasing toxemia, as evidenced by greater restlessness and irritability, by a higher temperature, often  $103^{\circ}$  to  $105^{\circ}$  F., by an increase in the pulse rate and, at times, by chills or convulsions. Vomiting, if previously present, is usually increased, the vomitus becoming greenish, then yellowish and finally malodorous, especially if fluids are being taken orally. The pain becomes more diffuse over the abdomen, but may not be too notable if the patient remains quiet, since movement increases it. Constipation is marked, and there is usually no response to *ill advised* suppositories or enemas.

The earliest sign, often present before subjective symptoms, is an increased area of abdominal tenderness and muscular resistance. Rebound pain on sudden release of pressure is indicative of peritoneal irritation, and this too becomes more diffuse. Peristalsis is usually absent unless laxatives or foods have been taken. Later, free peritoneal fluid may be demonstrable by percussion, and some distention occurs. By this time duskeness or cyanosis is usually evident, and apathy or delirium appears.

Rectal examination reveals diffuse tenderness because of the irritation of the pelvic peritoneum. The white blood cell count is usually 16,000 to 25,000 per cubic millimeter, the polymorphonuclear elements being above 90 per cent and immature forms increasing. As the disease advances, the white blood cell count often decreases.

**Treatment.** Of great importance in reducing mortality is a period of preoperative preparation, usually of six to eight hours. Adequate hydration (see p. 195), gastric suction and antimicrobial therapy parenterally are urgently required. Relief of pain by Demerol, morphine or codeine also contributes to improvement. The pulse rate should

be reduced below 120 and the temperature below  $102^{\circ}$  F. if possible. Severely ill patients may require mild hypothermia.

Only when the foregoing has been accomplished is it safe to operate for removal or repair of the viscus producing the infection. Morbidity and mortality may be decreased by aspiration of the peritoneal contents, breaking up of localized abscesses, and repeated lavage of the entire peritoneal cavity with saline solution containing one million units of penicillin and 1 gm. of streptomycin per 500 ml., finally leaving 100 to 200 ml. in the peritoneal cavity as the abdomen is closed. Drainage is best omitted after lavage unless a nonreactive Babcock metal "sump" drain is available. The tube should be introduced into the pelvis and removed as soon as serum only appears in the collection bottle.

Postoperatively the modified Ochsner treatment is effective. It consists of (1) Fowler position, (2) constant gastric suction, (3) nothing by mouth except saline (or water) which is withdrawn by gastric tube, (4) no peristaltic stimulants such as enemas, Prostigmin or Urecholine, (5) Demerol, morphine or codeine for restlessness, and (6) the maintenance of nutrition and fluid and electrolyte balance by parenteral routes. Adequate amounts of vitamins B and C should be given parenterally, and *small* daily transfusions may assist in combating infection by supplying complement. Penicillin and streptomycin or broad-spectrum antibiotics should be continued parenterally; bacterial cultures and sensitivity studies are helpful in selecting appropriate antibacterial agents.

This regimen should be maintained until symptoms have disappeared and peristalsis is effective in passing gas per rectum. Then enemas and increasing diet may be permitted after withdrawal of the gastric tube.

**Prognosis.** Owing to improvements in treatment, the case fatality rate has decreased to approximately 1 per cent.

#### ACUTE SECONDARY LOCALIZED PERITONITIS

##### (ABSCESS)

**Etiology.** A single, localized pyogenic abscess, which most often is secondary to a perforation of an inflamed appendix, is somewhat less common in children than in adults. The poor ability of young children to localize a peritoneal infection of appendiceal origin has been attributed to a lower order of resistance and to a relatively smaller omen-



tum. Though localized peritoneal abscesses occur most often in the appendiceal region, they may be at any site, originating from various sources, or appendiceal infections may gravitate to other areas, notably the pelvic. An abscess in the subdiaphragmatic area may originate from an appendiceal or other intra-abdominal infection or, rarely, from an empyema. Appendiceal abscesses may result from perforation of the appendix, contamination of the region at the time of operation or failure to drain a contaminated area. Multiple abscesses may be part of a diffuse peritonitis, resulting from the matting together of loops of intestines and other abdominal viscera by adhesions.

**Clinical Manifestations.** The general symptoms of peritoneal abscess are continued fever or recurrences of it, poor appetite, and vomiting upon the ingestion of food. The white blood cell count is increased, with a predominance of polymorphonuclear cells. In addition, peritoneal abscesses may produce more or less characteristic manifestations dependent upon their location.

In the appendiceal area, tenderness in the right lower quadrant is extended, and there is often a palpable mass.

A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small stools containing mucus, or bladder irritability. Rectal examination reveals a bulging tender mass anteriorly which impinges on the rectal lumen.

A subphrenic abscess is evidenced by physical signs at the base of the lung, usually the right, due to elevation of the diaphragm, and frequently by the presence of pleural fluid. The diagnosis can often be established roentgenographically. The diaphragm is elevated and the liver depressed if the infection is on the right side, and there is frequently a pocket of air just below the diaphragm, owing to production of gas by bacteria.

**Treatment.** General treatment of peritoneal abscesses consists in maintenance of fluid and nutritive requirements by parenteral routes, if necessary, and in broad-spectrum antibiotic therapy. Adequate drainage remains the best method of treatment. Pelvic abscesses are preferably drained into the rectum through its anterior wall. A subphrenic abscess can be approached through the bed of the resected twelfth rib. If there is an associated empyema, the tenth or eleventh rib is resected rather than the twelfth, and each infection can be drained through the same

incision, with a tube directed into each cavity.

The appendix should be removed if easily accessible. Otherwise it should be removed after infection has subsided.

#### CHRONIC NONTUBERCULOUS PERITONITIS

**Etiology.** Chronic infections of the peritoneum, the majority of which are caused by tuberculosis, are relatively uncommon. There is a wide variety of etiologic agents. A chronic, localized purulent peritonitis may follow an acute infection, and occasionally there is a chronic diffuse involvement. In other instances localized or widespread adhesions remain after the infection itself has been controlled. Fetal peritonitis may have become chronic by the time of birth, or there may be adhesions without evidence of active infection. Pick's syndrome or a polyserositis involving the pericardium, pleura and peritoneum, often attributed to tuberculosis, may apparently be caused by other agents. Non-purulent peritoneal involvement is occasionally seen in children with active rheumatic fever, and there may be an etiologic relationship. Actinomycosis, although not primary in the peritoneal cavity, may be responsible for chronic indolent infections of it.

Tuberculous peritonitis (see p. 468).

W. EMORY BURNETT

#### REFERENCES

- Brayton, D.: Acute Perforated Appendicitis in Childhood; Analysis of Management, Including the Use of Hypothermia. *California Med.*, 85:89, 1956.
- Burnett, W. E., and others: The Treatment of Peritonitis Using Peritoneal Lavage. *Ann. Surg.*, 145: 5, 1957.
- Burnett, W. E., Rosemond, G. P., and Caswell, H. T.: The Use of Sump Drains in Peritoneal Infection. *S. Clin. North America*, 24:1316, 1944.

#### TUMORS OF THE PERITONEUM AND MESENTERY

*Mesenteric cysts* are commonly lymphatic in type (lymphangioma, p. 1359) and probably are malformations rather than true neoplasms. They may be responsible for abdominal pain, constipation, intestinal obstruction or simply large intra-abdominal masses which must be differentiated from the various intra-abdominal neoplasms; large mesenteric cysts may simulate ascites. The treatment is surgical removal. Other cystic malformations or neoplasms involving the mesentery include

duplications of the gastrointestinal tract, dermoid cysts and teratomas. Primary neoplasms of the peritoneum are exceedingly rare; we have observed one example of a mesothelioma in an inguinal hernial sac in a child. Lymphosarcoma may be primary in the stomach, small intestine or the mesenteric lymph nodes. A variety of other mesenchymal neoplasms may occur in the mesentery.

## HERNIA AND HYDROCELE

Hernias of various types may be present at birth or develop subsequently, often because of congenital defects. The uncommon femoral hernia and the rare internal hernias other than that of the diaphragm will not be discussed. Congenital omphalocele and umbilical hernia are discussed on page 340.

### INGUINAL HERNIA

**Etiology and Pathology.** Most inguinal hernias are of the indirect rather than the direct type and occur much more frequently in boys than in girls. The hernia may be present at birth or may appear at any age thereafter; it is situated more often on the right side than on the left, but frequently is bilateral.

During embryonic life, as the testis descends retroperitoneally from the genital ridge, a sac of peritoneum (the processus vaginalis) precedes it into the scrotum. The lower portion of this sac envelops the testis to form the tunica vaginalis, and the remainder normally atrophies by the time of birth. The indirect inguinal hernia results from a persistence of the processus vaginalis and becomes manifest as a mass in the inguinal region when an abdominal structure or peritoneal fluid is forced into it. The persistent sac may vary from a short one not extending beyond the external inguinal ring to one which extends into the scrotum and maintains its continuity with the tunica vaginalis. The hernial sac is thus present at birth, but it usually remains empty for a variable period of time. At a later date, commonly by two or three months of age, when the infant becomes more active and is able to increase his intra-abdominal pressure sufficiently to open the sac, peritoneal fluid or an abdominal organ is forced into it. It then appears as a bulge in the inguinal region, extending into the scrotum or toward the labia, depending on the length of the peritoneal sac which it enters.

**Clinical Manifestations.** There are no

symptoms associated with an empty hernial sac. When abdominal contents are intermittently forced into it, symptoms of incomplete bowel obstruction with pain, fretfulness, difficult defecation, poor eating and local pressure may result. However, there may be few or no symptoms associated with a filled hernial sac. If a loop of intestine becomes incarcerated in the sac, there may be all the manifestations of intestinal obstruction ultimately leading to strangulation of the bowel and death. In female infants the ovary may prolapse into the hernial sac and appear as a 1- to 2-cm. movable, nontender, usually transient inguinal mass. Immediate surgical exploration and oophorectomy are required if strangulation occurs. Occasionally the neck of the sac becomes twisted after peritoneal fluid has been forced into it and traps the fluid as an encysted, nontender irreducible hydrocele in the cord in the male or in the canal of Nuck in the female.

**Diagnosis.** A history of the intermittent appearance of a mass in the inguinal region of an infant or child is characteristic. If the hernial sac is full at the time of examination and can be emptied by gentle compression or if it can be made to fill when the infant cries or strains or the older child stands or coughs, the diagnosis is established. Often, however, a suggestive history is the only criterion for diagnosis. Inspection may reveal a fullness on the affected side, especially following recent incarceration. Palpation for an enlarged internal ring by invaginating the scrotum is fruitless during the early developmental stage of the hernia, since the ring is not enlarged, nor are the muscles weakened. However, gentle palpation by rolling a finger over the spermatic cord at the level of the pubic tubercle will reveal thickening of the cord on the involved side, and often the "silk glove" sensation may be elicited by the rubbing together of the two sides of the empty hernial sac. This maneuver should be performed as part of routine physical examinations in infants in order to discover the presence of a hernial sac so that it can be removed before incarceration occurs.

The only difficulty in diagnosis is in distinguishing hernia from hydrocele. A hernial sac is often opaque to transmitted light, whereas the hydrocele is translucent. A hernia, however, may also be translucent if only distended and empty bowel is present in the sac. The inguinal hernia is usually reducible with gentle manipulation and tends to slip suddenly into the peritoneal cavity.



By contrast, the encysted hydrocele is not reducible, and, although the communicating one is, it is usually accomplished by manipulation only with great difficulty and without sudden emptying of the sac. Characteristically it is reduced most readily while in the horizontal position for a prolonged time as during a night's sleep. The coexistence of a communicating hydrocele and an inguinal hernia is relatively common.

**Treatment.** The treatment of inguinal hernias in healthy infants and children is by surgical repair as soon as the defect is diagnosed. If there is a suggestive thickening or a "silk glove" feeling on the opposite side, bilateral exploration is recommended. The operation consists essentially in removing the hernial sac and transfixing the neck at the internal ring. It is well tolerated by even small infants and obviates the possibilities of incarceration, testicular atrophy, secondary enlargement of the internal ring and weakening of the floor of the canal from prolonged pressure. Treatment by injection of sclerosing agents is contraindicated in infants and children.

Trusses are not recommended, except rarely for temporary use. They are difficult to apply correctly, impossible to keep clean, may cause testicular atrophy from pressure, and do not cause the hernial sac to obliterate permanently. When operation must be deferred and it seems desirable to avoid protrusion of the hernia, a yarn truss or the type described by Potts may be used temporarily. The latter consists of a small triangular cotton pad held in place over the inguinal ring by a T binder or belt made of gum rubber. It has the advantage that the small cotton pads, which are buttoned on, can be easily replaced when soiled.

**Incarcerated inguinal hernia.** Incarceration of inguinal hernias is common in children (20 per cent have a history of it) and occurs most often in the first six months of life. It is manifest by the appearance of a firm, tender, globular, irreducible swelling below the external inguinal ring. The infant is fretful and often vomits. Unless relieved, abdominal distention, cessation of bowel movements, persistent vomiting, fever and leukocytosis will develop as impairment of the blood supply progresses.

Manipulative reduction of an incarcerated hernia which has been present for less than twelve hours and has not been accompanied by a bloody stool is the treatment of choice. The infant is adequately sedated (with a

barbiturate under six months of age or with morphine in an older patient). He is then placed in the Trendelenburg position with a roll of cloth under the buttocks, and an ice bag is placed on the affected side to decrease the edema. After an hour or more when the sedation has taken effect and the parents have quieted the infant to sleep, the mass is gently grasped with all fingers of the physician's warmed hand and squeezed with gentle equal pressure by all digits toward the inguinal canal. This maneuver frequently leads to reduction. The patient should then be observed closely for several hours for signs of peritoneal irritation to make certain that non-viable bowel has not been reduced. During the next several days the infant's metabolic upset is corrected, and the edema in the hernial sac is permitted to subside; elective herniorrhaphy is then performed.

If the incarcerated hernia cannot be reduced or if it is inadvisable to attempt it because of its duration, emergency surgical correction must be undertaken, with provisions available for bowel resection if it is necessary.

#### HYDROCELE

A hydrocele is the presence of fluid anywhere along the course of the processus vaginalis.

Newborn male infants whose processus vaginalis has obliterated frequently have residual peritoneal fluid in the tunica vaginalis of the testis. This common type of *non-communicating hydrocele* forms an oval, fluctuant, tense, translucent sac, and the spermatic cord and ring can usually be felt above it. The fluid gradually absorbs during the first year of life, and surgical correction is rarely required.

If the processus vaginalis remains open, peritoneal fluid may be forced into it, forming a hydrocele of the spermatic cord or of the canal of Nuck in the female. An inguinal hernia is often associated. Frequently the parents note that the "testis seems larger" in the evening after an active day, and smaller the following morning. This history is highly suggestive of the *communicating hydrocele* (see Diagnosis under Inguinal Hernia). The length of the hydrocele is dependent upon the extent of the patency of the processus vaginalis. If it extends into the tunica vaginalis, then the elongated fluctuant mass extends to the lower part of the scrotum. When the occlusion is at a higher level, the hydrocele is a fluctuant swelling above the scrotum or extending only a short way into it.



FIG. 201. Congenital diaphragmatic hernia. A, Film exposed shortly after birth: distortion of shadow of left leaf of diaphragm, with huge, masslike density in left chest displacing heart to right. B, Film exposed about 20 minutes after A. As the result of swallowed air, coils of air-filled small bowel are now demonstrated in the left chest. The esophagus is outlined by swallowed contrast material. Operative correction was attempted because of extreme dyspnea. Infant died  $5\frac{1}{2}$  hours after birth.

Occasionally the fluid becomes trapped in the sac and forms a firm globular mass which is irreducible and resembles an incarcerated inguinal hernia. If the fluid is at some distance below the external inguinal ring or has been present for several days and is neither tender nor symptomatic, the diagnosis of a hydrocele may safely be made. The sudden appearance of an irreducible hydrocele near the external ring is usually impossible to differentiate from an incarcerated hernia. Transillumination is of no value in such a case, since an incarcerated intestine will also transmit light before it becomes hemorrhagic. Emergency surgical exploration may be necessary for differentiation.

Since the appearance of a hydrocele some time after birth is evidence of a persistent processus vaginalis, the hydrocele should be extirpated by the inguinal route and the hernial sac removed. Aspiration of the tunica vaginalis or injection of sclerosing solutions is not warranted; either one may cause ad-

hesions, which makes the ultimate operation more difficult and may damage the testis.

#### EPIGASTRIC HERNIA

Epigastric hernias occur in the midline between the umbilicus and the lower end of the sternum. They are not common and, except for their location, are similar to umbilical hernias. They should be repaired surgically.

#### INCISIONAL HERNIA

Postoperative hernias should be repaired as soon as the local condition of the wound and the general condition of the child warrant it. There is no justification for permitting children to continue with the discomfort attendant on this type of hernia.

#### DIAPHRAGMATIC HERNIA

**Etiology.** Diaphragmatic hernia may be congenital or acquired. In the former there may be no diaphragmatic tissue at the position of the opening, or the hernia may occur



through the esophageal hiatus (p. 642), the canal of Bochdalek or the foramen of Morgagni. It occurs more frequently on the left than on the right side. Diaphragmatic eventration is, strictly speaking, not a hernia, but somewhat similar in effect, since abdominal viscera displace thoracic structures because of the weakness and ballooning of half of the diaphragm. In some instances eventration occurs in infants born by breech delivery who have received an injury to the phrenic nerve alone, or in association with one of the brachial plexuses. Acquired diaphragmatic hernias are usually traumatic in origin.

**Pathology.** There are all degrees of protrusion of the abdominal viscera through the diaphragmatic opening into the thoracic cavity. In extensive cases the stomach and a large part of the intestines displace the lungs and heart, and there may be an abnormal depression of the abdominal wall. There may be an associated incomplete rotation of the cecum and, at times, duodenal constricting bands. The lung on the affected side is often hypoplastic, and hypoplasia of the opposite lung has also been observed.

**Diagnosis.** There may be no symptoms, and the condition may be discovered only by chance roentgenographic examination. On the other hand, there may be symptoms of severe respiratory distress present from birth, including dyspnea and cyanosis; there may also be persistent vomiting and other evidences of intestinal obstruction. When symptoms are not present at birth, they may appear at any time and include such digestive disturbances as discomfort after eating, severe colicky pain, vomiting and constipation. Acute intestinal

obstruction is always a possibility in these cases.

The physical examination varies considerably. The percussion note over the part of the thorax containing the stomach and intestines may be more tympanitic or duller than usual, and the respiratory murmur absent, decreased or increased, in either case; at times the sounds of intestinal peristaltic movements can be heard over the chest. The diagnosis can usually be established by roentgenographic examination, often without the aid of a contrast medium; but when there is any doubt about abnormal intrathoracic masses, examination after ingestion of a contrast material other than barium should be made to determine whether the "mass" consists of stomach and intestines.

The *symptoms* of traumatic hernia may be obscured by those of other injuries, but are usually dyspnea, cyanosis and shock.

**Treatment.** This is surgical. When there are acute symptoms, the procedure is an emergency and there is considerable risk. When there are no symptoms or only intermittent ones, operation is elective, but should be performed as early as possible.

WALDO E. NELSON

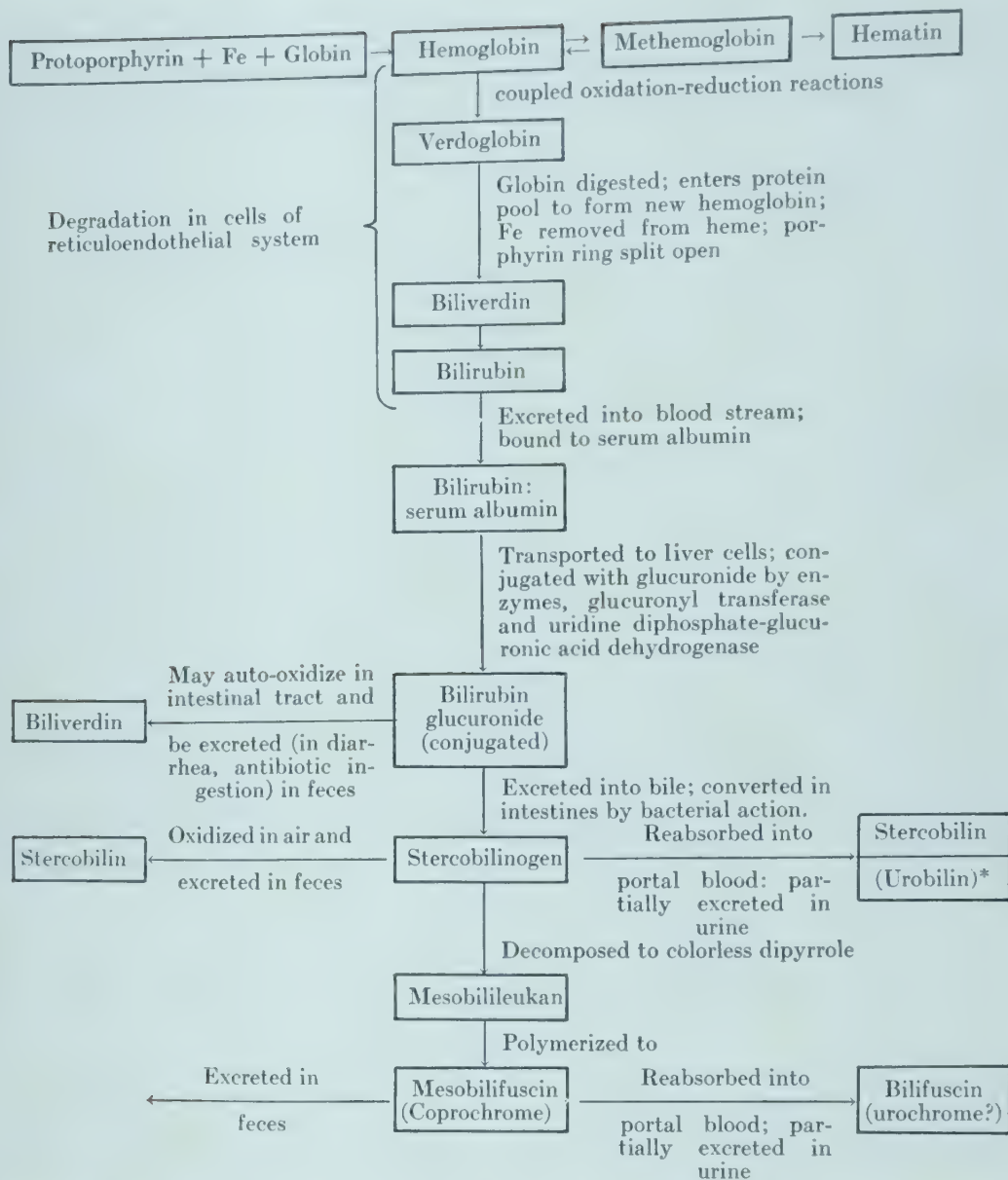
#### REFERENCES

- Cresson, S. L.: Management of Hernias in Infants and Children. *M. Clin. North America*, 36:1767, 1952.
- Gross, R. E.: The Surgery of Infancy and Childhood. Philadelphia, W. B. Saunders Company, 1953.
- Potts, W. T.: A Truss for Inguinal Hernia in Infants. *J.A.M.A.*, 117:1440, 1941.

## THE LIVER

**Anatomy.** The liver of the full term infant weighs 120 to 160 gm. at birth. The weight is doubled at two years and tripled at three years; at nine years it has increased six times, and at puberty, ten times. The liver of the adult is twelve to thirteen times as large as that of the newborn infant. The relative sizes of the lobes of the liver change with age; at birth the right lobe is twice as large as the left lobe; in young children and adolescents it is about three times as large. The functional right and left lobes, drained by the right and left hepatic ducts and supplied with corresponding portal venous branches and hepatic

veins, differ from the anatomic lobes. The anterior surface of the liver is gradually roofed over by the ribs and diaphragm. In the newborn infant the liver edge is usually less than 2 cm. below the costal margin in the right midclavicular line. The upper border of hepatic dullness is at the level of the fifth or sixth rib in the mammary line and extends nearly horizontally. In the axillary line it is usually in the seventh intercostal space and posteriorly in the ninth space. The lower border of the liver may be normally palpable about 1 cm. below the subcostal margin throughout childhood.



\* In the intestinal tract only stercobilinogen is produced by bacterial reduction of bilirubin. Urobilinogen is produced by cellular enzymatic activity in the liver and biliary passages and does not normally appear in the urine; under physiologic conditions only stercobilinogen and stercobilin appear in the urine.

FIG. 202. Metabolism of hemoglobin and bile pigments.

The lobules are not clearly demarcated at birth. They increase in size with age, and almost the entire growth of the liver is due to increase in their size. Extramedullary hematopoiesis, varying inversely in amount with the birth weight, may be found normally in the liver of infants for a few weeks after birth.

**Congenital Anomalies and Malpositions.** Absence of the liver has been reported in still-born fetuses in association with other severe anomalies. The lobes of the liver may vary in size and shape; either one may be absent, or there may be more than two. Riedel's lobe is the tongue-like downward projection of the

right lobe. A "floating liver" occurs when there is congenital elongation of the ligaments which support the organ. In situs inversus the liver is on the left side; with diaphragmatic hernia it may be located in the thorax.

Downward displacement of the liver is produced by contractural deformities of the thorax (rickets), relaxation of the abdominal musculature (severe malnutrition, amyotonia congenita and other paralyses) or increased intrathoracic pressure (empyema, pneumothorax or emphysema). Subphrenic abscess or a collection of air (perforation of the gastrointestinal tract) will push the liver down-



ward. The less common upward displacement of the liver may be caused by ascites, abdominal tumors or paralysis of the diaphragm.

**Physiology.** The liver has multiple and complex physiologic functions. It secretes bile and takes an important part in metabolism, blood formation, and detoxification.

**Bile.** The important biliary constituents are the bile salts, the bile pigments, cholesterol and lecithin. The bile salts, made solely by the liver cells, are excreted into the intestine, reabsorbed and returned to the liver by the portal blood stream for re-excretion.

Bile pigments are formed by the entire reticuloendothelial system. It is estimated that the reticuloendothelial cells of the liver (Kupffer's cells) make only a minor portion of the bilirubin excreted.

Bile pigment is formed chiefly from hemoglobin, but myoglobin and possibly the enzymes containing heme pigment (catalases, peroxidases, cytochromes) may also be degraded to bilirubin. After phagocytosis, hemoglobin is transformed by coupled oxidation-reduction reactions to a green compound, *choleglobin* (verdoglobin). The globin moiety is enzymatically digested and enters the protein pool of the body; iron is released from heme and is stored in the liver; the remaining porphyrin ring is split into an open chain tetrapyrrole compound, biliverdin, which is reduced to bilirubin. Excreted into the blood, bilirubin is bound by albumin and carried to the liver cells, where it is conjugated with glucuronide and excreted into the bile. The enzymes, glucuronyl transferase and uridine diphosphate-glucuronic acid dehydrogenase, are involved in this conjugation (Fig. 203).

In the intestinal tract, bilirubin is reduced to stercobilinogen by bacterial action and is excreted in part in the stools in its oxidized form, stercobilin. If it escapes oxidation, e.g., during the ingestion of antibiotics, bilirubin auto-oxidizes to biliverdin and imparts a green color to the stools. Part of the stercobilinogen is reabsorbed into the portal circulation, carried to the liver and almost entirely excreted in the bile, forming the so-called *enterohepatic circulation of bile pigments*. Stercobilinogen, which gets into the general circulation, is

excreted by the kidney as urobilinogen; it is quickly oxidized to urobilin after the urine has been passed. Stercobilinogen is in part further decomposed in the intestines to mesobilileukan (pro-mesobilifuscin), a dipyrrole compound, which is rapidly polymerized to mesobilifuscin (or coprochrome) and is responsible for some of the brown color of feces. It is possible that the pigment of the urine, urochrome, is bilifuscin, a derivative of coprochrome.

The average normal fecal excretion of urobilinogen is 3.9 mg. a day for infants under one year of age; this increases with age to a level of 45.5 mg. by ten to fourteen years of age. When the liver is unable to excrete all the stercobilinogen brought to it by the portal circulation, abnormal amounts appear in the general circulation and in turn are excreted in the urine. This may occur with excessive hemolysis or when there is extensive disease of the liver.

The porphyrins are another series of pigments related to hemoglobin, differing from the bile pigments in that the porphyrin ring is not split open. Porphyrins are present in the stool, presumably excreted by the bile, and in the urine. Other than their association with the various clinical types of porphyria, little is known of their normal physiology during infancy and childhood. Their metabolism is disturbed in various forms of hepatic disease; the retention of porphyrins in hepatic failure may be connected with the cerebral dysfunction of hepatic coma.

Phosphatase is excreted in the bile. Whether the elevated serum phosphatase of obstructive jaundice is due to failure of biliary excretion or to excessive release from injured hepatic cells is not known.

**Metabolic functions.** Owing to its important role in the metabolism of the various foodstuffs, the liver has been aptly termed the commissariat of the body.

The liver plays the leading role in maintenance of the normal blood sugar level. It forms and stores glycogen from glucose, levulose, galactose and dextrolactate. It converts the glycogenic amino acids and the glycerol fraction of fats into dextrose, which is de-

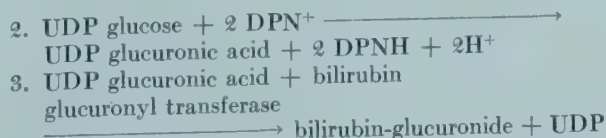
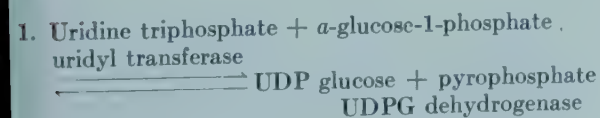


FIG. 203. Enzymatic steps in glucuronide synthesis. UDP = uridine-diphosphate; DPN = diphosphopyridine-nucleotide. (Modified from Brown and Zuelzer: J. Clin. Invest., Vol. 37.)

posited as glycogen (glycogenesis). Glycogen can be reconverted into glucose by the liver (glycogenolysis). Thus the liver serves as a storehouse of readily available glucose which can be delivered to the blood when required. The livers of young infants contain proportionately less glycogen than those of older children.

The liver is the site of both synthesis and oxidation of fat. Hepatic lipogenesis from acetate and pyruvate depends upon the normal functioning of both the anaerobic glycolytic (Embden-Meyerhof) and phosphoglucuronate pathways of carbohydrate metabolism. Most, if not all, of the fat mobilized in the liver is combined with lecithin and changed to phospholipid, a change which is apparently necessary for its transport and subsequent use. Dietary deficiency of lipotropic factors (e.g., choline, inositol or compounds which can contribute methyl groups for the formation of choline) prevents the formation of the more soluble phospholipid, so that fat accumulates in the liver. Cholesterol is formed in the liver from its esters or by synthesis from acetic acid. Cholesterol esters, i.e., compounds of cholesterol and fatty acids, which constitute 70 per cent of the plasma cholesterol, are also formed in the liver and are a means for the rapid transport of cholesterol. The plasma lipoproteins which transport triglycerides also appear to be, in part, formed in the liver.

The liver (and kidney) breaks down long-chain fatty acids into ketone bodies, which are burned by and supply energy to the muscles and other tissues which cannot form them. When fat is burned in excess (starvation and diabetes), the large amounts of ketone bodies produced appear in the blood and urine. The formation of ketones is an incompletely developed function in young infants (Heymann).

Urea is formed exclusively in the liver by the deamination of amino acids; it is apparently a waste product of the conversion of glucogenic amino acids to glycogen. The liver is concerned with the formation of many fractions of the serum proteins.\* Fibrinogen, a globulin, is formed exclusively in the liver. Prothrombin and other coagulation factors and probably all the serum albumins are of hepatic origin. The liver also serves as a

storage depot for protein. There is a large labile fraction of the hepatic proteins which increases with a high protein diet and decreases during starvation. In many disease states of the liver there is an increased concentration of serum globulins.

Vitamins A, C and D are stored in the liver, and considerable amounts of A and D remain for a long time after the administration of single large doses. The precursors of vitamin A are converted into vitamin A in the liver. The damaged liver has a reduced storage capacity for vitamin A and a lowered capacity for the conversion of its precursors. Riboflavin and vitamins E and K have important metabolic storage relationships to the liver.

**INFLUENCE OF DIET UPON THE LIVER.** The vulnerability of the liver to toxic agents may be reduced or eliminated by various dietary constituents. A high carbohydrate diet has a protective action for the liver. This has been attributed to the resultant increased glycogen content of the liver, but may be due to other factors, since the young infant with a low hepatic glycogen content is more resistant than the adult to a hepatic poison such as carbon tetrachloride. An adequate protein intake also shields the liver from toxic injury; *methionine* and *cystine* are recognized as some of the protective elements in protein.

Dietary deficiencies lead to hepatic injury. A low protein diet results in massive hepatic necrosis, specifically as a result of cystine deficiency. Absence of tocopherol from the diet also predisposes to this type of liver damage. Protein deficiency of lesser degree or a high fat diet produces fatty infiltration of the liver which slowly progresses to diffuse hepatic fibrosis. This sequence of hepatic injury may be prevented by the inclusion of choline or methionine in the diet, both of which tend to prevent fatty infiltration of the liver.

**Blood formation.** In the fetus the liver is an active site of blood formation. Hematopoiesis is common in the livers of premature and occasionally of full term infants as a remnant of this fetal function. In conditions such as hemolytic anemias in which excessive demands are placed on the blood-forming mechanisms the liver undergoes myeloid metaplasia and resumes its hematopoietic activity. The liver also serves as a storehouse for iron during the early months of infancy and is used when the infant's diet is chiefly milk and is low in iron. With depletion of this store by about the fifth

\* A case reported by Thompson, McQuarrie and Bell emphasizes the role of the liver in the formation of the serum proteins. In a child with generalized edema and hypoproteinemia the sole finding at autopsy was an idiopathic atrophy of the hepatic cells.



month, hypochromic anemia develops if the diet is not planned to contain foodstuffs with a high iron content.

**Detoxifying functions.** The liver can alter various exogenous toxic substances by conjugating them with sulfuric acid, glucuronic acid (an oxidation product of glucose) or amino acids. The conjugation mechanism is probably more concerned with increasing the solubility of the toxic substance so that it can be more easily transported through the body

fluids and excreted than it is with a direct reduction in toxicity. Thus sulfanilamide is converted into the more soluble but more toxic compound, acetyl sulfanilamide. The liver also appears to be the principal site for removal of ammonia from the blood. The natural and synthetic estrogenic and androgenic substances are inactivated by the liver. Excess of these hormones in the body, when the damaged liver fails to dispose of them, results in abnormal physiologic effects.

## TESTS OF LIVER DISTURBANCES AND FUNCTION

Since there is no test which specifically detects active parenchymal hepatic disease, laboratory tests have their greatest usefulness in the presence of clinically obvious liver disease by supplying some measure of the progress of the disease—information that is of assistance in prognosis and management. They are helpful in differentiation of the various types of jaundice and in detection of hepatic derangement in nonicteric patients.

Tests utilized to study liver disease may be divided into two main classes, depending upon whether they do or do not measure liver function.

### TESTS NOT MEASURING DERANGEMENT OF LIVER FUNCTION

A large group of tests do not measure any known physiologic function of the liver, but are seemingly dependent upon the presence in the body fluids of some by-product of active liver damage. These tests are at best presumptive indicators of the continued presence of an active pathologic process in the liver.

**Cephalin-Cholesterol Flocculation Test.** This test is based upon the capacity of the serum of patients with active liver disease to flocculate a colloidal cephalin-cholesterol suspension. Alterations in serum albumin and alpha globulin, which normally act as stabilizers of the suspension, are thought to be responsible for flocculation. The test is not specific for liver disease, but provides useful prognostic data. There is often a positive reaction in the newborn infant during the early days of life, which is apparently not due to liver disease; postpartum women also have a positive test for several days.

**Thymol Turbidity Test.** This test is based on the production of turbidity within thirty minutes in a saturated buffered thymol solution by the serum of patients with hepatic disease, largely owing to increases in beta globulin content. The serums of normal persons and of patients with uncomplicated obstructive jaundice produce little or no turbidity.

**Colloidal Gold Reaction of Blood Serum.** This test is based on the changes in stability of colloidal gold suspensions produced by alterations in the globulin and albumin patterns resulting from hepatic damage. The Takata-Ara, formol-gel and Weltmann's coagulation band reaction tests have a similar basis.

**Erythrocyte Sedimentation Rate Test.** This test is as useful in following the course of an active infection of the liver as it is for many other diseases.

**Tyrosinuria and Leucinuria.** The amino acids tyrosine and leucine are present only in traces in normal urine. When present in clinically demonstrable quantities, they indicate autolysis of the liver. Thus in acute yellow atrophy of the liver a high percentage of patients have tyrosine in the blood and urine.

**Coproporphyrin in Urine.** The urinary coproporphyrins are increased in hepatic disease. In acute hepatitis and the cirrhosis following it, coproporphyrin I is increased; in alcoholic cirrhosis, coproporphyrin III is increased. Normally, 20 to 120 gammas of total urinary coproporphyrin are excreted daily by adults.

**Serum Levels of Transaminases.** The levels of serum glutamic-oxaloacetic and glutamic-pyruvic transaminases are elevated when hepatic cells are injured by disease or trauma. These tests are of value diagnostically and in following the clinical course, for example, of hepatitis.

### TESTS MEASURING FUNCTIONAL CAPACITY

The manifold functions of the liver make it obvious that no single test can be depended upon to measure the over-all functional capacity of the liver. The use of a suitably selected test or group of tests repeated periodically, however, may furnish valuable information. The so-called large reserve of functional capacity is stressed as a factor limiting the sensitivity of these tests. This reserve is predicated chiefly upon the fact that after surgical removal of a large part (80 to 95 per cent) of the normal liver there is still adequate hepatic function. It is likely that this reserve may be more illusory than real in the diseased liver, for many hepatotoxic agents can inactivate hepatic metabolic mechanisms without visibly apparent cellular damage. Since most liver function tests measure but a single function of this organ, they may be classified according to the function measured.

### TESTS DEPENDENT UPON THE ROLE OF THE LIVER IN CARBOHYDRATE, PROTEIN AND FAT METABOLISM

#### CARBOHYDRATE TOLERANCE TESTS

These tests furnish an index of the capacity of the liver to convert the monosaccharides, glucose, levulose and galactose, into glycogen (glycogenesis). Liv-

ington and Bridge have standardized these tests for infants under two years of age.

The diet of the patient has an influence on the type of response. A high carbohydrate diet results in a low blood sugar curve, and a high fat diet or starvation causes a high, prolonged curve in the tolerance tests, the so-called starvation diabetes. Accordingly, the patient should be fed a diet of average caloric content which provides about 50 per cent of the calories as carbohydrate for three days preceding any of the carbohydrate tolerance tests. Since frequent repetition of the dextrose tolerance test results in successively flatter tolerance curves, tests should not be repeated at intervals of less than three days. A twelve-hour fast should precede the test for infants receiving four to five feedings daily. A nine-hour fast is adequate for premature infants or for infants receiving six or more feedings daily.

**Glucose Tolerance Tests. Oral.** The following test doses of glucose administered in a 25 per cent solution have been suggested by Bridge and Mulholland:

0-18 months . . . . .	2.50 gm. of glucose/kg.
18 months-3 years . . .	2.00 gm. of glucose/kg.
3-12 years . . . . .	1.75 gm. of glucose/kg.
12 years or older . . . .	1.25 gm. of glucose/kg.

A blood sugar determination is obtained before administration of the sugar (fasting) and subsequently at one-half hour, one hour, two hours and three hours. A rise in venous blood sugar to 140 to 155 mg. per 100 ml. within a half-hour or an hour and a return to a normal level within two to three hours is a normal response. The sugar levels of arterial or capillary blood during the immediate postprandial phase are somewhat higher (20 to 50 mg. per 100 ml.) than are those of venous blood; fasting levels are essentially equal. It must be remembered that other factors, such as poor intestinal absorption (as in celiac disease, intestinal tuberculosis, nephrosis), influence the oral glucose tolerance curve.

**Intravenous glucose tolerance test.** See page 1219.

**Epinephrine Test.** See page 1219.

**Galactose Tolerance Test.** This monosaccharide is probably not utilized by the tissues, but is metabolized almost entirely in the liver. After an oral dose of 1.75 gm. per kilogram of body weight, urine is collected for a period of four hours. If more than 3 gm. of galactose appear in the urine during this time, it is presumed that the liver's capacity to convert galactose to glucose is impaired.

#### TESTS DEPENDENT UPON HEPATIC FAT METABOLISM

**Cholesterol Partition of Blood Plasma.** Normally the ratio of cholesterol esters to free cholesterol is approximately 2:1. A reduction in the amount of esterified cholesterol occurs in patients with liver damage. Since other factors may disturb the amounts of cholesterol esters, a single determination has little value in assessing liver damage.

#### TESTS RELATED TO HEPATIC PROTEIN METABOLISM

**Serum Protein Concentrations.** The total serum proteins are usually reduced in liver disease with a resultant decrease in serum colloid osmotic pressure.

The decrease is almost entirely due to a lowered concentration of serum albumin. The small increases in serum globulin fractions which occur in most liver diseases are also seen in nonhepatic disorders, since they stem from hyperactivity of the reticuloendothelial system. Increased alpha, beta and gamma globulin fractions are in part the causes of the flocculation, precipitation and turbidity in the tests for hepatic injury. A large increase in serum globulin is invariably due to hypergammaglobulinemia.

**Plasma Amino Acid Tolerance Curves.** Spontaneous increase in the plasma level of amino acids is rare and is usually due to amino acids (tyrosine) liberated from autolyzed liver tissue and not to failure of removal of amino acids by the liver. A retention of plasma amino acids occurs in patients with liver disease after their intravenous injection.

**Prothrombin Concentration of the Blood.** The liver plays a dual role in the regulation of the prothrombin level of the blood. Bile salts are necessary for the absorption of vitamin K, a precursor of prothrombin, from the intestinal tract. This factor explains the bleeding tendency of patients with obstructive jaundice. The diseased liver is impaired in its capacity to utilize vitamin K in the formation of prothrombin. Failure to obtain an elevation of a lowered prothrombin time after the parenteral injection of vitamin K is presumptive evidence of impaired liver function.

#### TESTS BASED UPON THE SECRETORY AND EXCRETORY FUNCTIONS

**Bilirubin—The van den Bergh Reaction.** Normally the two forms of bilirubin, the direct (or conjugated) and the indirect (or unmodified) types, are transported in the circulation in loose combination with serum albumin. Direct-reacting bilirubin is conjugated to glucuronic acid; in the plasma it is a mixture of the monoglucuronides and diglucuronides of bilirubin. The total concentration of both types ranges normally from 0.2 to 1.4 mg. per 100 ml., with 0.2 mg. per 100 ml. as the upper limit for the direct type. Since concentrations of bilirubin are often expressed in van den Bergh units per liter, it is to be noted that 1 van den Bergh unit per liter is equivalent to a bilirubin concentration of 5 mg. per liter.

When Ehrlich's diazo reagent (a mixture of sulfanilic acid, hydrochloric acid and sodium nitrite) is added to a solution of bilirubin glucuronide, a reddish violet color (azobilirubin) is produced. The term *direct* is applied to either this type of bilirubin or to the van den Bergh reaction itself when the color develops rapidly in an untreated bilirubin solution. No color results when the diazo reagent is added to a solution of unmodified bilirubin. However, if alcohol is added to the unmodified bilirubin solution, it then reacts with the diazo reagent to produce the reddish violet color. The term *indirect* is thus used for either unmodified bilirubin or the van den Bergh reaction in which alcohol is used as a catalyst to allow the color to develop.

The van den Bergh reaction serves as both a qualitative and quantitative test for bilirubin. Qualitatively, it differentiates the types of bilirubin (conjugated and unmodified). As a quantitative test it is used to measure the total amount of bilirubin or



the separate quantities of conjugated or unmodified bilirubin present in a serum sample. The presence of direct bilirubin is revealed by the prompt development of color when the diazo reagent is added: a photoelectric colorimetric reading of the color intensity after one minute quantitates this type of bilirubin. A photoelectric colorimetric reading taken on an alcohol-treated serum specimen one-half hour after diazotization measures the total bilirubin content. Indirect bilirubin is calculated by subtracting the direct from the total bilirubin content. Qualitatively, the following inferences may be drawn from the van den Bergh reaction: (1) Direct bilirubin as the sole or predominant pigment demonstrable is indicative of obstructive (regurgitation) jaundice. (2) The occurrence of indirect bilirubin in abnormal concentrations signifies a hemolytic (retention) jaundice. (3) Increased amounts of both direct and indirect bilirubin are found in toxic and infectious jaundice in which there is simultaneously retention and regurgitation of bilirubin.

As a quantitative test the van den Bergh reaction is useful in diagnosis and prognosis and in following the course of the disease process.

**Bilirubin clearance rate or removal of injected bilirubin from the blood.** Weech and his co-workers developed a quantitative test which measures the

rate at which the liver removes injected bilirubin from the blood.

**The icteric index.** In this test, which has limited usefulness, the color of the plasma is compared with that of a standard potassium dichromate solution. The color intensity of the standard is taken as unity. Values greater than 9 units are considered indicative of an increase in total serum bilirubin. Carotenemia, turbidity due to lipemia, and hemolyzed samples all result in false readings.

**Urobilin excretion\* (urine and stool).** A study of urobilin excretion aids in differentiating various types of jaundice. In jaundice due to excessive hemolysis there is an increased urinary urobilin, owing to the larger amounts of stercobilinogen formed in the intestine from the excessive bilirubin made available by hemolysis. In almost all hemolytic anemias there is also subnormal function of the liver, so that stercobilinogen is not adequately removed from the blood by the liver and is excreted in the urine. Slight degrees of hepatic damage allow the escape of urobilinogen into the general circulation, to be excreted by the kidneys. Thus an excessive amount of urobilin

\* Urobilinogen excretion as measured by the Ehrlich reagent measures both urobilinogen and stercobilinogen indiscriminately.

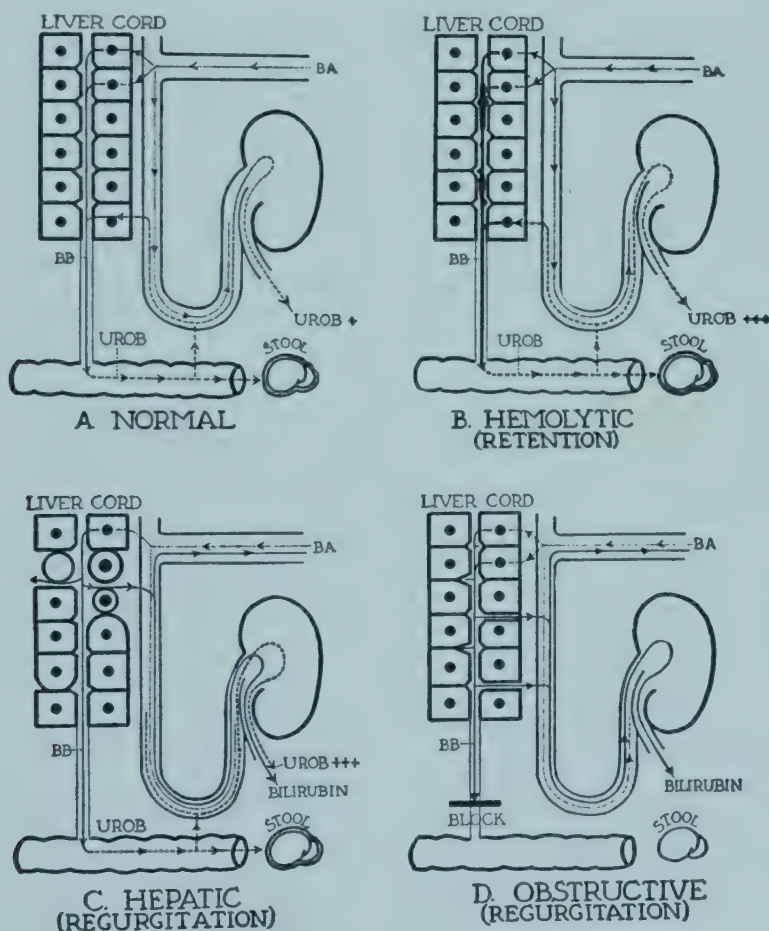


FIG. 204. Schematic drawing explaining the changes of the metabolism of bile pigments in the various forms of jaundice. (Modified from Steigmann, Popper and Meyer: J.A.M.A., Vol. 122.)

BA – Unmodified bilirubin (indirect)  
 BB – Conjugated bilirubin (direct)  
 UROB – Urobilinogen (stercobilinogen)

is found in the urine of patients who have incomplete obstruction of the bile ducts. In portal cirrhosis, urobilin is found in excessive amounts in the urine, because it can pass from the portal to the systemic circulation through collateral venous channels without passing through the liver.

In infectious hepatitis there is increased urinary urobilin only at the beginning and end of the disease, since, it is believed, during the height of the disease the finer bile passages are completely obstructed.

Fecal excretion of urobilin is diminished when the liver is unable to excrete bilirubin properly because of obstruction or cellular damage. Increased fecal urobilin is indicative of increased production of bile pigment from excessive blood destruction.

**Bile Salts Determinations.** The concentration of bile salts in the blood and urine is increased in obstructive jaundice, but decreased in material obtained by duodenal intubation.

**Phosphatase Level.** The phosphatase level of the blood is increased in obstructive jaundice, since phosphatase spills back into the blood along with the other constituents normally excreted in the bile.

**Measurement of Excretion of Foreign Substances by the Bile. Bromsulphalein test.** This test is a sensitive indicator of mild hepatic dysfunction. It is performed after a carbohydrate breakfast, since fat in the plasma interferes with estimation of the color. After intravenous injection of 5 mg. of this dye per kilogram of body weight a blood sample (5 to 10 ml.) is withdrawn after forty-five minutes, which may contain 0 to 4 per cent of the dye injected. Retention of more than 6 per cent of the dye is abnormal.

Similar tests using other dyes ( $I^{131}$ , bengal rose,

azorubin S) are available. These tests are most useful in detecting liver damage in patients who do not have biliary obstruction, i.e., without hyperbilirubinemia.

#### TESTS BASED ON THE "DETOXIFYING" ACTION

Several tests assess the capacity of the liver to oxidize or conjugate various substances. The best known of these tests is the hippuric acid synthesis test.

**Hippuric Acid Synthesis Test.** This test measures the rate at which the liver can synthesize glycine, which, when conjugated with benzoic acid, forms hippuric acid. Actually, this test would seem to evaluate one phase of hepatic protein metabolism, rather than of a detoxifying mechanism. After an oral or intravenous dose of sodium benzoate the urinary excretion of hippuric acid is determined. In children five to eleven years of age 0.9 gm. of sodium hippurate is excreted in the first hour after oral administration of 2 gm. of sodium benzoate dissolved in 20 cc. of water.

The oral test is unreliable. The intravenous test is performed after a light carbohydrate breakfast—20 cc. of 8.85 per cent sodium benzoate are injected over a five- to ten-minute period. In the hour following injection adults excrete from 0.7 to 1.1 gm. of hippuric acid. The test is of no value when the blood urea nitrogen is elevated.

#### BIOPSY OF THE LIVER

Histologic examination of liver tissue obtained by needle biopsy or surgical exploration may furnish valuable diagnostic and prognostic data in many instances.

## HEPATIC DISORDERS

### CIRCULATORY DISTURBANCES

#### CHRONIC CONGESTION OF THE LIVER

**Etiology.** Cardiac failure (p. 893) is the principal cause of passive congestion of the liver. Though acute myocardial decompensation such as that associated with the crises of hemolytic anemias and with hypertensive acute glomerulonephritis will produce temporary passive hyperemia of the liver, more striking changes result from the prolonged passive congestion associated with chronic disease of the heart. Long-standing pulmonary disease with stasis in the right side of the heart will also engorge the liver. Occasionally a collection of pleural fluid or a thoracic tumor, by compressing the inferior vena cava, may retard the return of blood from the liver.

As the liver becomes congested, the central veins are distended, but the liver cords remain intact. With continuation of the

hyperemia the liver cells surrounding the central vein undergo degenerative changes due to anoxemia and become atrophic, giving the liver the appearance described as the nutmeg liver.

The large firm liver of either of these two stages may result in some pain or tenderness in the hepatic region. Subclinical or mild jaundice may be present.

With long-standing and particularly with recurrent episodes of congestive cardiac failure, hepatic fibrosis (cirrhosis) may occur, which involves either or both of the portal and central portions of the lobule. It is thought that infection in combination with venous stagnation is productive of cirrhosis.

#### JAUNDICE

**Clinical Forms.** Jaundice is the yellow coloration of the body tissues and fluids caused by excess bilirubin. It is usually



apparent when the serum bilirubin reaches levels of 2.5 to 3 mg. per 100 ml. (range, 1 to 7 mg.). Conjugated bilirubin causes more intense jaundice than unmodified at equal blood concentrations, because it is more diffusible, being water soluble. The bile pigments apparently bind easily to elastin, a fact which accounts for the unequal staining of various tissues and for the persistence of cutaneous pigmentation after the blood bilirubin level has fallen during recovery.

The most useful classification divides jaundice into hemolytic (indirect-reacting bilirubin) and obstructive (direct-reacting bilirubin) varieties. The obstructive type is further divided into extrahepatic and hepatocellular or intrahepatic obstruction.

**Hemolytic jaundice.** This type of jaundice results from excessive destruction of hemoglobin with the creation of more bilirubin in the plasma than the liver can excrete, despite its ability to increase its excretion of bilirubin manyfold. The bilirubin is the indirect-reacting form, which is not excreted into the urine. Since both forms of bilirubin are bound to serum albumin, it is difficult to understand why conjugated bilirubin appears in the urine, and the unmodified variety does not. There is an increase of fecal urinary urobilin, since the liver is excreting more bilirubin than usual. Hemolytic jaundice may occur in the congenital hemolytic syndromes (thalassemia, sickle cell anemia, congenital microspherocytosis) and in acquired hemolytic anemias of various causes.

The normal liver, as indicated, is capable of increasing the excretion of bilirubin tremendously. During periods of anoxia or infection, however, it may be so handicapped as to be unable to handle even the usual excretion of bilirubin. The liver of the newborn is normally deficient in one or more enzymes and cannot excrete bilirubin as well as the adult liver. Genetic defects of these enzymes for bilirubin conjugation occur in congenital familial nonhemolytic jaundice with kernicterus (Crigler-Najjar disease) and in constitutional hepatic dysfunction (Gilbert's disease) with resultant elevations of indirect-reacting bilirubin.

**Obstructive jaundice.** Under usual circumstances bilirubin is conjugated with glucuronide to form the direct-reacting variety and is excreted into the intestine. When this exit is blocked, the conjugated

bilirubin enters the blood stream, and jaundice ensues. This type of jaundice is termed regurgitative or obstructive. It may be the result of rupture of the biliary canaliculi due to congenital or acquired obstruction of the bile ducts (extrahepatic) or to obstruction of the canaliculi by swollen hepatic cells as in hepatitis (hepatocellular) or to fibrotic changes in cirrhosis. It is believed that the bile passes into the lymphatics and through the thoracic duct into the blood.

Direct bilirubin is secreted by the renal tubules and appears in the urine; since less bilirubin reaches the intestine than normally, the fecal and urinary concentrations of urobilin are decreased, or urobilin is absent with complete obstruction. The concentration of bile salts is also elevated in the plasma with obstructive jaundice, and they appear in the urine.

In many conditions there is a combination of hepatocellular dysfunction and obstruction of the bile ducts so that plasma concentrations of both direct- and indirect-reacting bilirubins are elevated.

**Clinical Manifestations.** Jaundice, seen first in the sclera and conjunctiva, soon becomes visible in the mucous membranes of the lips, hard palate and sublingual area, and finally stains the skin. Edematous areas and paralyzed parts may show little or no discoloration. Jaundice may be missed in artificial light; it varies in color and intensity from pale yellow through deeper shades of orange to many hues of green. Bilirubin imparts an orange color to the skin; its oxidation product biliverdin is responsible for the green color. The different icteric tints are dependent upon the proportions and amounts of these two pigments. The sweat, breast milk and blister fluid become bile-stained. Tears, saliva and gastric and pancreatic juices are not stained. The cerebrospinal fluid is only slightly discolored, but may become stained deeply if there is meningeal irritation. As a rule there are no manifestations other than the skin discoloration referable to hemolytic jaundice. In obstructive jaundice the urine is discolored, and the stools are clay-colored with an increased fat content. Pruritus and bradycardia in severe obstructive jaundice are ascribed to the increased concentration of bile salts in the body fluids. Although high levels of unconjugated bilirubin are held responsible for kernicterus of newborn infants with hemolytic disease, circulating bilirubin or

Table 89. Laboratory Findings in Different Types of Jaundice

Laboratory Studies		Hemolytic (or Prehepatic) Jaundice	Obstructive Jaundice			
Test	Extrahepatic		Intrahepatic or Hepatocellular			
	Incomplete		Complete	Acute	Chronic	
Urine	Bilirubin	Absent	Present	Present	Present	Present
	Urobilinogen	Increased	Normal	Decreased	Normal, increased or decreased	Normal
Stool	Urobilinogen	Increased	Normal	Acholic	Normal, increased or decreased	Normal
Blood	Conjugated bilirubin	Normal	Increased	Increased	Increased	Increased
	Total bilirubin	Increased	Increased	Increased	Increased	Increased
	Serum transaminase*	Normal (5–40 units)	57–320 units		540–1890 units	13–286 units
	Alkaline phosphatase	Normal	Increased	Increased	Normal or increased	Normal or increased
	Ratio $\frac{\text{cholesterol esters}}{\text{total cholesterol}}$	Normal	Decreased	Decreased	Decreased	Decreased
	Cephalin flocculation	Normal	Normal	Normal	Increased	Increased
	Thymol turbidity	Normal	Normal	Normal	Increased	Increased
	Thymol flocculation	Normal	Normal	Normal	Increased	Increased
	Prothrombin time	Normal	Normal	Normal or increased	Normal or increased	Normal or increased
	Serum albumin	Normal	Normal	Normal	Normal	Decreased
Serum globulin	Normal	Normal	Normal	Normal	Increased	

\* Serum transaminase activity parallels active cellular destruction. Levels are *very high* in early stages of hepatitis and are diagnostic; they are moderately elevated in biliary cirrhosis, Laennec's cirrhosis and obstructive jaundice.

bile salts are not the cause of the cerebral dysfunctions of severe hepatic disease evident as noisy delirium, flapping tremors of the hands, coma and electroencephalographic changes. This syndrome of hepatic encephalopathy is more likely related to increased blood levels of ammonia. Bleeding from the oral mucous membranes or gastrointestinal tract secondary to prothrombin deficiency is a frequent accompaniment of jaundice.

#### CONSTITUTIONAL HEPATIC DYSFUNCTION

(GILBERT'S DISEASE, FAMILIAL NON-HEMOLYTIC ICTERUS; HEREDITARY NONHEMOLYTIC JAUNDICE, CONSTITUTIONAL HYPERBILIRUBINEMIA)

This benign hereditary condition was delineated by Gilbert in 1901 and named

*cholémie simple familiale*. Its sole clinical manifestation is icterus, which may become apparent at any age. The inborn metabolic error responsible for the inability to conjugate bilirubin with glucuronic acid is a deficiency of the hepatic enzyme, glucuronyl transferase (p. 281). The defect is transmitted by an autosomal dominant gene.

Other than easy fatigability in some patients and occasional anxiety which may be engendered by fluctuations in intensity of jaundice, there are no symptoms. The elevated bilirubin is always indirect reacting, rarely exceeds 6 mg. per 100 ml. and may be intermittent or persistent. The diagnosis of constitutional hepatic dysfunction is made by exclusion of hemolytic processes. A mild hemolytic disorder without anemia may be



differentiated by estimation of fecal urobilinogen excretion. The bilirubin clearance test may be helpful; patients with Gilbert's disease show impaired ability to clear the blood of injected bilirubin. Liver biopsy specimens, unless examined for enzymatic activity, show no changes.

The disorder does not impair health or life expectancy.

#### CONGENITAL FAMILIAL NONHEMOLYTIC JAUNDICE WITH KERNICTERUS

(CRIGLER-NAJJAR DISEASE, CONGENITAL HYPERBILIRUBINEMIA)

This rare type of congenital severe hyperbilirubinemia, first described by Crigler and Najjar (1952) in eight members of a single large kinship, is a serious disorder in which abnormally high plasma bilirubin levels and encephalopathy result from hepatic disability to conjugate bilirubin with glucuronide. Deficiency of the hepatic enzyme, glucuronyl transferase, transmitted as an autosomal recessive trait, is the basic hereditary molecular defect. Severe central nervous system disturbances of the extrapyramidal type usually appear during the early weeks of life, but may develop later in infancy or during early childhood. Febrile episodes, apparently of central nervous system origin, are common.

Bile thrombi are present in the hepatic canaliculi, but the parenchymal cells appear normal. Evidences of excessive hemolysis are absent. There is bile staining of the basal nuclei, characteristic of kernicterus.

Serum bilirubin levels range from 10 to 44 mg. per 100 ml., with 80 to 90 per cent of the total in the indirect form. Urobilinogen excretion in the urine is increased, with less than half the normal amount present in the feces. The bilirubin excretion test is abnormal. Absence of evidences of hemolytic disease, of blood group incompatibilities and of obstructive jaundice helps to distinguish this disorder from the common causes of neonatal jaundice.

The *prognosis* is poor; the extent of central nervous system involvement determines the duration of life. Most patients die during early infancy, but a number of young children with the disorder are recorded, and Jervis has reported an affected woman forty years of age with the dystonia syndrome typical of kernicterus. By inhibiting oxygen consumption and by uncoupling oxidative

phosphorylation, bilirubin is toxic to cerebral tissue, especially in its unmodified form, which is lipophylic. Conjugated bilirubin, which is water soluble, does not stain cerebral tissue. Thus the encephalopathy of this disorder may be attributed to the hyperbilirubinemia. A mutant strain of Wistar rats described by Gunn has congenital hyperbilirubinemia and kernicterus. Administration of sulfonamides intensifies the cerebral damage and staining in these animals. A similar potentiating effect of sulfonamide drugs on the toxicity of bilirubin has been observed in premature infants with jaundice.

*Treatment* is symptomatic and supportive; sulfonamide drugs should be avoided.

#### CHRONIC IDIOPATHIC JAUNDICE

(DUBIN-JOHNSON SYNDROME, MAVERO-HEPATIC ICTERUS, BLACK LIVER JAUNDICE)

This disorder, in which jaundice is the single invariable symptom, is characterized by a green-black discoloration of the liver due to accumulation of coarsely granular brown pigment in the parenchymal cells. Often familial, it is benign and lifelong and is probably the result of an inherited disability of the hepatic cells to excrete conjugated bilirubin. In two thirds of the cases jaundice is apparent before the age of twenty; the time at which it is first noted varies from early infancy to adult life. About one quarter of the cases are asymptomatic. Pain over the liver is the most common symptom, and weakness, anorexia, nausea, vomiting and diarrhea are less frequently complaints, recurring with each bout of jaundice.

The liver is enlarged and tender in about half of the cases. Bile and increased urobilinogen are often present in the urine; the stools may be acholic, and hepatic function tests are sometimes abnormal during episodes of jaundice. The gallbladder is seldom visualized by oral cholecystography. Jaundice may be intermittent or persistent with fluctuations in intensity.

The maximum values of the fluctuating concentrations of serum bilirubin range from 2.4 to 19 mg. per 100 ml.; it is predominantly of the conjugated type. Biopsy specimens of the liver are diagnostic; the cells have centrilobular distribution of the pigment granules, which are probably a lipofuscin. The *prognosis* for life is good.

## INFECTIONS

### INFECTIOUS HEPATITIS

(VIRAL HEPATITIS, ACUTE CATARRHAL JAUNDICE)

**Etiology.** There are at least two forms of infectious hepatitis which are etiologically distinct, but pathologically and clinically indistinguishable (see table on p. 706). Each is caused by a virus or strains of viruses to which immunity is established after infection, but there is no cross immunity. The naturally transmitted infection is termed *infectious hepatitis*, or *endemic* or *epidemic hepatitis*; the one artificially transmitted by administration of plasma or blood or of vaccines made from human serum is termed *serum hepatitis*, or *homologous serum hepatitis*.

**Infectious hepatitis (viral hepatitis A; IH hepatitis).** The gastrointestinal tract is the usual portal of entry for the virus, which has also been demonstrated in the blood and feces during the preicteric and early icteric stages of the disease. It may also be present in the stools until recovery is complete.

**Serum hepatitis (viral hepatitis B; SH hepatitis).** Injection of human serum products (convalescent serums, whole blood, plasma, the older type of yellow fever vaccine or the topical application of human thrombin as a hemostatic agent in neurosurgery) may result in an infection clinically and pathologically indistinguishable from the more common infectious hepatitis, which has a natural epidemiology. The virus (or viruses) transferred by the injections of infected serum, however, is a different strain (or strains) than the one of the naturally transmitted infection. Even minute amounts of infective material as in incompletely cleansed syringes may be causative. Presumably the virus can survive in stored serum or plasma for a long time and can withstand desiccation and various other physical and chemical treatments.

**Incidence.** There is a high incidence (up to 90 per cent) of nonicteric cases during epidemics of infectious hepatitis. The seeming rarity of the illness below the age of two years has been attributed to lack of exposure. It is now apparent that infectious hepatitis is often anicteric in infants and young children and is therefore undetected rather than nonexistent. Above the age of four years the attack rate, i.e., patients with jaundice, during an epidemic bears no relation to age. The infected nonicteric infant may serve as a reservoir from which sporadic

cases and small epidemics of jaundice in older children and adults are initiated. Non-icteric "carriers" of the virus of infectious hepatitis are known to exist; the extent to which they disseminate infection is undefined.

There is no natural epidemic pattern for serum hepatitis, although the infection may occur in epidemic form when the agent is transmitted through vaccines, plasma or blood to large population groups as during World War II. *Transplacental passage* of the virus of serum hepatitis apparently infects the fetus and is responsible for hepatitis in newborn and young infants. This does not appear to be so with the virus of infectious hepatitis.

**Pathology.** Serial biopsy studies in adults show the same pathologic changes in the liver in both types of hepatitis. The hepatic lobules show varying degrees of cellular necrosis and autolysis, beginning in the center of the lobules and spreading radially as the disease advances. There is thickening of the reticular fibers. Evidences of cell regeneration, i.e., increased mitotic figures, are prominent in the early stages of the disease. Accompanying the hepatocellular necrosis is widespread infiltration with inflammatory cells, polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells. In the later stages lymphocytes predominate. There is a diffuse reticuloendothelial reaction; the reticulum becomes thickened and assumes the staining properties of collagen. The periportal areas are widened because of infiltration with large numbers of macrophages, plasma cells and lymphocytes and smaller numbers of polymorphonuclear cells and eosinophils. Proliferating bile ducts appear in the perilobular portal areas, and bile stasis is visible. The clinical manifestations of viral hepatitis are expressions of the hepatocellular necrosis, intrahepatic biliary obstruction, portal obstruction and diffuse inflammatory reaction in the liver. With recovery, complete regeneration of the liver cells occurs without scarring. In fulminating and fatal cases the hepatic changes are typical of yellow atrophy. About 15 per cent of the fatal cases studied by Lucké showed changes in the brain consisting in acute degeneration of ganglion cells and mild meningoencephalitis.

**Clinical Manifestations.** The incubation period of infectious hepatitis preceding the onset of jaundice is fourteen to forty days; if measured to the onset of initial symptoms, it may be three to five days less.



The incubation period of serum hepatitis is 60 to 135 days.

In most patients symptoms begin three to five days before the appearance of jaundice. Fever, malaise, mild headache and chilliness are present at the onset. Signs of a mild upper respiratory tract infection are found in many patients. Anorexia is an invariable early symptom, frequently followed by nausea and vomiting. The breath is often foul, and older children may complain of a sour or bitter taste. Upper abdominal distress and pain are frequent complaints. Constipation is more common than diarrhea. The presence of bile in the urine is the first sign of developing jaundice and usually precedes its clinical appearance by one to three days.

In about one sixth of all patients the disease is manifest by the appearance of jaundice without any preceding symptoms. Jaundice may vary from a slight discoloration of the scleras, where it is first seen, to a deep pigmentation involving the entire body. Fever usually disappears with the onset of icterus, but anorexia continues, and severe prostration and vomiting secondary to pylorospasm may occur, especially in deeply jaundiced patients. The stools are light or clay-colored at this stage. Pruritus is infrequent in the jaundiced child. In severely ill children extreme lassitude and irritability may be present.

In more than half the cases the liver is enlarged and tender; in a small number there is an enlarged tender spleen. Ascites is almost never present. Bradycardia, common in the adult, is usually absent in children. Seborrheic dermatitis, morbilliform rashes and hemorrhagic phenomena are uncommon.

**Diagnosis.** The van den Bergh reaction is

direct during the early days of jaundice and changes to a biphasic reaction as recovery begins. During the terminal phase of recovery the reaction may be indirect only. The serum bilirubin is increased, ranging as high as 10 mg. per 100 ml. With the onset of jaundice there is an increased urinary excretion of urobilinogen, due to the inability of the damaged liver to excrete reabsorbed urobilinogen, formed from bile which is still entering the intestine. As the jaundice becomes more intense, owing to complete regurgitation of bile so that it does not enter the intestine, urobilinogen disappears from the urine, since it is not being formed in the intestine. With the subsidence of jaundice resulting from the resumption of excretion of bile into the intestine, urobilinogen is again formed and appears once more in the urine in large quantities, the liver still being incapable of removing it from the blood (Fig. 205).

The bromsulphalein retention test tends to parallel the retention of bilirubin in the blood, but is often abnormal for a longer time. The serum glutamic-oxaloacetic and glutamic-pyruvic transaminases are elevated early in the course; their return to normal heralds the end of the active disease and the beginning of recovery.

There is often a large reduction in the ester fraction of the plasma cholesterol and a lesser one in total cholesterol during the acute phase of the disease. Early in the recovery period levels of both total and esterified cholesterol may be temporarily higher than normal. Plasma phosphatase concentration is increased during the early icteric phase, but not always to abnormal levels. The cephalin flocculation and thymol turbidity tests are

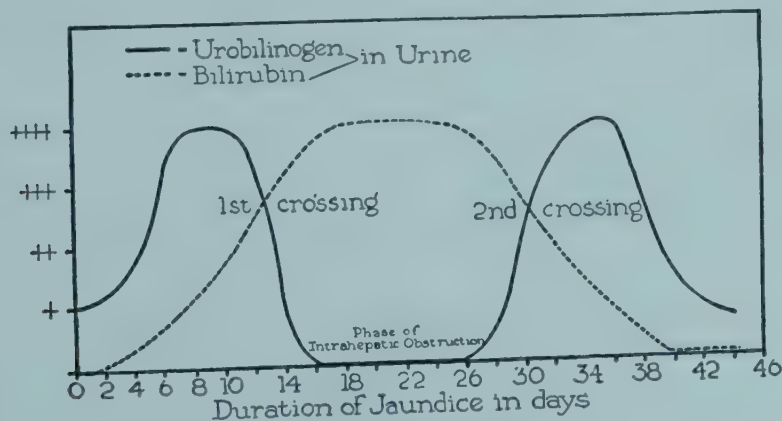


FIG. 205. Schematic curve of the results of qualitative analysis for bilirubin and urobilinogen in a typical case of parenchymatous jaundice with intrahepatic obstruction. (From Steigmann, Popper and Meyer: J.A.M.A., Vol. 122.)

fairly reliable indicators of activity of the hepatitis, as are the transaminase levels. The sedimentation rate is increased in some cases. There are no significant changes in the serum protein concentration on routine determination, but an increase in gamma globulin can be demonstrated by electrophoretic analysis.

No single test furnishes complete information about the functional state of the liver, so that, to ascertain the degree of functional restoration, a group of tests must be used. There are no consistent changes in the total leukocyte count, but a monocytosis as high as 25 per cent is occasionally observed. Hypoglycemia and acetonuria are frequent findings. On occasion serologic tests for syphilis are falsely positive.

The diagnosis may often be made several days before the appearance of jaundice by means of the methylene blue test (Myers) or the Harrison spot test (Godfried). Both tests are based on the presence of small amounts of bilirubin in the urine.

In the *methylene blue test* 2 drops of Löffler's methylene blue solution are added to 10 cc. of urine. The solution remains dark blue if no bilirubin is present, but turns a brilliant green when bilirubin is present.

In the *Harrison spot test* 10 cc. of urine are mixed with 5 cc. of 10 per cent barium chloride solution and filtered. The filter paper is then spread on another dry piece of filter paper, and 1 or 2 drops of Fouchet's reagent are dropped on the precipitate. A green or blue color indicates bilirubin.

**Differential Diagnosis.** The differential diagnosis of infectious hepatitis presents few difficulties. The finding of bile in the urine, the acholic stools and the direct van den Bergh reaction establish the obstructive nature of the jaundice and rule out the acute hemolytic anemias. Though the other causes of obstructive jaundice should be considered possibilities, *leptospirosis* is the condition most often confused with infectious jaundice. The labial herpes, hemorrhagic exanthem, fever, leukocytosis, muscle pains and albuminuria occurring in leptospirosis should serve to distinguish the two diseases. The specific agglutination test, the isolation of the spirochete from the blood or serum, or the successful inoculation of a guinea pig confirms the diagnosis of leptospirosis. Involvement of the liver in infectious mononucleosis may mimic viral hepatitis at times.

Stokes summarizes the differences between infectious hepatitis and serum hepatitis as follows:

	Infectious (Epidemic) Hepatitis (A)	Serum Hepatitis (B)
Symptomatology	More stormy onset with a chill or chilliness and a sudden rise in temperature	Slow insidious onset with mild prodromes and little fever except in the fatal cases
Route of inoculation	Oral, rectal or parenteral	Parenteral only
Incubation period	14-40 days	60-135 days
Usual age range	Below 30 years	All ages
Epidemic spread	Common	Rare, if at all
Virus demonstrated	Blood and feces	Blood, ascitic fluid and arthritic fluid
Blood carriers	0	+
Immunity	Homologous immunity present; cross immunity absent	Homologous immunity present (up to 1 year); cross immunity absent
Increased susceptibility	Previous attack of serum hepatitis increases susceptibility	Previous attack of epidemic hepatitis increases susceptibility
Gamma globulin for prophylaxis	Prevents clinical disease; does not prevent infection	Not effective

**Course and Prognosis.** Infectious hepatitis has its highest incidence, but lowest mortality, among children of school age. Compared with the clinical course in adults, the disease is milder and of shorter duration in this group, the average case with jaundice lasting three weeks, with a range of four to eighty days. Not infrequently a child feels well by the time the jaundice appears; usually the other clinical manifestations are gone by the seventh day of jaundice. Apparently much more common among children than the icteric form of the disease is a milder, but immunizing, anicteric infection caused by type A hepatitis virus with symptoms predominantly those of an intestinal or respiratory illness.

"Congenital" or neonatal viral hepatitis occurs in the early weeks of life, apparently acquired in utero by transplacental transmission of virus B. Characterized by early onset of jaundice, hepatosplenomegaly, bilirubinuria and acholic stools, its definitive diagnosis by liver function tests is often difficult; twelve infants in one series of forty



subjected to surgery were found to have hepatitis. Identification of most reported cases has been by needle or surgical biopsy or at necropsy. Cirrhosis is a sequel in about one fourth of affected infants. Complete recovery without relapse is usual, but in a small number of instances viral hepatitis occurs in a fulminant form. This disastrous form of the disease often leads to death in less than ten days. Infrequently the course is slowly progressive with death within two to nine months in hepatic failure or with clinical and laboratory remission after several months. In the latter case the final outcome is in doubt; the suggestion has been made that chronic fibrosis of the liver (Laennec's cirrhosis) may develop when factors are encountered which, acting synergistically with the virus, lead to fibrosis, e.g., nutritional deficiency, metal and chemical poisoning, alcoholism, infections with amebae, *Salmonella typhosa*, *S. choleraesuis*, and the like.

**Treatment.** This is symptomatic. Rest in bed until jaundice disappears is advisable, since activity aggravates the symptoms, and it is impossible to determine which patient will have yellow atrophy. Application of local heat may relieve epigastric distress, but at times sedation is required. For this purpose chloral hydrate is preferable to the barbiturates or opiates, which are hepatotoxic. Anorexia and vomiting may also be ameliorated by sedation, but severe vomiting is often dramatically stopped by intravenous administration of 5 per cent glucose in isotonic solution of sodium chloride. Frequent small meals of carbohydrate and protein (fruit juices, carbonated drinks, skimmed milk, gruels, lean meat) are better tolerated than large meals at longer intervals. Fats are moderately restricted, since they tend to aggravate nausea and vomiting, especially when bile is completely absent from the intestinal tract. A full, unrestricted diet may be given as soon as the patient can tolerate it.

On theoretic grounds the inclusion of supplements of the entire vitamin B complex to the diet should aid in the prevention of further hepatic injury. In fulminating and comatose cases exclusion of protein from the diet and bowel sterilization with a broad-spectrum antibiotic, preferably neomycin, suppress the production of toxic nitrogenous compounds in the intestines by bacterial degradation of protein. Cleansing enemas and magnesium sulfate purgation are at times of value for the same purpose. These measures

help prevent or minimize the accumulation of ammonia in the blood and the neurologic manifestations of hepatocerebral intoxication. Daily intravenous administration of albumin may be of value if edema or ascites occurs. Corticosteroids appear to be of benefit on occasion in fulminating as well as in chronic hepatitis.

The therapeutic value of L-arginine and L-glutamic acid in hepatic coma is as yet undetermined. Glutamic acid detoxifies the circulating ammonium ion by forming innocuous glutamine; arginine, by providing intermediates for the Krebs' ornithine cycle in the hepatic cells, removes ammonia as urea. However, the role of ammonia in the genesis of hepatic encephalopathy is not satisfactorily defined. Methionine and choline are of no value in treatment and may be toxic to patients with hepatic coma. Similarly, sulfonamides, ammonium salts, urea, acetazolamide and chlorothiazide should be avoided. In the rare case with hemorrhagic phenomena, vitamin K should be given parenterally.

Children usually do not require as prolonged convalescence as do adults, and most may quickly resume normal activities.

Intramuscular injection of human gamma globulin in doses as small as 0.02 ml. per kilogram of body weight is effective prophylaxis against type A virus infection, even when given as late as six days before the expected onset of symptoms. It appears that gamma globulin does not prevent infection in exposed susceptibles, but attenuates the disease to a subclinical level, and in many instances results in acquisition of active immunity. Gamma globulin has no protective action against infection with type B virus (homologous serum hepatitis).

The "enteric precautions" utilized for any stool-borne infection should be observed by family contacts and personnel caring for patients with viral hepatitis. Since the duration of infectivity of stools is undetermined, quarantine and isolation regulations are based on arbitrary grounds.

For Parasitic Infestations and Echinococcus Disease, see page 574.

#### LIVER ABSCESS

##### SOLITARY ABSCESS

The pyogenic solitary abscess is an occasional complication of a variety of infections, including typhoid fever, bacillary dysentery, Brucella infection, influenza, tuberculosis and

Friedländer's bacillus infection. Rarely it is secondary to ileocecal actinomycosis as a large honeycomb abscess. Most often, however, the single hepatic abscess is due to the *Staphylococcus* or *Streptococcus*. The infective agent may reach the liver directly by a penetrating injury or by extension from an adjacent infected area, as, for example, from a pleural empyema. Occasionally roundworms have resulted in liver abscess by wandering into the bile ducts, causing hepatic injury and permitting secondary pyogenic infection. Amebic abscess, the commonest solitary abscess of adults, is almost unknown in children in the United States.

**Clinical Manifestations.** Occasionally an abscess of the liver may be latent if it is well encapsulated, or it may be overshadowed by the symptoms of the disease from which it has its origin. More often symptoms are present, of which fever is the most constant, usually being accompanied by chills, sweating and prostration. Nausea, vomiting, diarrhea and meteorism may be prominent symptoms. Pain is usually present over the liver and may be severe; at times it may be referred to the right shoulder or the epigastrium. Upward enlargement of the abscess may produce cough or dyspnea by irritation of the diaphragm. Cachexia is a feature of the longstanding abscess. Mild icterus is present in many and ascites in a few cases. Moderate enlargement of the liver, usually of the right lobe, both upward and downward occurs.

**Diagnosis.** The upward enlargement of the liver can be demonstrated on the roentgenogram. Tenderness may be elicited by palpation or by mild percussion with the fist over the liver. Repeated exploratory punctures until the abscess is located will furnish a positive diagnosis, but it is generally agreed that this procedure should not be used unless incision and drainage are carried out immediately after obtaining pus. Such exploratory punctures are safest when the liver is exposed by laparotomy; this procedure is always advisable in infants.

**Complications.** The abscess may rupture spontaneously into the thorax, the peritoneum, the intestines or, rarely, the pericardium. Metastatic abscesses of the lung or brain may occur. Subphrenic abscess is an occasional complication.

**Treatment.** Appropriate antibiotics should be given for pyogenic abscesses, and emetine for amebic abscesses. Surgical drainage should be performed when necessary.

## MULTIPLE ABSCESSSES

Multiple liver abscesses arise from septicemia or from ascending infection of the portal vein (pyelophlebitis). In the newborn infant infection extending along the umbilical vein is a common cause of multiple hepatic abscesses. These abscesses are small and usually are not detected during life.

## CIRRHOSIS

**Etiology.** Cirrhosis is characterized by degeneration of hepatic cells, followed by a nodular disorganization of regenerated cells with distortion of the vascular pattern and an increase in fibrous connective tissue. Cirrhosis may follow a number of hepatic disorders, although frequently the etiology is unknown. Severe or prolonged hepatic cellular damage is common to all known conditions predisposing to cirrhosis. However, even though the initial disturbance becomes quiescent, the cirrhotic process may continue. The progression may be related in part to cellular anoxia produced by constrictive fibrous bands, which results in further cellular damage and further attempts at regeneration with additional fibrosis. Complete understanding of the pathogenesis of cirrhosis remains to be achieved. Fibrosis without disturbance of the hepatic architecture should not be termed cirrhosis.

Cirrhosis may have its origin in a congenital defect as in hepatolenticular degeneration (Wilson's disease). This is a familial disorder of copper metabolism (p. 257), in which copper is deposited in the liver. The cirrhosis may cause death before symptoms of central nervous system involvement are evident.

Biliary cirrhosis may follow prolonged biliary obstruction from any cause, atresia of the bile ducts being the most common cause during infancy. Cirrhosis secondary to prolonged vascular congestion may occur with cardiac decompensation and with intrahepatic obstruction of the portal vein. Chiari's disease (thrombosis of the hepatic vein) may also be responsible for cirrhosis.

Numerous infections of the liver may ultimately lead to cirrhosis. Infectious hepatitis would appear to be the most common one during childhood. Bacterial infection of the umbilical vein in newborn infants or of the pelvic or mesenteric veins in older children may extend to the liver and cause cirrhosis. Syphilis, malaria and kala-azar are also relatively common causes. Cirrhosis is seen in



patients who recover from acute hepatic poisoning, as for example with carbon tetrachloride.

It is probable that some factor or combination of factors, in addition to cellular damage itself, is required to produce cirrhosis. Such factors may include general or specific genetic defects, prolonged exposure to toxic agents and iso-immunization. See cirrhosis in Indian children (p. 711).

**Incidence.** Cirrhosis is not common among children in the United States. In the Near East and in the Orient biliary cirrhosis is relatively frequent (p. 711).

**Forms of Cirrhosis.** Traditionally, cirrhosis has been divided into portal (Laennec's cirrhosis) and biliary types. In children mixed forms of the two pathologic types of cirrhosis are more common than either of the pure forms.

In *portal cirrhosis* bands of fibrous tissue radiate from the portal triad and surround the hepatic lobules; there is degeneration of hepatic cells with evidence of a chronic inflammatory reaction. *Biliary cirrhosis* secondary to obstruction of the bile ducts is characterized by accumulation of bile in the distended canaliculi and fibrosis radiating from the distended bile ducts. As both types progress, however, this differentiation is lost; frequently it is impossible to classify the type of cirrhosis when confronted with the nodular fibrotic changes characteristic of the later stages of the disease.

**Clinical Manifestations.** The liver is usually enlarged and firm; the edge may be smooth or nodular. In late stages the liver may contract, but even at autopsy it is usually enlarged.

Other manifestations of cirrhosis occur only (1) when the liver fails in some of its physiologic functions, or (2) when the pressure of the portal vein is sufficiently elevated to produce symptoms.

The functional reserve of the liver is great; indeed, cirrhosis may exist for many years, or death may occur by exsanguination from esophageal varices without evidence of deficiency of hepatic function. When cirrhosis is sufficiently advanced to interfere with hepatic function, many nonspecific symptoms such as malaise, anorexia, bloating and loose, frequent stools may appear.

Low grade fever is a common symptom. Serum albumin is depressed, and peripheral edema may be present. The serum globulin is usually elevated, but may be normal. Jaundice is common; usually both the direct- and

indirect-reacting serum bilirubin levels are elevated, but either may predominate. Pruritus and bradycardia may accompany the jaundice, but are not common in children. Hypoprothrombinemia with epistaxis or other bleeding manifestations is frequent; failure of prothrombin to rise after administration of vitamin K is a grave sign. Anemia is usually present. Neurologic signs, such as coma and convulsions, are frequent in the terminal phase or during crises of hepatic insufficiency. Spider angiomas and liver palms occur, but less commonly than in adults. Symptomatic hypoglycemia is rare. Growth retardation is common and may be extreme.

Symptoms resulting from obstruction of the portal venous flow include enlargement of the spleen, the formation of gastric and esophageal varices, ascites and collateral venous circulation in the veins of the abdominal wall (*caput medusae*). Ascites may be related to hypoproteinemia and/or portal hypertension and may be massive. The splenomegaly may be associated with hemolytic anemia, neutropenia or thrombocytopenia (Banti's syndrome, p. 986). Hemorrhage from esophageal or gastric varices may be the initial sign of cirrhosis; such hemorrhages may be made more severe by hypoprothrombinemia or thrombocytopenia. Hemorrhoids and varicoceles of the spermatic veins are uncommon in children. Clubbing of the fingers and toes may occur in the more protracted and severe cases.

In the so-called *Cruveilhier-Baumgarten cirrhosis*, which develops as a result of failure of obliteration of the umbilical vein, a well marked *caput medusae* is seen. In addition to the striking periumbilical venous dilatation, a loud venous murmur is audible at the umbilicus. There is no ascites associated with this cirrhosis.

**Diagnosis.** With the exception of biopsy of the liver, no specific diagnostic measures are available. Abnormal hepatic function may be demonstrated by hypoalbuminemia with reversal of the albumin-globulin ratio due in part to hyperglobulinemia, by hypoprothrombinemia and by low levels of cholesterol esters in the blood. The concentration of blood ammonia may be high and be responsible for coma and convulsions. If jaundice is not present, poor excretory function may be demonstrated by retention of bromsulphalein. If jaundice is present, bile may appear in the urine, and the urinary urobilin may be increased. The cephalin flocculation, thymol turbidity and thymol flocculation tests may be

positive. These tests, which reflect the presence of abnormal proteins in the plasma, are often normal, however, even in the presence of severe hepatic dysfunction. Biopsy of the liver by needle aspiration is being used increasingly for diagnostic and prognostic purposes.

**Treatment.** The patient with biliary cirrhosis may be greatly improved if any existing obstruction is relieved. No specific treatment is available for other forms of cirrhosis.

In milder cases of cirrhosis a high caloric diet with liberal protein content and fat as desired by the patient should be provided. If signs of encephalopathy are noted, the protein should be discontinued or greatly reduced. Supplements of the B vitamins may be beneficial, as may added choline. Methionine is valueless and may actually precipitate coma. In anorexic patients glucose should be administered intravenously. Edema and/or ascites is treated by rigid restriction of sodium (200 mg. daily); diuretics may prove beneficial, particularly chlorothiazide (Diuril), but this should not be used if hepatic coma is present or impending. Corticosteroid therapy may have a favorable effect on ascites and deserves a trial in most cases. Massive ascites may require paracentesis; this procedure should be limited to patients with respiratory distress, owing to the dangers of peritoneal infection.

Measures which lower the concentration of blood ammonia may abolish or reduce the symptoms of hepatic encephalopathy. Such measures include a diet containing no or very little protein and the oral administration of broad-spectrum antibiotics to reduce the intestinal flora. The intravenous administration of arginine may have some added benefit by aiding in the removal of ammonia from the blood. Vitamin K should be administered if there is hypoprothrombinemia; if it is ineffective, as is often the case, transfusion of fresh blood may be required to supply prothrombin. Management of bleeding from esophageal or gastric varices includes sedation, avoidance of oral feeding, tamponade by means of the three-lumen Blakemore-Sengstaken tube, which may be lifesaving, and transfusions of whole blood. Several surgical procedures have been devised to reduce the pressure in the varices by shunting blood from the portal circulation to the systemic veins. The relative merits of these procedures and of other forms of surgical treatment are still to be assessed.

The over-all management of the child and his family, as in other chronic, progressive

disorders, requires a good deal of understanding on the part of the physician, who can do much to make the situation tolerable if he will take the time.

#### HEPATIC CIRRHOSIS WITH ARTHRITIS AND AMENORRHEA IN FEMALES

(KUNKEL'S SYNDROME; PLASMA CELL HEPATITIS)

Kunkel has drawn attention to a syndrome of chronic liver disease in young females, characterized by cirrhosis with intensive hepatic infiltration by plasmocytes, extreme hypergammaglobulinemia and clinical features such as arthritis, obscure febrile episodes and hormonal disturbances, not usually seen in Laennec's cirrhosis. A few cases may be sequels of anicteric viral hepatitis, but in most instances the etiology is unknown. The disease begins insidiously, usually about puberty, with fatigue or lassitude or occasionally with bleeding gums or epistaxis. Amenorrhea is an early symptom; at times acne, pigmented striae, hirsutism, moon facies and/or obesity are noted before signs of liver disease are present.

Hepatomegaly and splenomegaly are usually the earliest signs of liver disease. Spider telangiectases occur in most patients, and esophageal varices are present in about half the cases. Ascites develops only late in the course. Many have febrile episodes, at times associated with severe respiratory and cardiac disturbances. Swollen painful joints often accompanied by fever and hepatic pain are frequent. In two instances rheumatic nodules were found. The good nutritional status during the early stages of the illness is remarkable. Death from esophageal hemorrhage or hepatic coma usually occurs within ten years of onset.

In addition to the usual chemical changes of hepatic cirrhosis, the elevation of plasma gamma globulin is impressive; in one case it was 9.4 gm. per 100 ml. Jaundice is commonly present, and bromsulfalein retention is found in all cases.

At necropsy the liver is moderately enlarged and shows diffuse nodular cirrhosis, resembling the postnecrotic type. The inflammatory exudate in the liver contains a preponderance of plasma cells, and serial biopsy studies show a correlation of the number of these cells with the degree of hypergammaglobulinemia.

The response to corticosteroid therapy is often dramatic, resulting in complete remis-



sion in many instances. The ultimate effect of this treatment must await further observation.

### NUTRITIONAL LIVER DISEASES

Dietary protein deficiency produces two types of hepatic injury in experimental animals. One, acute massive hepatic necrosis with post-necrotic scarring, is caused by deficiency of sulfhydryl groups (cystine and methionine) and alpha tocopherol. Its analogue in human disease is the necrosis seen in fulminating viral hepatitis and various kinds of poisoning. The second type, fatty liver with fibrosis, results from the dietary deficit of lipotropic labile methyl groups (lecithin, choline and methionine). A number of clinical syndromes of human nutritional liver disease, collectively designated as the *kwashiorkor syndrome*, occur among native populations of tropical and subtropical regions. Owing to ready availability of carbohydrate-containing foods, the dietaries of these peoples are adequate in calories, but are deficient in protein; the various syndromes include the following:

1. *Classical kwashiorkor or malignant malnutrition* (p. 357).

2. *Protein malnutrition complicated by Senecio (ragwort) poisoning* in South Africa. The Senecio alkaloids are hepatotoxic and are apparently ingested as a contaminant of wheat bread. Hepatomegaly and ascites are characteristic.

3. *Protein malnutrition with siderotic cirrhosis of the liver* in native South African children. The iron pigment in the cirrhotic liver of these children appears to come from the iron cooking utensils in which their carbohydrate foods are prepared.

4. *Infantile and childhood cirrhosis* in Hindu children (see below).

5. *Vomiting sickness of Jamaica*, probably due to toxic substances in "bush teas" made from the bitter cassava or unripe ackee fruit, which produces severe hepatic damage in malnourished children. Severe vomiting after meals, associated with hypoglycemic manifestations, characterizes this disorder, which is epidemic in the winter months. Death occurs in many instances in two to three days.

6. *Veno-occlusive disease of West Indian children*, a third variety of nutritional liver disease in this region.

MILTON RAPOPORT

### INDIAN CHILDHOOD CIRRHOSIS

greater prevalence of cirrhosis of the liver in children in the tropics and subtropics than

in the temperate zones is generally recognized, but in two widely separated regions, Jamaica and India, it is sufficiently common to constitute a public health problem. There seem to be certain differences, however, between the types encountered in these two areas. The Jamaican cases, known also as veno-occlusive disease, have an abrupt onset with acute hepatomegaly and ascites followed by a sub-acute phase with persistent hepatomegaly, with or without ascites, and finally by chronic cirrhosis. By contrast, the onset of the cases in India is often insidious or subacute, and ascites is a later manifestation. (See also Etiology.) Whereas neonatal hepatitis, giant cell hepatitis and biliary cirrhosis secondary to congenital atresia of the bile ducts are seen in infants in India as in Europe and America, the frequent occurrence of cirrhosis of unknown etiology in many areas of India among children, generally between one and five years of age, justifies the separate clinical designation, "Indian childhood cirrhosis."

**Etiology.** The cause or causes responsible for this damage to the liver in Indian children are not known. Congenital syphilis, malaria and kala-azar do not seem to be factors. Poor nutrition has been blamed, but does not seem to be directly responsible, since the condition is infrequent among the poorest classes, among whom kwashiorkor is endemic.

The similarity of histologic changes in the liver to those in the chronic phase of viral hepatitis and the frequency of jaundice at some stage of Indian childhood cirrhosis have given rise to speculation whether some cases of the latter might represent viral hepatitis. Unlike the situation in Jamaica, where a toxic alkaloid in the bush tea consumed by children is believed to be responsible for the hepatic changes, no poison has been found in the diets of Indian children. It is possible that there may be different etiologic factors in the Indian cases. The common occurrence of several cases in the same family has suggested the possibility of a genetic factor or more likely of an environmental factor.

**Pathology.** Study of liver biopsy specimens obtained by the Vim Silverman needle has shown that the most constant change in the early stage is varying damage of the liver cells, either patchy or widespread. Fatty vacuolation of the liver cells is absent at all stages. Cellular infiltrates are often present. In the stage of cirrhosis there is postnecrotic scarring with regenerating nodules. Pseudolobulation is commonly present, though some cases show a basket-like network of fibrous tissue

with groups of liver cells with advanced degenerative changes. Occlusion of hepatic vein radicles, a common feature in the Jamaican cases, is apparently an uncommon feature in the Indian ones.

**Clinical Manifestations.** In the majority of instances the onset is insidious with vague symptoms of poor appetite and slight abdominal distention. The child lacks pep and is often peevish, and growth is retarded. Intermittent phosphaturia has been reported. Occasionally the onset is acute, comparable to that of viral hepatitis. Enlargement of the liver is invariably present from the beginning. The degree of hepatic enlargement varies; usually the liver extends to the umbilicus within a few months, contracting to some extent in the late stages, when it becomes increasingly firm. The surface of the liver may also feel granular, or rarely nodular. Jaundice is common in the late stages, and also often occurs for a short period in the early phase, or occasionally there is a history of preceding jaundice.

Fever is inconstant, but never high. At times there is a discoverable cause such as an upper respiratory tract infection, but more often there is none, and the fever seems to be due to further hepatic parenchymal destruction. The child deteriorates during such febrile episodes. Portal hypertension with ascites, evidences of collateral circulation and hematemesis may be terminal manifestations. Splenomegaly and hypoproteinemic edema are also common in the late stages. The clinical manifestations can be attributed to hepatic dysfunction (peevishness, poor appetite, pale stools), to portal hypertension (ascites, tympanites, hematemesis) and to hypersplenism in the late stages (anemia, leukopenia and purpura due to thrombocytopenia).

The course is prolonged from a few months to a year or two; even in the more severe and prolonged cases, recovery may occur and be complete as shown by liver biopsies. In general, however, the outlook is poor when the disease becomes far advanced.

**Diagnosis.** The diagnosis is obvious in the stage of cirrhosis with ascites, but in the earlier stage of vague symptoms the only definite sign is the enlarged firm liver. Other causes of hepatomegaly or hepatosplenomegaly, such as malaria, kala-azar, leukemia and various anemias must be excluded by appropriate laboratory tests. Liver biopsy has been helpful in questionable cases; the possibility of a bleeding tendency should first be

eliminated, and vitamin K should be administered before undertaking biopsy.

**Treatment.** Treatment is mainly symptomatic. Hematemesis may necessitate transfusion, and extensive ascites may require drainage.

S. T. ACHAR

## REFERENCES

- Achar, S. T., and Chacko, R.: Pathological Changes in the Liver in Hepatic Cirrhosis of Childhood Commonly Known as Infantile Biliary Cirrhosis. *Indian J. M. Sc.*, 8:442, 1954.  
 Jelliffe, D. B., Gerrit Bras and Mukherjee, K. L.; Veno-occlusive Disease of the Liver and Indian Childhood Cirrhosis. *Arch. Dis. Childhood*, 32: 369, 1957.  
 Report of Liver Disease Sub-committee, Indian Council of Medical Research. *Indian J. M. Research*, 43:4, 1955.

## NEOPLASMS

See page 1352.

## CYSTS OF THE LIVER

Large, solitary nonparasitic cysts of congenital origin, but unknown derivation, are described. Several of these have been so large as to interfere with delivery of the fetus. Most often hepatic cysts are multiple and small. Such cysts are congenital anomalies, arising from dilatation of partially canalized bile ducts. About 25 per cent of patients with polycystic kidneys have hepatic cysts (p. 1024).

## POISONING

(ACUTE DIFFUSE HEPATIC NECROSIS, ACUTE LIVER ATROPHY, ACUTE YELLOW ATROPHY)

**Etiology.** Acute atrophy of the liver is a rare disease, usually fatal, in which there is an acute diffuse necrosis of the liver. Though the disease is commonly termed acute yellow atrophy, a red atrophy which is a later stage of yellow atrophy is also described. Different toxic agents are recognized as etiologic factors, such as phosphorus, arsenicals, chloroform, bismuth, trinitrotoluene, tetrachlor ethane and mushrooms (*Amanita phalloides*). Syphilis has also been known to cause hepatic necrosis. There is also a relation between infectious hepatitis and yellow atrophy. Selander reported that 3.4 per cent of a series of 1190 cases of infectious hepatitis progressed



to acute yellow atrophy. It is likely that predisposing factors such as malnutrition, concurrent illness and individual hypersensitivity are operative. The incidence is relatively high in tropical and subtropical countries.

**Clinical Manifestations.** The clinical picture is similar to, but more severe than, that of infectious hepatitis. Three stages of the disease are described, but, in some instances, fulminating hepatic necrosis without any prodromes leads to rapid death. The prodromal stage, consisting in constitutional disturbances (fever, headache, asthenia, articular pains) and gastrointestinal symptoms (anorexia, nausea and vomiting), is followed in six to fourteen days by the icteric stage. In one sixth of the reported cases icterus was the initial symptom. The jaundice fluctuates in severity, but is usually extreme. Hemorrhagic phenomena are especially common during the terminal stage, which is characterized by the occurrence of grave nervous symptoms. Increased muscular irritability is followed by increasing drowsiness leading to coma. Convulsions are uncommon.

The breath often has a characteristic odor, "fotor hepaticus." The liver may be enlarged initially, but usually shrinks progressively as the disease advances. The spleen is enlarged in almost all cases. All functions of the liver are depressed to low levels, and tyrosine is found in the urine.

**Treatment.** In most instances acute liver necrosis ends fatally. Owing to loss of most hepatic functions, replacement and supportive therapy is indicated; fluids, electrolytes, glucose and protein (plasma and serum albumin) should be supplied by parenteral means to supplement the oral intake. Potassium-containing foods or 0.5 gm. of potassium chloride (per day) should be given to provide the needs of a high carbohydrate intake. Large doses of vitamin B complex, vitamin K, liver extract and tocopherol should be given intramuscularly, and choline chloride is administered by gastric tube. One of the tetracyclines may be given intravenously. Corticosteroids have had no favorable effect.

## FATTY INFILTRATION

**Pathology.** Fatty infiltration of the liver results from deposition of dietary or mobilized tissue fat in the hepatic cells. Various lipotropic factors prevent the accumulation or accelerate the removal of excessive hepatic fat in the experimental animal. Choline and a large number of its chemical analogues in-

hibit the deposition of neutral fats and cholesterol esters and cause more rapid removal of these lipids from the livers of animals fed excessive fat. Choline also has an influence upon ketosis. Many proteins have a lipotropic action, probably due to specific amino acids. Thus methionine definitely has been shown to be lipotropic.

Fat is deposited in normal liver cells and, in larger amounts, in damaged liver cells in a variety of clinical conditions. Fatty infiltration of the liver occurs in many metabolic disorders such as obesity, starvation, galactosemia, diabetes mellitus and familial hyperlipemia. It is encountered frequently in chronic tuberculosis and osteomyelitis and occasionally after pneumonia. Large fatty livers occur in poisoning with phosphorus, phlorhizin, chloroform, alcohol, arsenic and mushrooms, and in severe anemic states in which it is assumed the liver is damaged by anoxia.

A familial occurrence of fatty liver was described by Bjorun. One of his patients showed beginning cirrhosis.

Fatty infiltration of the liver is a common secondary condition in childhood. Wollstein encountered it in more than half of a series of 345 consecutive autopsies.

**Clinical Manifestations.** Infiltration of the liver by fat is usually not directly responsible for symptoms or abnormalities in hepatic function. When hypoglycemia and ketosis are present, the hepatomegaly may be confused with glycogen disease. The usual clinical finding is hepatic enlargement, which may be extreme in some instances.

**Differential Diagnosis.** Fatty infiltration of the liver should not be confused with *fatty degeneration* of hepatic cells, in which pre-existent invisible cell lipids are altered chemically and become visible as fat droplets. In fatty infiltration the normal lipid content of the liver (3 to 5 per cent) may increase to 40 per cent. In fatty degeneration there is a change in the cellular lipids with an alteration in the normal proportion between hepatic cholesterol and other hepatic lipids, but no absolute increase of liver fat. Occasionally, with hyperlipemia, the Kupffer cells of the liver will phagocytize fat droplets and become swollen.

**Treatment.** Reduction of fat intake with a liberal allowance of protein would seem to be indicated. Beneficial effects have been described after administration of choline and its analogues (betaine), but are difficult to evaluate.

## THE GALLBLADDER

**Anatomy.** The gallbladder in the newborn infant is deeply embedded in the liver and usually does not reach the liver edge. The gallbladder is three times as long as it is thick. In the young infant it is tubular; it gradually assumes its pear shape in later infancy. In the adult the gallbladder is 8 to 11 cm. long. The volume is 3.2 ml. in the young infant, 40 ml. in the adult.

**Congenital Anomalies.** Congenital anomalies of the gallbladder, which are rare, include double gallbladder; bilobed gallbladder; diverticulum of the gallbladder; floating gallbladder, which is suspended from the liver by a mesentery and is freely movable; anomalous position of the gallbladder, which may be left-sided, intrahepatic and retrodisplaced; absence of the gallbladder without other anomalies of the biliary system or liver; and absence of the gallbladder with congenital atresia of the extrahepatic ducts.

### CHOLECYSTITIS

Inflammation of the gallbladder, though uncommon, is not as rare as it is generally thought to be. It may be due to a variety of bacterial infections, including typhoid fever. Migration of such intestinal parasites as *Ascaris* and protozoa in the child is ordinarily unaccompanied by inflammation, which is

common in the adult. The *symptoms* are nausea, vomiting, fever, abdominal distention and pain in the right upper quadrant. Since the disease is usually due to bacterial infection in children, sulfonamide and antibiotic therapy should be used before resorting to surgery. With advancing symptoms, however, surgery is advisable. The *diagnosis* is not easily made, since most pain in the right upper quadrant in children is not of gallbladder origin. In many instances a preoperative diagnosis of intestinal obstruction is made.

### CHOLELITHIASIS

Biliary calculi are infrequent in early life, but are more common than infection of the gallbladder. Calculi have been reported in still-born fetuses. Cholelithiasis in childhood is chiefly a complication of congenital hemolytic anemia in white children and sickle cell anemia in Negroes. Though the stones are composed almost entirely of the excessive blood pigment liberated by hemolysis, calcium is deposited in some, so that a shadow may be cast on the roentgenogram. The pure pigment stone without calcium casts no shadow and is demonstrable on the roentgenogram only by the use of gallbladder contrast medium.

## THE BILE DUCTS

### CYSTIC DILATATION

**Etiology and Pathology.** Choledochus cyst, or cystic dilatation of the common bile duct, is an idiopathic congenital condition. In 80 per cent of the recorded cases the patients are females less than ten years of age. Often there is no demonstrable mechanical obstruction. The dilatation is usually localized to the common duct, in contradistinction to the dilatation resulting from obstruction which involves the entire biliary tract and gallbladder. Occasionally the dilatation may involve the cystic and hepatic ducts. A choledochus cyst may grow to large dimensions; cysts with a capacity of 2 liters are recorded.

**Clinical Manifestations.** The clinical findings in choledochus cyst are pain, jaundice and abdominal tumor. The liver is often en-

larged and cirrhotic and is frequently infected. Fever occurs at times and is indicative of infection in the biliary tract or liver. The pain is in the upper abdominal or umbilical region and is usually "dragging." Jaundice is usually present. Exacerbations and remissions of symptoms are common.

**Treatment.** This is surgical. The operation of choice is a primary anastomosis between the biliary system and the intestinal tract. The results following operation are good.

### CONGENITAL ATRESIA

**Etiology.** Congenital obliteration of the bile ducts results from a maldevelopment of the biliary ducts. Inflammatory processes have been advanced as a theoretic cause, but careful study has failed to reveal evidence to



support it. In early fetal life the bile ducts are patent, but later become obliterated by epithelial proliferation and form solid cords. As normal development continues, the solid cords become canalized by the formation of vacuoles which coalesce, and the lumens of the ducts are thus re-established. An arrest in development at the solid cord stage would explain the congenital atresia.

**Pathology.** On postmortem examination the tissues are jaundiced, and there is usually ascites from portal obstruction. The firm liver has a nodular surface and may be two or three times its normal size; histologically, the findings are those of biliary stasis and biliary cirrhosis. If death occurs early, biliary stasis predominates; if late, cirrhosis is more prominent. The gallbladder may be absent or be represented as a canalized cord containing clear, thick mucoid material. At times it may be distended with "white bile," which is an accumulation of the secretion of its own mucosal glands. In obstruction of the common duct the gallbladder may be of normal appearance and contain bile, or it may be greatly distended with bile if the obstruction is low. The spleen is enlarged because of portal obstruction secondary to biliary cirrhosis. In cases of long duration the bones may show osteoporosis, a result of the poor absorption of calcium which is excreted.

The various anatomic malformations in this condition have been classified into the following groups by Ladd: (1) absence of the extrahepatic ducts; (2) atresia of the hepatic ducts; (3) atresia of the common duct; (4) a gallbladder represented by a moderate-sized cyst which is not connected with the common duct and in which there may or may not be any common or hepatic ducts; (5) a gallbladder which connects directly with the duodenum, but in which there are no ducts connecting the liver and gallbladder or the liver and intestine; (6) stenosis of the common duct due to plugging with inspissated bile, causing complete obstruction; (7) narrowing of the common duct, causing partial obstruction. In some instances there is absence of the intrahepatic ducts.

**Clinical Manifestations.** Jaundice is the outstanding manifestation. In most instances it is not discerned until two or three weeks after birth, though it may be apparent earlier. After its appearance the jaundice increases progressively without remission, and the infant assumes a deepening greenish bronze color. The olive-green component of the pigmentation results from deposition of biliver-

din, the oxidation product of bilirubin, in the tissues. The van den Bergh reaction is direct. The urine is intensely bile-stained and contains bile salts; since bile is excluded from the intestine, urobilinogen is not formed and is accordingly absent from the urine. The tears and saliva may be pigmented.

At times so-called liver breath, an odor resembling that of decaying liver tissue, is noted. The stools are abnormal before jaundice is conspicuous. Though the early meconium may appear normal, the stools are always putty-like in consistency and white or clay-colored, owing to their high content of fat and absence of pigment. In intensely jaundiced, and usually older, infants the stools may contain a low concentration of bile pigment derived from the secretions and desquamation of the bile-stained intestinal mucosa, so that a faint yellowish tinge is added to the predominant grayish color. There is, however, never the intermittent deeper staining with bile which is seen in the stools of many infants with biliary obstruction resulting from choledochus cyst, inspissation of bile or neonatal hepatitis. The liver is enlarged, and its firm, smooth edge may extend below the umbilicus. The spleen may be moderately enlarged. Ascites is frequently present.

The nutritional status of these infants, except for a reduced amount of subcutaneous fat, may remain surprisingly good for months, but slowness of movement and a lack of alertness are apparent in many of them. The appetite is good. Constipation is more frequent than diarrhea or vomiting. Deficiencies of the fat-soluble vitamins A, D, and K eventually develop. Protein metabolism is not disturbed. Carbohydrate absorption is normal, but the gradually developing cirrhosis of the liver interferes with hepatic glycogen storage and liberation, so that hypoglycemia may occur in older infants.

If obstruction cannot be relieved surgically, the prognosis is poor. Death was formerly due mainly to infection or hemorrhage. With the availability of antibiotics and vitamin K longer survival is being observed; one patient is known to have lived nine and one-half years.

**Diagnosis.** Congenital malformation of the bile ducts must be differentiated from numerous other causes of jaundice in early infancy. Elimination of conditions responsible for icterus during the first week of life, including physiologic jaundice, erythroblastosis due to RH, ABO and other rarer incompatibilities, and a group of less common disorders such

as sepsis, congenital syphilis, galactosemia and familial nonhemolytic jaundice with kernicterus, presents few difficulties. In these situations the jaundice is of the hemolytic type, characterized by elevation of indirect bilirubin. In atresia of the bile ducts the regurgitated bilirubin gives a direct reaction and is usually first evident as clinical jaundice after the first week of life. The acholic stools of biliary atresia are an additional differential point.

In addition to biliary atresia, clinical jaundice may appear in neonates in association with such conditions as neonatal hepatitis (type B), obstruction by inspissated bile in erythroblastosis fetalis or from unknown causes, rarely with prolonged physiologic jaundice, congenital and acquired hemolytic jaundice, syphilis and pressure occlusion of the biliary ducts by tumors and the like. Toxoplasmosis, infection with herpesvirus and galactosemia may produce jaundice in the early days of life.

Surgical exploration for atresia of the bile ducts is indicated when (1) bile is absent from the stools and duodenal secretions; (2) urobilinogen is absent from the urine; (3) the amount of direct-reacting bilirubin has increased progressively to high levels from an initial range of 5 to 10 mg. per 100 ml.; (4) the cephalin-cholesterol flocculation and thymol turbidity tests are negative; (5) there is no evidence of erythroblastosis fetalis.

Contrariwise, biliary atresia is unlikely and surgery may be deferred when (1) incomplete biliary obstruction is suggested by the finding of bile even in small amounts in the stools or duodenal contents and the urinary excretion of urobilinogen is normal; (2) erythroblastosis fetalis is indicated by an initial bilirubin level of 10 to 30 mg. per 100 ml. and by the finding of blood group incompatibilities; or (3) obstruction by inspissated bile of unknown etiology (type B viral hepatitis?) is suggested when serial determinations show a fluctuating bilirubin content instead of a progressively increasing one.

**Treatment.** Biopsy of the liver, either by laparotomy or by needle aspiration, is frequently required to differentiate biliary atresia from neonatal hepatitis or the inspissated bile syndrome. Needle biopsy requires familiarization with the technique, but is less traumatic than laparotomy. If laparotomy is performed, cholangiography with radiopaque solutions should take the place of manual exploration of the ducts, since the latter carries a high mortality rate in infants with hepatic

disorders. The various surgical procedures for establishing a pathway for bile into the intestinal tract are described by Gross. Not more than 16 per cent of infants with atresias are amenable to surgical repair.

Biliary obstruction resulting from inspissated bile has been relieved by duodenal intubation of 25 per cent magnesium sulfate and by the use of other cholagogues. The prognosis in infants with erythroblastosis is excellent; all of one group of twenty-three patients recovered completely. More than half of another group of thirty infants with obstruction due to inspissation of bile of unknown etiology recovered completely.

MILTON RAPOPORT

## REFERENCES

### General

- Series of Reviews on Physiological, Biochemical and Clinical Aspects of Liver Disease. Brit. M. Bull., 13:75, 1957.
- Gross, R. E.: *Surgery of Infancy and Childhood*. Philadelphia, W. B. Saunders Company, 1953.
- Popper, H.: *Liver: Structure and Function*. New York, Blakiston Division, McGraw Hill Book Company, Inc., 1957.
- Sherlock, S.: *Diseases of the Liver and Biliary System*. Springfield, Ill., Charles C Thomas, 1958.

### Physiology and Anatomy

- Aldrich, R. A., Labbe, R. F., and Talman, E. L.: A Review of Porphyrin Metabolism, with Special Reference to Childhood. Am. J. Med. Sc., 230: 675, 1955.
- Bondy, P. K.: Some Metabolic Abnormalities in Liver Disease. Am. J. Med., 24:428, 1958.
- McDermott, W. V.: Mechanism and Toxicity of Ammonia. New England J. Med., 257:1076, 1957.
- McNicholl, B.: Palpability of the Liver and Spleen in Infants and Children. Arch. Dis. Childhood, 32:438, 1957.
- Najjar, V. A.: The Metabolism of Carbohydrates, Fats and Bile Pigments by the Liver and the Alterations in Hepatic Disease: A Review of Recent Advances. Pediatrics, 15:444, 1955.

### Tests of Liver Function

- Bridge, E. M., and Mulholland, W. M.: Intermediate Carbohydrate Metabolism; in Brenemann's Practice of Pediatrics. Hagerstown, Md., W. F. Prior Company, 1957, Vol. 3, Chap. 24.
- Bruton, O. C., Metzger, J. F., and Sprinz, H.: Experience with Needle Biopsy of the Liver in Infants and Children. Pediatrics, 16:836, 1955.
- Harris, R. C.: Liver Function Tests in Infancy. Bull. New York Acad. Med., 28:721, 1952.
- Kove, S., Goldstein, S., and Wroblewski, F.: Measurement of Activity of Transaminases in the Serum as an Aid in Differential Diagnosis of Jaundice in the Neonatal Period. Pediatrics, 20: 590, 1957.



Stowars, D., and Chun, R. W.: Needle Biopsy of the Liver in Pediatrics. *Modern Med.*, page 109, Jan. 15, 1958.

#### *Chronic Congestion of the Liver*

Katzin, H. M., Waller, J. V., and Blumgart, H. L.: "Cardiac Cirrhosis" of the Liver; Clinical and Pathologic Study. *Arch. Int. Med.*, 64:457, 1939.

#### *Jaundice*

Billing, B. H., and Lathe, G. H.: Bilirubin Metabolism in Jaundice. *Am. J. Med.*, 24:111, 1958.

With, T. K.: The Pathogenesis and Different Forms of Jaundice. *Acta. med. Scandinav.*, 128:25, 1947; also in *Liver Disease*, Ciba Foundation Symposium, Philadelphia, Blakiston, 1951.

#### *Disorders in Which Jaundice Is Primary Disturbance*

Arias, I. M., and London, I. M.: Bilirubin Glucuronide Formation in Vitro; Demonstration of a Defect in Gilbert's Disease. *Science*, 126:563, 1957.

Axelrod, J., Schmid, R., and Hammaker, L.: A Biochemical Lesion in Congenital Non-obstructive, Non-hemolytic Jaundice. *Nature*, 180:1426, 1957.

Baroody, W. G., and Shugart, R. T.: Familial Non-hemolytic Jaundice. *Am. J. Med.*, 20:314, 1956.

Crigler, J. F., and Najjar, V. A.: Congenital Familial Non-hemolytic Jaundice with Kernicterus. *Pediatrics*, 10:169, 1952.

Dubin, I. N.: Chronic Idiopathic Jaundice. *Am. J. Med.*, 24:268, 1958.

#### *Hepatitis*

Echenwald, H. F.: Viral Hepatitis: Clinical Laboratory and Public Health Aspects. U. S. Public Health Service Publication 435, 1955.

Hartman, F. W., LoGrippo, G. A., Matteer, J. G., and Barron, J., editors: *Hepatitis Frontiers*. Sixth Henry Ford Hospital International Symposium. Oct. 25-7, 1956. Boston, Little Brown and Company, 1957.

Ward, R., Krugman, S., Giles, J. P., Jacobs, A. M., and Bodansky, O.: Infectious Hepatitis: Studies of Its Natural History and Prevention. *New England J. Med.*, 258:407, 1958.

#### *Liver Abscess*

Anspach, W. E.: Subphrenic Abscess in Children, with Special Reference to Roentgen Signs to Transphrenic Infection. *J. Pediat.*, 13:157, 1938.

Kutsunai, T.: Abscess of the Liver of Umbilical Origin in Infants; Report of Two Cases. *Am. J. Dis. Child.*, 51:3185, 1936.

#### *Cirrhosis of the Liver*

Bearn, A. G., Kunkel, H. G., and Slater, R. J.: The Problem of Chronic Liver Disease in Young Women. *Am. J. Med.*, 21:3, 1956.

Klatskin, G.: Subacute Hepatic Necrosis and Post-necrotic Cirrhosis Due to Anicteric Hepatitis. *Am. J. Med.*, 25:333, 1958.

Linton, R. R.: The Surgery of Portal Cirrhosis of the Liver. *Am. J. Med.*, 24:941, 1958.

Popper, H.: Pathologic Aspects of Cirrhosis. *Am. J. Med.*, 24:593, 1958.

Ruggieri, B. A., Baggenstoss, A. H., and Logan, G. B.: Juvenile Cirrhosis: A Clinico-pathologic Study of 27 Cases. *A.M.A. Am. J. Dis. Child.*, 94:64, 1957.

Watson, C.: Current Status of Treatment of Cirrhosis of the Liver. *J.A.M.A.*, 166:764, 1958.

#### *Acute Liver Atrophy*

Prigosen, R. E., and Gordon, M. B.: Acute Yellow Atrophy of the Liver: Report of Case in Twelve-Year-Old Girl with Autopsy Findings. *J. Pediat.*, 20:208, 1942.

Snaveley, J. R.: Fatal Hepatitis. *Am. J. M. Sc.*, 219:89, 1950.

#### *Fatty Infiltration of the Liver*

Bjorum, A.: The Occurrence of Fatty Livers in Families. *Acta. paediat.*, 6:225, 1926.

#### *The Gallbladder*

Flannery, M. G., and Coster, M. D.: Congenital Abnormalities of Gallbladder: 101 Cases. *Surg., Gynec. & Obst. (Internat. Abst. Surg.)*, 103:439, 1956.

Glenn, F., and Hill, M. R., Jr.: Primary Gallbladder Disease in Children. *Ann. Surg.*, 134:302, 1954.

Walker, C. H. M.: Etiology of Cholelithiasis in Childhood. *Arch. Dis. Childhood*, 32:293, 1957.

#### *The Bile Ducts*

Ahrens, E. H., Jr., Harris, R. C., and McMahon, H. E.: Atresia of the Intrahepatic Ducts. *Pediatrics*, 8:628, 1951.

Horne, L. M.: Congenital Choledochal Cysts. *J. Pediat.*, 50:30, 1957.

Krahulik, L., Shoob, M. P., Morales, S., Snyderman, S. E., and Holt, L. E., Jr.: Congenital Obliteration of the Bile Ducts, with Particular Reference to Dictotherapy. *J. Pediat.*, 41:774, 1952.

Myers, R. L., Baggenstoss, A. H., Logan, G. B., and Hallenbeck, G. A.: Congenital Atresia of the Extrahepatic Biliary Tract. *Pediatrics*, 18:767, 1956.

## THE PANCREAS

**Anatomy.** The pancreas originates from three separate outgrowths from the duodenum. The three segments fuse as the embryo develops, but anatomically the head, body and tail can be distinguished in the pancreas of the newborn infant, the head being pro-

portionately larger than in the adult. In the embryo the duct of Santorini runs from the separate posterior segment to the duodenum, and the duct of Wirsung drains the two anterior segments. As the three segments fuse, the two ducts become jointed at an acute

angle in the body of the pancreas, but maintain their separate openings into the duodenum; Wirsung's duct opens into the ampulla of Vater with the common bile duct, and Santorini's duct opens into the duodenum, somewhat closer to the pylorus.

The pancreas of the newborn infant is 4 to 5 cm. long and about 12 mm. thick, and weighs 2 to 3.5 gm. At one year of age it weighs about 10 gm., about 20 gm. at four to five years and 30 gm. at ten to twelve years. In the young adult it varies in weight from 66 to 102 gm.

In the newborn infant the islets of Langerhans are relatively more numerous in relation to the acinar tissue than in the adult. New islets appear until the child is about four years of age, when the acinar tissue begins to proliferate rapidly.

**Anomalies of the Pancreas.** Anomalies of the pancreas are rarely the cause of clinical disturbances. Absence of the pancreas has been noted in severe monster formation. Occasionally the tail of the gland has been bifid or the organ has existed as two separate glands with separate ducts to the duodenum. The pancreas may partially or completely surround the descending duodenum (annular pancreas) and cause acute or recurrent intestinal obstructions. Roentgenologic examination reveals dilatation of the first portion and collapse of the third portion of the obstructed duodenum. Accessory pancreatic tissues (pancreatic heterotopia) complete with their own small ducts have been discovered in the stomach, duodenum, jejunum and ileum. Ectopic pancreatic tissue, in rare instances, has served as the lead point of an intussusception. Pathologic changes in aberrant pancreatic tissue include inflammation with erosion of the intestinal mucosa leading to ulceration and hemorrhage, fat necrosis and single or multiple islet cell tumors causing hyperinsulinism.

Deviations of the pancreatic ducts of Wirsung and Santorini from their usual anatomic arrangements are of little clinical significance. Congenital stenosis of the pancreatic ducts has been described as a cause of meconium ileus.

Congenital hypoplasia of the exocrine part of the pancreas associated with steatorrhea and undernutrition has been recorded. Absence of fibrosis, of dilatation of the ducts and of characteristic pulmonary changes differentiates this congenital defect from fibrocystic disease of the pancreas.

**Physiology of the External Secretory Glands of the Pancreas.** The secretion of pancreatic juice is regulated by both nervous and hormonal influences. Parasympathetic nervous (vagus) stimulation produces a small flow of juice of high protein and high enzyme content. This so-called cephalic phase of pancreatic secretion is probably a reflex from the oral cavity through the vagus nerve resulting in "psychic" secretion. It is abolished by atropine. Various drugs which stimulate the vagus mechanism—pilocarpine, acetylcholine, acetyl-beta-methylcholine chloride (Mecholyl chloride), physostigmine and neostigmine—produce an increased concentration of enzymes without much increase in volume of the pancreatic juice. Stimulation of the splanchnic nerve (sympathetic) causes increases in the amounts of pancreatic juice and of trypsin secreted per unit of time. Various phenomena inhibit pancreatic secretion reflexly, e.g., overdistention of the stomach, vomiting, and emotional reactions such as rage and mental discomfort. Vasoconstriction of the pancreatic blood vessels decreases or abolishes pancreatic secretion.

Secretin, a hormone liberated by the mucosal cells of the upper intestinal tract, is transported by the blood to the pancreas, where it incites the flow of a thin watery juice of high bicarbonate and low enzyme concentration. Contact of the intestinal mucosa with a variety of substances (hydrochloric acid, proteins, fats, carbohydrates and digested foodstuffs such as peptones and amino and organic acids) leads to secretion of secretin. The products of fat digestion increase pancreatic secretion by stimulation of the vagal endings in the duodenum. The generalization is made that the vagus regulates the enzyme content of pancreatic juice, and secretion regulates the volume and sodium bicarbonate content. Fractionation of the crude extract of duodenal mucosa from which secretin is prepared yields pancreozymin, along with several other hormones, which stimulates pancreatic excretion of viscid juice with high enzyme and low bicarbonate content. However, there is no evidence that it is secreted into the blood by living intestinal mucosa.

Pancreatic juice, a clear or slightly opalescent alkaline (average pH, 8.3) fluid, contains mucus, mucoproteins and three enzymes, usually designated amylase, lipase and trypsin. Actually there are two amylases, alpha and beta; one lipase, and four prote-



olytic enzymes. Starches are split to maltose by the amylases. An intestinal enzyme, maltase, completes the hydrolysis of maltose to glucose. Secreted in an inert form, pancreatic lipase is activated by bile salts and other substances, including bacteria, and converts neutral fat into fatty acid and glycerol.

The proteolytic enzymes are secreted as inactive substances combined with specific enzyme inhibitors. Trypsin by its enzymatic action and the intestinal hormone enterokinase, by antagonizing the inhibitors, activate the proteolytic enzymes. Trypsin and chymotrypsin, each acting separately, digest proteins to peptides, which are split to amino acids by pancreatic and intestinal carboxypeptidases (erepsins).

Secretin and the pancreatic enzymes, trypsin, lipase and amylase, are present in the newborn infant and are probably present in the fetus as early as the fifth month, the proteolytic activity being responsible for the liquid state of the meconium in the intestinal tract of fetuses.

TESTS OF PANCREATIC FUNCTION

Studies of Pancreatic Enzymes Obtained by Duodenal Intubation. The fluid obtained from the duodenum is normally clear and watery, and may be colorless or varying shades of yellow, depending on its bile content. It is usually alkaline with a pH of about 8.3, but may vary from pH 6.5 to 9. The amount of fluid varies from time to time in the same person, but there is usually an increase with age. Infants under two months of age yield 1 to 5 cc. per hour, averaging 3 cc.; infants one year of age about 6 cc.; older children, as much as 48 cc. In children with chronic nutritional disturbances or idiopathic celiac disease there is no change in the appearance of the fluid, although larger volumes are at times obtained from children with celiac disease. The fluid obtained from patients with pan-

creatic fibrosis is diminished in volume and is thick and sticky. The mucoprotein fraction of normal duodenal fluid is completely soluble in water, whereas in patients with cystic fibrosis a considerable portion of it is water-insoluble.

The enzyme activities of the duodenal fluids of normal infants and children have been quantitated by Andersen and by Farber and his co-workers. The values in Table 90 are typical findings. The enzyme values were all within the normal range in patients with nutritional disturbances. With hypoproteinemia, as in kwashiorkor, there may be an absence of pancreatic enzymes, presumably due to lack of amino acids for formation of enzymes by the acini. In idiopathic celiac disease and in chronic diarrhea there is a significant depression of amylase concentration in infants older than six months of age, and in marasmic infants there is a depression of the level of all three enzymes. Agren, Lagerlof and Berglund pointed out the frequency with which pancreatic injury results in a reduction in the secretion of amylase alone and suggest that this represents the mildest form of damage in pancreatitis. In patients with pancreatic fibrosis all enzyme activity is commonly absent or, when present, is very low. Andersen has suggested a simple test for trypsin activity as a diagnostic aid for pancreatic fibrosis. This may be an adequate index of total pancreatic enzymatic activity in most instances, but selective deficiency of pancreatic enzymes has been observed in about 10 per cent of cases, and an occasional patient may show normal activities of all three enzymes.

Intravenous administration of secretin results in an increased volume of more alkaline duodenal fluid. Though there is some increase in amylolytic and lipolytic activity in normal persons after stimulation of secretin, there is no increase in tryptic activity. In patients with pancreatic fibrosis the volume of duodenal fluid is not increased after secretin injection, and the activity of trypsin is unchanged; that of lipase and amylase may be slightly decreased at times.

Studies of Pancreatic Enzymes in Stools. In the feces of the normal person, amylase and trypsin, but not lipase, are demonstrable. Though the adult with complete occlusion of the pancreatic ducts shows an absence of fecal amylase, the extreme fluctuations

Table 90. Pancreatic Enzymes in Duodenal Juice of Normal Infants and Children\*

Age	Trypsin		Amylase		Lipase	
	Units per CC.		Units per CC.		Units per CC.	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
0- 2 months.....	137.6	125.6	4.3	3.9	21.2	10.4
2- 6 months.....	138.8	98.1	25.3	23.1	26.6	21.2
6-12 months.....	250.5	211.5	113.9	63.3	34.6	27.6
1- 2 years.....	262.0	268.0	117.4	207.5	18.8	11.1
2- 5 years.....	195.0	106.8	243.9	249.0	19.6	12.8

From D. Andersen: Am. J. Dis. Child., Vol. 63.  
\* Enzyme activities expressed in units per hour rather than per volume of duodenal fluid give a more accurate picture of normal values, since the enzyme content is fairly constant with time, but varies inversely with the rate of flow (dilution) of pancreatic juice. Farber, taking cognizance of this fact, expressed the values in terms of units per hour.

in the normal person make fecal quantitation of enzyme activity un dependable.

*The demonstration of trypsin in the stools by its ability to digest the gelatinous coating of photographic film is a simple and crude screening test for patients with cystic fibrosis of the pancreas.* Its value as a diagnostic test is not great, because proteolytic activity may be present in stools of bacterial origin (gelatinase) or due to ingestion of honeydew melon, pineapple or pancreatin. Also normal amounts of trypsin may disappear completely during passage through the intestinal tract. The accuracy of this test may be improved by special dilution techniques or by adding soybean trypsin inhibitor, which abolishes pancreatic trypsin activity, but does not affect bacterial gelatinases.

**Studies of Pancreatic Enzymes in the Blood and Urine.** Normally, slight lipase and amylase activity is present in blood serum. In experimental and clinically acute inflammatory disease of the pancreas and in acute obstructions of the pancreatic ducts in adults there is regurgitation of pancreatic juice into the blood stream from ruptured small pancreatic canaliculi with resultant elevation of serum lipase and amylase. Elevated values are encountered a few hours after the onset of pancreatic inflammation; they reach a maximum in forty-eight to seventy-two hours and return to normal in ten to fourteen days. Salivary ptyalin may regurgitate into the blood and add to its amylolytic activity, e.g., in mumps.

The urinary amylase, derived from the blood, rises after pancreatic inflammation and reaches a peak in thirty-six to forty-eight hours, subsiding to normal in three to four days. Urinary amylase is increased in children with acute pancreatitis.

**Studies of Absorption of Fat from the Intestinal Tract.** The study of the changes in the blood fat levels after oral administration of fat (fat tolerance tests) is useful in demonstrating poor absorption of fat. A low fat tolerance curve is encountered in pancreatic achylia, but is more frequently the result of a variety of nonpancreatic conditions that cause poor intestinal fat digestion or absorption.

**Fat tolerance test.** After the oral administration of 2 gm. of fat per kilogram of body weight the normal child shows a rise in total blood fat of 200 mg. per 100 ml.; the elevation in the blood of the celiac patient does not exceed 50 mg.

**Vitamin A tolerance test.** After an oral dose of 7000 international units of Vitamin A (as halibut liver oil) per kilogram of body weight, normal children show a rise of 100 units per 100 ml. of blood in two to six hours. Children with celiac disease, though they have normal fasting vitamin A blood concentrations, exhibit only small increases of 8.2 to 26.5 international units in the tolerance test. Such children show impaired absorption if vitamin A is administered in either the ester or alcohol form; patients with cystic fibrosis of the pancreas can absorb the alcoholic form of vitamin A, but not the esterified compound.

**Fat absorption tests using iodized oil (Lipiodol).** Qualitative tests for iodine in varying dilutions of urine collected twelve to eighteen hours after oral ingestion of Lipiodol (5 to 10 cc., depending upon weight) are useful screening procedures for fibrocystic disease. A positive test for iodine in urine diluted 1 to 4 or greater probably excludes this dis-

order as a diagnosis. No inferences may be drawn from a negative test.

Quantitative iodine estimations on urine specimens taken at six, twelve and eighteen hours after ingestion of Lipiodol show differentiations between normal and abnormal values. The values for iodine in normal urine range from 140 to 340 mg. per 100 ml.; in celiac disease they do not exceed 120 mg., and in fibrocystic disease are below 40 mg. per 100 ml.

**Absorption of Protein Products from the Intestinal Tract.** The extent of protein digestion and absorption is indicated by the rise in blood amino acid concentration after a protein test meal. One such test measures the blood proline level two hours after feeding casein or gelatin (1.5 gm. per kilogram). The level in normal infants rises from the basal range of 5 to 35 micrograms per 100 ml. to values ranging from 100 to 120 micrograms. Patients with cystic fibrosis show no increase.

**Analysis of Stools for Undigested and Unabsorbed Food.** The appearance of excessive amounts of fat, carbohydrate (starch) or protein in the stool may be indicative of poor digestion resulting from pancreatic insufficiency or other causes, or from poor absorption from the intestinal tract. Estimations of fecal starch and fat content are commonly used in the study of children with the celiac syndrome.

**Estimation of fecal starch.** Undigested vegetable cells containing starch are present in normal stools. Recent studies indicate that an increased amount of extracellular starch, formerly considered an abnormal finding indicative of starch intolerance or malabsorption, is common to all diarrheal states, and is an occasional finding in normal children.

**Estimation of fecal fat.** Steatorrhea cannot be determined by inspection of the stool, since a fatty stool may appear normal, and at times a typically foul, frothy stool suspected of containing excessive fat may have a normal fat content.

Microscopic examination of stool specimens stained with scharlach R or Sudan IV is useful as a screening method. If, while the patient is on a normal diet, no fat is visible, the presence of steatorrhea can be ruled out. Conversely, the detection of large amounts of fat is significant.

Quantitative estimation of the average daily fecal fat excretion is an objective index of the presence or absence of steatorrhea. In normal infants this value does not exceed 3 gm. a day. The percentage of ingested fat which is absorbed is an even better criterion for steatorrhea.

Owing to the many factors responsible for the presence of an excess of fat in the stools, the following classification may be helpful in the evaluation of this finding.

## CAUSES OF STEATORRHEA

### Poor Digestion of Fat

1. Exclusion of bile from the intestine in obstructive jaundice caused by  
Congenital obliteration of bile ducts  
Choledochal cysts  
Viral hepatitis, and the like
2. Exclusion of pancreatic juice from the intestine caused by



- Cystic fibrosis of the pancreas
- Obstruction of ducts by *Ascaris*
- Starvation and protein-deficient diets in infants; atrophy of acini with decreased secretion of enzymes (e.g., kwashiorkor)
- Congenital hypoplasia of exocrine pancreatic glands
- Congenital cystosis of the pancreas

#### Poor Absorption of Fat

1. Excessive formation of insoluble soaps caused by Excessive intake of alkaline earths, such as calcium and magnesium
2. Excessive intake of fat containing long-chain saturated fatty acids, e.g., tripalmitin and tristearin (short-chain unsaturated fatty acids favor absorption)
3. Diseases and defects in intestinal wall caused by Resections and fistulas of intestine  
Regional enteritis  
Amyloid disease  
Scleroderma
4. Obstruction of intestinal lymphatics caused by Tuberculosis

- Hodgkin's disease
- Intestinal lipodystrophy (Whipple's disease)
- Lymphosarcoma and lymphadenoma

5. Disturbances of salt and water metabolism (e.g., dehydration and adrenal insufficiency impair the absorption of neutral fat, which is normally absorbed when the particle size is smaller than 0.5 micron in diameter)
6. Defective absorption of obscure mechanism caused by  
Celiac disease  
Sprue  
Infestation with *Giardia intestinalis*

#### Combination of Poor Digestion and Poor Absorption of Fat

1. Increased motility of small intestine in Diarrhea of any kind  
Intestinal allergy (when edema of intestinal wall may be an additional factor)  
Stenotic lesions of small intestine  
Gastrocolic fistula  
Malrotation of intestinal tract

## CELIAC DISTURBANCES\*

In a classic paper entitled "On the Coeliac Affection," Samuel Gee in 1888 vividly described the clinical picture of a state of chronic nutritional failure in infancy and childhood. The fully developed case is characterized by (1) pale, bulky, offensive stools; (2) abdominal distention; (3) wasting, which may be extreme; (4) stunting of growth, which may be severe enough to be termed infantilism; (5) severe anorexia and other nervous symptoms; and (6) clinical evidence of vitamin and mineral deficiencies.

Since this pattern of clinical findings may result from a variety of disturbances, it is termed the celiac syndrome. The more or less clearly defined entities belonging to this group are (1) true or idiopathic celiac disease, also called the malabsorption syndrome, a chronic disorder of intestinal assimilation of unknown nature, apparently hereditary in origin, which expresses itself in various patterns of nutritional disturbance and failure; (2) celiac syndrome resulting from mechanical obstruction of the pathways of digestion and/or absorption; (3) pancreatic insuffi-

ciency (cystic fibrosis of the pancreas); (4) severe dietary deficiency (starvation, kwashiorkor); (5) gastrointestinal allergy; (6) chronic intestinal infection (bacterial, parasitic, viral).

### TRUE OR IDIOPATHIC CELIAC DISEASE

(MALABSORPTION SYNDROME, CHRONIC IDIOPATHIC STEATORRHEA, GEE-HERTER DISEASE, HEUBNER-HERTER DISEASE, GEE-THAYSEN DISEASE, CHRONIC INTESTINAL INDIGESTION)

Idiopathic celiac disease is a chronic disorder of infants and children in which intestinal malabsorption, as evidenced by steatorrhea with varying degrees of losses of other nutrients, is prominent. The basic defect is obscure; a familial incidence suggests an underlying constitutional peculiarity, possibly of genetic origin. The proteins (glutens) of wheat, rye and oats are especially conspicuous as triggering agents, causing a gradual or acute increase in the manifestations of celiac disease in most patients. The deleterious action of wheat gluten is apparently a toxic one, rather than an allergic reaction, and is produced by its gliadin fraction. Ingestion of wheat or purified gliadin results in increased concentrations of blood glutamine in celiac patients, but not in normal controls. This phenomenon

\* Though evidence of pancreatic involvement in the various forms of the celiac syndrome is lacking except in the cases of cystic fibrosis of the pancreas and of congenital obstruction of the ducts of Wirsung and Santorini, the other clinical forms are included here in order to avoid unnecessary repetition in the general description of the symptom complex if they were located in other sections of the book.

has been made the basis of a gliadin tolerance test.\*

In one patient reported by Davison, beta lactoglobulin, one of the two whey proteins of milk, evoked steatorrhea, while ingestion of wheat gluten produced no harmful effect. In another child celiac disease was apparently associated with absence of bile salts, and in another case milk fat produced the malabsorption syndrome.

Parenteral infection, often of trivial degree, is a harmful stimulus in most children with celiac disease, and, in many, emotional and psychic disturbances lead to exacerbations of the disorder.

Andersen has designated as starch intolerance a mild disorder which she believes is a less severe form of celiac disease, characterized clinically by chronic and recurrent diarrhea and abdominal distention, with little evidence of malabsorption or malnutrition. However, other clinicians with experience in idiopathic celiac disease consider it to be a constitutional type of chronic nonspecific diarrhea associated primarily with water loss in the stools.

**Incidence.** There are no adequate data of the incidence, but inclusion of the milder forms of the disease in the clinical entity has made the disorder less rare than when only the severe forms were recognized. The disease has been seen in white children of almost all national origins; it is uncommon in the Negro race and unrecorded in Orientals. Both sexes are equally affected.

The occurrence of the disease in twins, fraternal and identical, and the numerous instances of multiple cases in one family speak for the inheritance of an unknown constitutional defect responsible for the disorder, apparently as a dominant character. Variable penetrance and expressivity of this genetic trait may account for the differing degrees of severity of the disease and the age at which it becomes manifest. It is also possible that the disease is inherited as a subclinical or very mild trait and is modified by extrinsic factors such as infection, dietary deficiency or psychic trauma, acting as trigger mechanisms, so that it becomes clinically evident at different ages, but usually within the first few years of life, and in varying degrees of clinical severity. The similarity between idiopathic celiac disease and sprue which occurs

in adults was first indicated by Gee. It would appear that the celiac state in the ages from five to twenty-five years may exist in a state of clinical remission. It may remain so or become reactivated to appear as sprue. The occurrence of sprue and celiac disease in different members of the same family is another way in which the relationship of the two conditions is expressed.

**Pathology.** The anatomic changes found in the rare postmortem examinations of patients with celiac disease are those resulting from (a) severe malnutrition, e.g., a small fatty liver, depletion of glycogen, atrophy of the body fat and lymphoid tissue; (b) secondary deficiency disease, chiefly rickets, but also scurvy, hypoprothrombinemia and hypoproteinemia.

**Clinical Manifestations.** *Severe form of idiopathic celiac disease (idiopathic steatorrhea).* The full-blown clinical picture of severe idiopathic celiac disease is most frequently seen during the second year of life. Careful inquiry, however, into the histories of such children reveals that the disease may begin insidiously or gradually with digestive disturbances at six to twelve months of age. During the evolutionary period, episodes of diarrhea accompanying and persisting after respiratory tract infection may occur at widely separated intervals. At times there may be alternating periods of constipation and diarrhea. The child may show marked loss of appetite with resultant failure of growth. Changes in behavior and disposition, usually marked by increasing irritability, are prominent. The disease is not seen in infants during breast feeding, and rarely appears within six months after they have been weaned.

**WASTING AND RETARDATION OF GROWTH AND DEVELOPMENT.** There is a decided loss of weight, most marked in the limbs and especially apparent in the buttocks, groins and axillary folds. The wrinkled skin of the flattened buttocks and groins may hang in loose folds. In contrast, the face, even in advanced cases, may be full and plump. Though the complexion is usually anemic or sallow, with dark rings or puffiness under the eyes, there is often a red flush on the cheeks. The sad, fretful expression, the plump face with red cheeks surrounded by sallow skin, and the shining bluish scleras produce an almost characteristic facies in children with celiac disease. There are marked, often daily, fluctuations in weight. Usually after mild respiratory or enteric infections, but at times with

\* Blood glutamine levels determined at one, two, three, four and five hours after ingestion of 350 mg. of gliadin per kilogram of body weight increase 40 per cent or more in patients with celiac disease.



no obvious antecedent, watery diarrhea and vomiting occur with resultant dehydration and acidosis, the so-called *celiac crisis*. This may be so severe as to result in death if not properly treated.

Retardation in growth involves height and weight; in severe cases a child three to four years of age may correspond in size to an infant one year of age. There is often great delay in the appearance of the epiphysial centers of ossification. Dentition is often delayed, and, in the rare instances of celiac disease in older children, puberty is also delayed.

**ABDOMINAL DISTENTION.** The abdominal enlargement is primarily caused by distention of a hypotonic intestinal tract by gas and fluid; relaxation of the abdominal musculature is also a contributory factor. Abnormalities in gastrointestinal motility have been noted in roentgenologic examinations, but are not characteristic.

**NERVOUS AND PSYCHOLOGIC SYMPTOMS.** There are profound changes in the behavior pattern with active celiac disease. Anorexia is a prominent symptom, at times culminating in refusal of all food, but more often expressed as a capricious appetite. The ill humor and moodiness, the bursts of temper and hysterical behavior, alternating with periods of great timidity, make these children a trial to even the most patient and loving parent. Sleep is often restless, with frequent grinding of the teeth, outcries and, not infrequently, night terrors and somnambulism. Vasomotor symptoms, such as excessive sweating and cold extremities, are frequent. With clinical improvement these abnormalities disappear. Owing to the combination of infantilism with a degree of intelligence which more closely parallels the child's age, the child is likely to appear precocious and unusually attractive during recovery.

**SYMPTOMS RESULTING FROM DIETARY DEFICIENCY.** The diarrhea and impairment of intestinal absorption, combined with an unbalanced diet, result in various dietary deficiencies, including those of specific vitamins.

**SYMPTOMS RESULTING FROM POOR ABSORPTION OF FAT.** The character of the stools varies with the severity of the disease and the nature of the diet. The classic celiac stool is a constant finding in the untreated patient of long standing and reappears during exacerbations resulting from an infection or dietary indiscretion. The typical celiac stool is bulky, weighing 100 to 1000 gm. as compared to a stool of normal weight of 40 to 80 gm.

Usually there is also an increased number of stools. The celiac stool is loose; during the periods of watery diarrhea accompanying celiac crises its water content may exceed 95 per cent. The stool is mushy, pale and frothy and, in addition, foul-smelling. At times it contains blood and excessive mucus, usually the result of a complicating enteric infection.

Removal of gluten (gliadin) from the diet usually causes disappearance of the frothiness and a decrease in the size of the stool, but it continues to be bulky and pale. With clinical improvement the stool may be formed and of normal color and at times become so hard as to cause constipation. Even during these periods it may contain excess fat.

On a mixed diet containing at least 20 gm. of fat the dried feces of a normal child contain 1.5 to 3 gm. of fat daily, and values above 4 gm. daily are abnormal. The stool of the patient with severe celiac disease contains more than this amount. The patient with celiac disease, however, absorbs a considerable portion of his ingested fat (from 65 to 80 per cent as compared to 90 to 98 per cent of intake in the normal child). The percentage of fat absorbed by the celiac patient is fairly constant with all levels of fat intake, so that a high intake is accompanied by an absolute increase in the amount of fat absorbed. The excess fecal fat is largely split fat, i.e., free fatty acids and soaps.

In the celiac patient there is no impairment in the digestion of fat, since the bile acids and pancreatic lipase are present in adequate amounts. Poor fat absorption is reflected in the low tolerance curves for olive oil, butter fat, vitamin A and Lipidol. Fasting blood vitamin A levels are usually within normal limits. There is, however, a great reduction and at times absence of the fat-soluble serum carotenoid pigments (the precursors of vitamin A), as is the case in any condition associated with steatorrhea.

**IMPAIRED CARBOHYDRATE ABSORPTION.** This is responsible for low oral glucose tolerance curves; the blood sugar rarely rises more than 40 mg. per 100 ml. in an active case. The intravenous glucose tolerance curves and the epinephrine tolerance tests are within the normal range, indicating that carbohydrates are handled normally after absorption from the intestinal tract. The absorption of d-xylose, estimated from the five hour urinary excretion test, is a more exact measure of carbohydrate absorption since it is not altered by the hepatic, endocrine or renal factors

which influence glucose. It is of value in demonstrating poor carbohydrate absorption in celiac disease.

**PROTEIN DEFICIENCY SYMPTOMS.** Moderate hypoproteinemia is a common finding in well developed celiac disease. Both serum albumin and globulin are usually reduced, but in some instances only the albumin level is depressed, at times to edema-producing levels. There is no impairment of protein digestion in celiac disease. Protein absorption is apparently normal during nondiarrheal periods.

**SYMPTOMS CAUSED BY LOSS OF MINERALS IN THE STOOL.** Loss of large amounts of dietary minerals in the stools has been ascribed to the formation of insoluble soaps. Although the amount of mineral loss varies directly with the severity of the disease, it does not bear a linear relationship to the fecal fat content.

The effects of loss of calcium have been indicated. Anemia results from loss of iron. Sodium and potassium are poorly retained; extensive losses of water and of these minerals during celiac crises may result in dehydration, shock, acidosis and symptoms of hypokalemia.

**Starch intolerance: The mild uncomplicated form of celiac disease (constitutional chronic nonspecific diarrhea).** The relationship of this relatively common mild disorder to the more severe classic form of idiopathic steatorrhea has not been established. The diagnosis is based on the finding of abundant extracellular starch granules in the feces after the feeding of starch or especially during relatively asymptomatic periods of infants and children with recurrent chronic diarrhea, abdominal distention and growth failure. Andersen has proposed that such cases represent a mild uncomplicated form of idiopathic steatorrhea. Steatorrhea and other findings of the more severe form of celiac disease are considered transitory complications, resulting from multiple nutritional deficiencies superimposed on the milder disturbance.

Many clinicians regard this relatively mild disorder not as a variant of the celiac syndrome, but rather as a familial type of chronic diarrhea due to hypermotility of the colon. Infectious episodes, emotional disturbances, food allergies and anatomic defects act as trigger mechanisms to the hyperirritable colon in instituting diarrhea. Davison has demonstrated considerable amounts of extracellular starch granules in the feces of normal children, and starch granules are regularly pres-

ent in diarrheal stools. Thus amyloorrhea would appear to be a manifestation of large bowel irritability rather than of starch intolerance.

**Prognosis.** The high mortality of former years (15 per cent in England before 1938) was in part a reflection of the inclusion of cystic fibrosis in the single category of celiac disease. With better understanding of dietary management and parenteral fluid therapy, and effective control of infection by antibiotics, death from celiac disease is unusual; improvement and clinical recovery are the rule. Recovery is a protracted, intermittent process: disappearance of the signs and symptoms usually occurs six to twenty-four months after beginning therapy, the time being conditioned by the duration of symptoms before treatment. The course is characterized by periods of rapid improvement, and equally rapid exacerbations often preceded by infection, dietary lapse or psychic disturbance and at times without apparent cause. Improvement usually proceeds according to the following pattern: vomiting, diarrhea, anorexia and edema disappear first; then the stools decrease in amount and fat content, assuming a more normal color and consistency. As appetite increases, the child's behavior and sense of well-being improve, and weight gain occurs, followed by resumption of growth in height. Anemia may be stubborn. It is felt that clinical recovery is a state of remission of the disorder; since celiac disease is a constitutional defect, it is doubtful whether actual cure takes place. In support of this viewpoint are the abnormal laboratory findings in "normal" patients, gliadin tolerance curves, decreased fat absorption, and the occasional recurrence of the disorder as sprue during adult life.

**Treatment.** Ignorance of the basic metabolic error precludes an etiologic approach to treatment, which is essentially empirical. The various dietary regimens effective in celiac patients have derived from clinical experience. Unfortunately, at times, this has resulted in undue preoccupation with the effect of treatment on the stools, to the neglect of the patient. Successful management is not as dependent upon strict adherence to a rigid dietary plan as it is upon judicious supervision of the diet by an informed physician guided by the child's growth responses, his altered behavior patterns and the emotional difficulties and anxieties of the parents.

The diet chosen at the beginning of treatment will depend upon the patient's condition. In deteriorated celiac patients or in those



with questionable powers of intestinal assimilation it is well to begin cautiously with skimmed or protein milks sweetened with glucose, sucrose or banana powder. Meats, eggs, cheese, fruits, vegetables and fruit juices are added singly at two- to three-day intervals, and a full but gluten-free diet may be achieved after two to three weeks. If gluten is strictly avoided, most patients will thrive on a diet which is normal in all other respects; in most instances the child should not eat with the parents. A properly constructed celiac diet is based upon the following considerations:

1. *An adequate caloric intake* to provide for both the repair of the deficit and the maintenance of normal growth and to compensate for continued fecal losses of nutrients. About 15 to 25 per cent more than the calculated requirement for expected weight and height may be necessary.

2. *Optimal amounts of protein*, usually ranging from 6 to 8 gm. per kilogram of body weight per day and at times up to 10 gm. Protein may constitute as much as 25 per cent of the total calories and be derived from milk, cheese, meat, fish, poultry and eggs. In the child with edema associated with hypoproteinemia it is wiser to remedy the plasma protein deficit by transfusions of serum albumin, plasma or blood than to rely on the slow regeneration from dietary protein.

3. *Carbohydrate in all its forms*. This is well tolerated and should furnish about half of the daily caloric intake. There is no convincing proof that disaccharides are not as well tolerated as the monosaccharides. The deleterious effects attributed to polysaccharides (starches) have been shown to be due to *gluten*. By excluding gluten-containing grains such as wheat, rye and possibly oats and barley from the diet, starches such as rice, corn, potato, buckwheat and pure wheat starch (prepared by removing gluten from wheat) may be given without ensuing difficulty.

4. *Normal amounts of fat* are tolerated by most celiac patients receiving a gluten-free diet. The percentage of fat absorbed by celiac patients is relatively constant at different levels of intake. As in any other patient with gastroenteritis, dietary fat is restricted in the acutely ill celiac child or following a crisis, and is reintroduced gradually as the ability to assimilate it is regained. Since unsaturated and short-chain fatty acids are absorbed better than other fats, replacement of some of the butter, margarine and animal fat by

vegetable oils (olive, corn, peanut, soybean, cottonseed) may be advantageous.

5. *Supplements of vitamins and minerals* in generous amounts for every celiac patient. From 15,000 to 25,000 units of vitamin A and 2000 to 6000 units of vitamin D are provided daily in water-miscible preparations. Vitamins of the B complex should be included in the polyvitamin preparations in doses two to three times the suggested prophylactic levels. From 75 to 100 mg. of ascorbic acid is an adequate daily allowance. It is well to add 0.5 to 1.0 gm. of iron as ferrous sulfate daily, and, if macrocytic anemia is present, supplementation with folic acid and vitamin B<sub>12</sub> would seem to be indicated. Parenteral administration of liver extract or vitamin B complex, once strongly advocated, may be useful during episodes of severe illness; otherwise it is unnecessary.

To assure rigid exclusion of gluten from the diet it is important to list for the parents the food products which contain wheat or rye in any form whatsoever, including gravies, processed meats, meat loaf, puddings and "breaded foods."

To satisfy the frequent craving for bread or cookies, substitutes made from pure wheat starch or buckwheat flour may be prepared.

Awareness and sympathetic understanding of the many psychologic difficulties associated with this chronic disorder are important for the successful management of the patient and his family. Parental anxieties expressed as feelings of guilt and ambivalence toward the child, overprotection and undue concern with the character of the stools are some of the problems with which the physician will have to cope.

The acute episodes of severe diarrhea, initiated most often by parenteral infections or dietary indiscretion, are termed celiac crises. They are especially common in hypoproteinemic patients and require prompt and vigorous treatment. The general principles of fluid and electrolyte replacement and maintenance therapy are utilized to overcome the dehydration, shock, hypoproteinemia and electrolyte imbalances (acidosis, hyponatremia and hypokalemia). If tetany occurs, calcium should be given until the serum calcium is restored to a normal level. Since infection is most often present, suitable antibiotic therapy should be provided.

Adrenal steroid therapy produces dramatic remissions in celiac disease. It may be extremely useful as emergency treatment during celiac crises, or in the management of severe

cases in which there is hypoproteinemia and edema. It is not a cure, since there is a relapse when the therapy is withdrawn.

#### **CELIAC SYNDROME SECONDARY TO OBSTRUCTION OF DIGESTIVE AND ABSORPTIVE PATHWAYS**

*Chronic, mechanically obstructive processes* involving the small intestine or the intestinal lymphatics may be responsible for impairment of absorption, especially of fat. Large fecal losses of unabsorbed fat and protein with their resultant clinical sequels occur when food is excluded from the small bowel by fistulous connections between the stomach and large intestine. Lesions of this sort are extremely rare. Disturbances of intestinal motility resulting from the presence of stenotic areas in the small intestine, from regional ileitis and from malrotation of the intestines have also led to steatorrhea and other symptoms of the celiac syndrome in infants. Surgical correction of such defects has resulted in disappearance of symptoms.

It has been suggested that heavy infestation of the wall of the small intestine by *Giardia intestinalis* acts as a barrier to absorption of fat. Véghelyi reported the disappearance of steatorrhea when giardiasis was cured by the administration of Atabrine (p. 614).

*Intestinal allergy* may be responsible for steatorrhea in infants. The sensitized small intestine reacts to contact with the offending antigen by an increase in motility and by the development of edema of the mucosa, so that poor intestinal absorption is a sequel. When cow's milk is the allergen, chronic diarrhea persists until the milk is replaced by a soy bean or casein hydrolysate substitute.

Since the largest part (60 per cent or more) of absorbed fat reaches the general circulation by way of the lymphatics, *chronic obstruction of the intestinal lymphatic pathways* leads to steatorrhea. The sprue syndrome in adults and the celiac syndrome in children have been observed as accompaniments of tuberculous mesenteric adenitis.

Among the nontuberculous conditions of the mesenteric nodes leading to steatorrhea, Whipple described a syndrome which he named intestinal lipodystrophy, to which the names "lipophagia granulomatosis" and "mesenteric chyladenectasis" have also been applied. This condition, occurring chiefly in adults, is characterized by inflammatory changes in the mesenteric lymph nodes, which are engorged with fat and contain foamy macrophages laden with glycoprotein.

The etiology of the disorder is obscure, but the occurrence of polyserositis and an increased glycoprotein content of the blood indicates that the lesions in the mesenteric nodes are only part of a generalized disturbance. Infiltration of the mesenteric nodes by Hodgkin's disease, lymphosarcoma and lymphoma is an uncommon cause of intestinal malabsorption. Whether acute mesenteric adenitis causes transient disorders of fat absorption is unknown.

#### **CYSTIC FIBROSIS OF THE PANCREAS (MUCOVISCIDOSIS)**

This is a congenital disease in which the clinical evidences of the celiac syndrome, resulting from pancreatic exocrine insufficiency, are combined with severe pulmonary disease.

Genetic studies indicate that pancreatic fibrosis is inherited as a mendelian recessive character. It has been estimated that one in fifteen to one in fifty in the population carries the gene responsible for the defect. Both parents must be carriers; the probabilities are 25 per cent than any one child will have the disease and 50 per cent that he will be a carrier.

**Etiology.** The disease is uncommon but not rare. Its incidence in the general population has been estimated to be in the range of 1:1000 to 1:10,000. It is encountered in 2 to 5 per cent of autopsies on infants and children. Both sexes are affected equally. Geographically, the disorder is widespread, although it is rarely seen in Negro infants and never in mongoloids.

**Pathology.** The characteristic lesion appears to be a widespread change of the mucus-secreting glands of the entire body, of which the striking findings in the pancreas are but one manifestation. The mucoproteins in duodenal fluid of most patients with cystic fibrosis have different physicochemical properties from those of normal persons. The changes in the pancreas result from obstruction by inspissated secretion which begins in the pancreatic acini and extends to the ducts. Initially there is dilatation of the acini and ducts, followed by atrophy of the acinar tissue with ultimate replacement with connective tissue, resulting in fibrosis of the entire gland. Grossly, the pancreas is usually smaller, thinner and firmer than normal. The ducts are often dilated, and at times white or yellow plugs can be seen extruding from the cross-sectioned ducts.

Microscopically, there is atrophy of the



exocrine parenchyma. The connective tissue is prominent, in part resulting from replacement fibrosis, but chiefly from condensation of the connective tissue framework of the pancreas secondary to atrophy and disappearance of acini. The acini and small and large ducts are dilated and filled with inspissated eosinophilic material. Occasionally there is an infiltration of lymphocytes and large mononuclear cells in the interstitial spaces. The islands of Langerhans are normal.

The most common early finding in the lungs is either emphysema or atelectasis, depending on whether thick, tenacious mucoid and mucopurulent secretions found in the trachea and bronchi produce complete or incomplete obstruction. Later in the disease, dilatation of bronchi and bronchioles, thickening of bronchiolar walls, bronchiolectatic abscesses and scattered areas of bronchopneumonia are seen. In long-standing cases there are pulmonary fibrosis and a chronic interstitial pneumonia. The tracheobronchial mucous glands are distended with inspissated secretion which has a microscopic appearance similar to that of the exudate observed in the pancreatic ducts and acini.

The liver is usually enlarged and infiltrated with fat. A distinctive type of *multilobular biliary cirrhosis with concretions* leading to portal hypertension occurs in about 2 per cent of cases. Apparently initiated by intrahepatic biliary obstruction from inspissated eosinophilic material (probably mucoprotein),

a trigger mechanism such as nutritional injury or infectious hepatitis is postulated to account for spreading of the localized lesions.

Distention of the acini and ducts of the salivary glands, of aberrant pancreatic tissue with inspissated secretion, and of the mucous glands of the esophagus, duodenum, jejunum and gallbladder is encountered so often as to indicate that these changes are characteristic of this generalized disease.

The sweat contains high concentrations of chloride, sodium and potassium. The saliva and tears also contain increased chloride and sodium, but normal potassium concentrations. The parotid glands tend to have an increased rate of secretion.

Chronic pulmonary heart disease, *cor pulmonale*, is evident in the right side of the heart, which shows the signs of chronic strain produced by the obstructive pulmonary disease; the right ventricle is hypertrophied, the right atrium is hypertrophied and dilated, and the walls of the pulmonary artery and the dilated pulmonary conus are thickened.

Nutritional disturbances, such as retardation of growth and wasting and disappearance of fat from the fat depots, are present in most cases. In about one quarter of Andersen's cases keratinizing metaplasia of the epithelium, characteristic of vitamin A deficiency, was found in the pancreas, upper respiratory tract, renal pelvis and salivary glands. Osteoporosis is common, but rickets is rare, probably owing to the slow rate of growth. In a

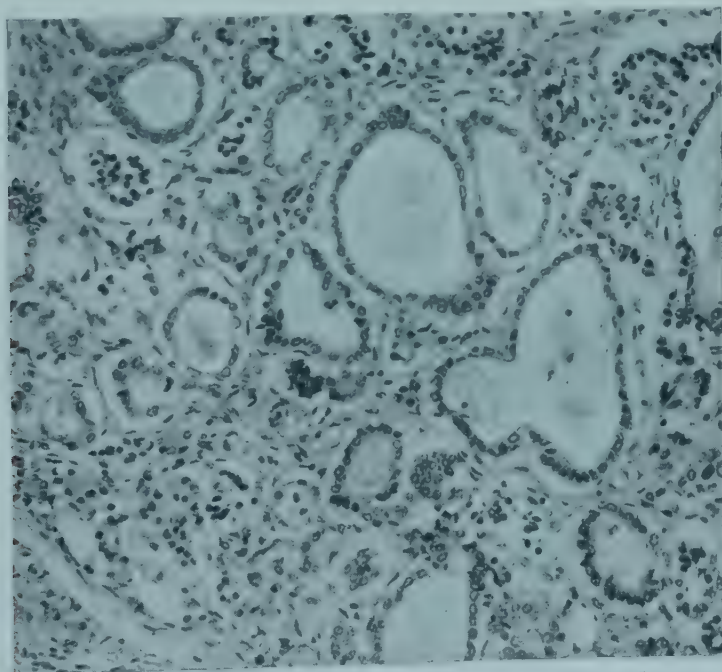


FIG. 206. Photomicrograph illustrating changes of pancreatic fibrosis. Note the generalized cystic dilatation of the acini and the interacinar fibrosis.

few cases evidences of vitamin K deficiency have been observed.

**Clinical Manifestations.** The earliest recognizable clinical disturbance is meconium ileus in the newborn infant (p. 331). Possibly because the deficiency of pancreatic enzymes is seldom complete, meconium ileus is not common. Otherwise, initial symptoms may be referable to poor intestinal digestion or infection of the respiratory tract.

Appearing normal at birth, the infant may or may not present easily detected evidence of impaired intestinal digestion. Failure of the newborn infant to regain his birth weight within the first ten days of life is suggestive. Although the stools are increased in weight and bulk from birth, this often is not noted because individual stool specimens may not appear abnormally large or loose. Almost always before the sixth month, and often before the fourth week, the abnormality of the stools becomes evident. Rarely appearing fatty, they may be loose but not frequent, or less commonly are unformed and numerous. The bulky stools of increased fat content may go unnoticed until the addition of cereal or other starch induces a foul-smelling, frothy stool. Fish liver oils given early are often detected by their odor in the fat-laden stools and at times separate out as fat droplets. After one year of age the stools are usually pale and fatty. The onset of pulmonary infection will frequently make the stools more diarrheal.

Failure to gain weight in spite of an adequate dietary intake is usually apparent early. Some infants have a ravenous appetite as a compensatory mechanism for the large fecal losses.

Manifestations of pulmonary disease are the first abnormality noted in many infants. Persistent upper respiratory and/or diffuse lower respiratory tract infections beginning within the first few weeks of life should always suggest the possibility of pancreatic fibrosis. There may be a severe spasmodic cough often followed by vomiting which is suggestive of pertussis.

Physical signs of obstruction of various parts of the bronchial tree are present at this time, and a generalized expiratory type of dyspnea and wheezing due to widespread bronchiolar obstruction is common. The severe cough results from difficulty in expelling the thick, tenacious mucus produced in the trachea and bronchi. Cyanosis and clubbing of the toes and fingers often develop, and the chest may become barrel-shaped. As a result of destructive lung disease, there is an insidious but increasing hypertrophy of the right

ventricle (cor pulmonale); the progress of the cardiac damage parallels the fluctuations in activity and severity of the pulmonary disease.

The potential length of life is undetermined; most patients die in infancy or early childhood. The longest recorded survival is about twenty-five years. Progression of pulmonary destruction is not inevitable, however; it may become stationary and infrequently has retrogressed.

In infants surviving the first six months of life the evidences of the celiac syndrome are prominent, and respiratory tract infection may at first be inconspicuous. Retardation of growth, abdominal distention, emaciation and behavior disturbances, such as occur in idiopathic celiac disease, are usually present. The stools are bulkier and more malodorous than in any other condition in childhood. Rectal prolapse is a common complication in about one fifth of patients; it is most frequent between six months and three years of age. Diabetes mellitus has been observed in a few children, becoming manifest in mid- or late childhood.

Patients with fibrocystic disease are prone to heat prostration in high environmental temperatures as a result of the abnormal losses of electrolytes in their sweat. Mothers are occasionally impressed by the "salty taste" of babies with this disorder, when kissing them.

**Diagnosis.** Demonstration of the derangements of pancreatic fibrosis by laboratory means is essential for diagnosis.

**Demonstration of deficiency of pancreatic enzymes.** The pancreatic enzymes (trypsin, lipase, amylase and carboxypeptidase) are absent or greatly reduced in the scanty, viscid duodenal fluid. For practical purposes the fluid need only be tested for the presence of trypsin; the absence of trypsin or a very low titer of it is a reliable substantiation of the diagnosis. The failure of digestion of the gelatinous coating of photographic film by application of serial dilutions of stool as spot tests is a rapid and useful screening test for the presence or absence of trypsin.\* Because other factors (bacteria) with tryptic activity may influence the test, it should not be used as a definitive diagnostic measure.

\* A piece of roentgenologic film cut to the size of a Petri dish is placed in the dish with the gelatin side up. A few drops of diluted stool (1:60, 1:120 and 1:180) prepared from a 1:6 dilution are applied to the film; water is used as a control. After incubation for one hour the film is studied for digestion of the gelatin. Dilutions of 1:120 minimize the falsely positive reactions due to bacterial gelatinase.



**Measurement of the chloride content of sweat.** The high concentration of chloride in sweat is a constant and easily demonstrable abnormality. The chloride content of sweat in normal persons does not exceed 60 mEq. per liter and usually is much less; in patients with cystic fibrosis of the pancreas it always exceeds this level. The concentrations of sodium and potassium in sweat are also elevated. The ranges of concentration of the chloride and sodium in sweat are shown in Table 91.

Shwachman has developed a screening technique in which a patient's hand is placed upon agar impregnated with silver nitrate. If the sweat chloride level is high, the hand-print is clearly seen as a precipitate of silver chloride. The test is valuable for screening patients, but it is not diagnostic.

The sweat abnormality occurs among the relatives of patients, indicating different levels of expressivity of the recessive gene in heterozygous persons.

**Deficient intestinal absorption of fat.** Increased fecal excretion of fat may be easily demonstrated by microscopic examination of diluted stool to which Sudan or scharlach stain has been added. Quantitative chemical determination of fat is more exact, but is not necessary. Poor absorption of fat may be demonstrated by the absence of free iodine in the urine after the oral administration of Lipidol. Low blood cholesterol is a constant finding and, at least in part, is secondary to the poor absorption of fats.

Poor absorption of vitamin A (p. 720) is another evidence of failure of fat digestion. Absorption curves with oily vitamin A preparations are flat, but with the alcoholic form of vitamin A they are normal, in contrast to the results in idiopathic celiac disease, in which both forms of vitamin A are poorly absorbed.

**Roentgenologic studies.** Roentgenograms of the intestinal tract reveal changes similar to those seen in idiopathic celiac disease: viz.,

clumping of the barium with alternate segments showing dilatation and spasm resulting in loss of the normal mucosal pattern. These findings, however, are not diagnostic. The earliest pulmonary changes are those of generalized obstructive emphysema with little evidence of infiltration later; patchy areas of atelectasis are evident. With the development of severe bronchial disease an increase in the density and extent of the hilar shadows, patchy areas of bronchopneumonia, bronchiectasis and bronchiolectatic abscesses can be visualized.

Right ventricular hypertrophy and prominence of the pulmonary conus are demonstrated in well advanced cases of pulmonary disease with cor pulmonale.

**Blood.** Other than the changes occurring with infection, there are no significant alterations in the red or white blood cells.

**Treatment.** Maintenance of good nutrition, the control of pulmonary infection and the prevention and/or restoration of abnormal losses of salt are the main objectives of treatment.

To compensate for the stool losses of nutrients, an unrestricted intake of a balanced diet providing 6 to 8 gm. of protein per kilogram of body weight and usual amounts of fat is preferable if it can be clinically tolerated. Dietary fat is usually reduced initially to control the bulk and character of the stools. Pancreatic extract (1 gm. of a patent pancreatin, such as Viokase, per 6 to 8 ounces of formula, or 2 to 3 gm. before each meal) is also helpful in improving the stools. Foods should be salted liberally, and in hot weather an additional 2 gm. should be provided daily.

For infants the dietary specifications may be fulfilled initially by a protein milk formula fortified with added skimmed milk powder and with banana powder, sucrose, glucose or honey. Vitamins in a water-miscible preparation should be given in amounts about three times those usually recommended. The caloric intake should range from 150 to 200

Table 91. Sweat Electrolyte Concentrations in Normal Persons and in Patients with Cystic Fibrosis of the Pancreas

	Chloride, mEq./L.			Sodium, mEq./L.			Potassium, mEq./L.	
	Range	Mean	S.E. Diff. Mean	Range	Mean	S.E. Diff. Mean	Mean	S.E. Diff. Mean
Normal.....	1-60	32	4	10-90	59	6.4	12	1.08
Cystic fibrosis.....	60-160	106		80-190	133		18	

calories per kilogram of body weight per day, if possible. By about three months of age, solid foods are added to the diet.

Some patients with pancreatic fibrosis have remained free from pulmonary infection on dietary management alone. Isolation during infancy and good hygienic surroundings for all children are important in the prevention of respiratory tract infection. Hospitalization, because of its hazard as a source of infection, should be as brief as possible. Prophylactic administration of antibiotics is indicated as soon as a diagnosis of pancreatic fibrosis has been made and, when combined with dietary therapy before pulmonary involvement has set in, offers the greatest hope of delaying the onset of respiratory infection and of prolonging life. The necessity for early diagnosis is obvious. Since the basic infection is usually due to staphylococci, penicillin is administered by inhalation (100,000 units five times daily) and by intramuscular injection (800,000 units daily), and one of the tetracyclines, chloramphenicol or erythromycin combined with sulfisoxazole (Gantrisin) is given orally. If gram-negative bacteria are present in the nasopharyngeal cultures, streptomycin is added to the inhalations (200 mg. five times daily) and to the intramuscular injections (30 mg. per kilogram per day in two divided doses). This antibiotic treatment is continued for seven to fifteen days, after which prophylactic therapy with one of the broad-spectrum antibiotics is continued as long as any signs of pulmonary infection are present. Antimicrobial therapy is best selected on the basis of dilution sensitivity tests *in vitro*. There is suggestive evidence that tetracycline may have beneficial effects on the nutrition, independent of its prophylactic antibacterial actions.

Information about the eugenic implications should be available to parents of a child with pancreatic fibrosis. The possibility that a child with this disease may reach adulthood leads to some interesting eugenic speculations.

### PANCREATIC DYSPLASIAS SIMULATING CYSTIC FIBROSIS OF THE PANCREAS

Several rare conditions are recognized in which congenital defects in the pancreas or its ducts obstruct the flow of pancreatic juice to the intestinal lumen. Such conditions which produce digestive failure resembling that of pancreatic fibrosis include (1) congenital obstruction of the main pancreatic ducts of Wirsung and Santorini; (2) con-

genital hypoplasia of the exocrine pancreas. In this rare embryologic maldevelopment the terminal pancreatic ducts fail to unite with the acini and larger ducts, so that the acini are replaced by fat. The ducts are not occluded or distended as in pancreatic fibrosis. (3) Congenital cystosis of the pancreas; this is a congenital malformation of the duct system in which isolated segments of duct form true epithelial cysts surrounded by normal pancreatic tissue.

It is noteworthy that bronchial abnormalities and infection and disordered formation of mucus by other glandular structures which occur with fibrosis of the pancreas are not associated with these other conditions, even though they completely exclude pancreatic juice from the intestine.

### ACUTE PANCREATITIS

#### MUMPS PANCREATITIS

Acute nonsuppurative pancreatitis occurs as a rather infrequent complication of mumps. It usually makes its appearance abruptly three to four days after the first sign of salivary gland involvement, but it may occur somewhat later. During epidemics of mumps some children have had symptoms typical of acute pancreatitis without involvement of the salivary glands. The onset of the disease is abrupt, with severe, constant abdominal pain localized most frequently about the umbilicus, but at times in the epigastrium. Shock, nausea, and vomiting are almost always present. Diarrhea is a frequent occurrence, but in rare instances the passage of large, fatty stools is recorded. Moderate fever is often present, and leukocytosis is a fairly constant finding. Polyuria and urinary frequency may occur. Transient hyperglycemia and glycosuria are noted infrequently either during or after the acute attack. Tenderness may be elicited in the upper abdomen in the region of the pancreas. The *prognosis* is usually good, complete recovery occurring in about one week. In a few instances suppuration of the pancreas has developed.

#### HEMORRHAGIC, SUPPURATIVE AND GANGRENOUS PANCREATITIS

Acute pancreatitis of this category, not uncommon in adults, in whom it is readily recognized clinically and is frequently associated with biliary tract disease and precipitated by overeating, is rare in childhood. When detected, it is usually an accidental finding at



an abdominal operation or at autopsy. Of thirty-eight cases up to 1958, twenty-four were of unknown etiology. Some cases have been secondary to trauma, and the signs of pancreatitis may be overshadowed by those of concomitant injury of the spleen or liver. Obstruction of the pancreatic ducts by *Ascaris* has initiated the disease in a few instances. Occasionally, septic emboli or extension of a neighboring infection (peritonitis or retroperitoneal abscess) is responsible. Rarely, hemorrhage into the pancreas from purpura or leukemia is the cause. Prolonged administration of corticosteroids may cause acute pancreatitis. It is postulated that alteration of pancreatic secretion leading to obstruction and release of pancreatic enzymes is responsible for the lesions. Irrespective of the etiologic agent, the evolution of the disease follows the same pattern. The zymogens, trypsinogen and steapsinogen, which have no enzyme activity in the pancreas or its ducts, are activated by a substance released from autolyzed injured pancreatic tissue. The activated enzymes, trypsin and steapsin, then produce autodigestion of the protein and fat of the pancreas and surrounding tissues. Absorption from the necrotic pancreas undergoing autolysis is responsible for the fulminating toxemia. Tetany due to binding of calcium by fatty acids may occur. Diabetes mellitus may develop during or after an attack, as a result of destruction of islet tissue. Pseudocyst formation is a relatively common complication.

The onset of the disease is sudden and is characterized by agonizing, constant upper abdominal pain, nausea, vomiting and symptoms of shock. If the nature of the disease is suspected, confirmation may be made by the finding of an increase in serum or urinary diastase. Treatment consists of parenterally administered glucose fluids and antibiotics to prevent secondary bacterial infections. Sympathicomimetic drugs (methantheline bromide) are used to reduce pancreatic secretion. Surgery is necessary if a pseudocyst, hemorrhage or abscess occurs as a complication.

#### INVOLVEMENT OF THE PANCREAS IN SYSTEMIC DISEASE

Acute and chronic changes in the pancreas are often associated with a variety of systemic diseases without producing symptoms that would lead to clinical recognition of pancreatic involvement. Infiltration of the pan-

creas by leukemia, Hodgkin's disease and other lymphogranulomatous conditions is common. Severe congenital syphilis involving the pancreas causes widespread fibrosis. Fibrotic changes with extensive atrophy of acinar tissue result from the chronic passive congestion of the pancreas produced by long-standing cardiac decompensation. Miliary abscesses occur in association with septicemia; tubercles, with miliary tuberculosis.

#### NEOPLASMS AND CYSTS OF THE PANCREAS

Tumors of the pancreas are exceedingly uncommon in infancy and childhood. Primary sarcoma and carcinoma are recorded, but their extreme rarity is indicated by Dargeon's tabulation in 1538 cases of malignant tumors in childhood, of which only three were in the pancreas. Metastases from melanosarcoma, hemangiosarcoma and lymphosarcoma may involve the pancreas, but carcinoma in childhood rarely metastasizes to this organ. Adenoma of the islets of Langerhans is discussed on page 1217.

A variety of pancreatic cysts is encountered in children. Post-traumatic *pseudocysts*, not infrequently sequels of bicycling accidents, are of especial interest because they grow rapidly to large size and cause pressure damage which may be irreversible. Vomiting and weight loss are common symptoms, and a large soft mass usually occupies the left upper abdominal quadrant. Roentgenograms taken after barium ingestion may show elevation of the left diaphragm and upward displacement of the stomach. Prevention of the serious pressure effects of pseudocysts by early surgical intervention depends upon an awareness of the possible development of the lesion after severe trauma to the pancreatic area.

Occasionally pancreatic cysts are congenital and associated with polycystic disease elsewhere. Retention cysts, lined with epithelium due to obstruction, may follow chronic pancreatitis. Extremely rare are neoplastic cysts (cystadenoma, cystadenocarcinoma or teratoma). Echinococcus cysts of the pancreas are encountered in areas where this parasitic disorder occurs.

MILTON RAPOPORT

#### REFERENCES

*Anomalies of the Pancreas*

Barbosa, J. J. deC., Dockerty, M. B., and Waugh, J. M.: Pancreatic Heterotopia—Review of the Lit-

erature and Report of 41 Authenticated Cases of Which 25 Were Clinically Significant. *Surg., Gynec. & Obst.*, 82:527, 1946.

Martinez, N. S., and others: Heterotopic Pancreatic Tissue Involving the Stomach. *Ann. Surg.*, 147: 1, 1958.

Weatherill, D., Forgrave, E. G., and Carpenter, W. S.: Annular Pancreas Producing Duodenal Obstruction in the Newborn. *A.M.A. Am. J. Dis. Child.*, 95:202, 1958.

#### *Physiology and Tests of Pancreatic Function*

Dreiling, D. A., and Janowitz, H. D.: Exocrine Pancreatic Secretion. *Am. J. Med.*, 21:98, 1956.

Volweiler, W.: Gastro-intestinal Malabsorptive Syndromes. *Am. J. Med.*, 23:230, 1957.

#### *Celiac Disease*

Adlersberg, D., ed.: *The Malabsorption Syndrome*. A Mt. Sinai Hospital Monograph. New York, Grune & Stratton, Inc., 1957.

Andersen, D. H., and diSant'Agnese, P. A.: Idiopathic Celiac Disease. I. Mode of Onset and Diagnosis. *Pediatrics*, 11:207, 1953.

Boyer, P. H., and Andersen, D. H.: A Genetic Study of Celiac Disease. *A.M.A. Am. J. Dis. Child.*, 91: 131, 1956.

diSant'Agnese, P. A.: Idiopathic Celiac Disease. II. Course and Prognosis. *Pediatrics*, 11:224, 1953.

Davidson, M., and Bauer, C. H.: The Value of Microscopic Examination of the Stool for Extracellular Starch in the Diagnosis of Starch Intolerance. *Pediatrics*, 21:565, 1958.

Holt, L. E., Jr.: Celiac Disease, What Is It? *J. Pediat.*, 26:369, 1955.

Sheldon, W., and Lawson, D.: The Management of Celiac Disease. *Lancet*, 2:902, 1952.

Weiijers, H. A., van de Kamer, J. H., and Dicke, W. K.: Celiac Disease; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1957, Vol. 9, p. 277.

#### *Giardiasis*

Cortner, J. A.: Giardiasis Causing the Celiac Syndrome; Clinical Observations and Studies of I-131 Fat Absorption. *Proc. Soc. Pediatric Research*, p. 33, May 6 and 7, 1958, Atlantic City, N.J.

Véghelyi, P.: Giardiasis. *Am. J. Dis. Child.*, 59: 793, 1940.

#### *Lymphatic Obstruction*

Hurst, A., Wright, G. P., and Ryle, J. A.: Sprue Syndrome from Obstruction of the Lacteals by Chronic Tuberculosis of the Mesenteric Lymph Nodes. *Guy's Hosp. Rep.*, 91:25, 1942.

Story, R. D., and Sagild, U.: Whipple's Disease (Intestinal Lipodystrophy) and Serum Glycoproteins. *J.A.M.A.*, 152:312, 1953.

#### *Cystic Fibrosis of the Pancreas*

diSant'Agnese, P. A.: Cystic Fibrosis of the Pancreas. *Am. J. Med.*, 21:406, 1956.

diSant'Agnese, P. A., and Blanc, W. A.: A Distinctive Type of Biliary Cirrhosis of the Liver Associated with Cystic Fibrosis of the Pancreas. *Pediatrics*, 18:387, 1956.

Kulczycki, L. L., and Shwachman, H.: Studies in Cystic Fibrosis of the Pancreas: Occurrence of Rectal Prolapse. *New England J. Med.*, 259:409, 1958.

May, C. D.: Cystic Fibrosis of the Pancreas in Infants and Children. Springfield, Ill., Charles C Thomas, 1954.

Shwachman, H., Leubner, H., and Catzel, P.: Mucoviscidosis; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1955, Vol. 7, p. 249.

#### *Acute Pancreatitis*

Blumenstock, D. A., Mithoefer, J., and Santulli, T. V.: Acute Pancreatitis in Children. *Pediatrics*, 19:1002, 1957.

Carone, F. A., and Liebow, A. A.: Acute Pancreatic Lesions in Patients Treated with ACTH and Adrenal Corticoids. *New England J. Med.*, 257:690, 1957.

Stickler, G. B., and Yonemoto, R. H.: Acute Pancreatitis in Children. *A.M.A. Am. J. Dis. Child.*, 95:206, 1958.

#### *Neoplasms and Cysts of the Pancreas*

Cattell, R. B., and Warren, K. W.: *Surgery of the Pancreas*. Philadelphia, W. B. Saunders Company, 1953.

Levitzky, E., Lance, E., and Armstrong, L.: Pseudocysts of the Pancreas in Childhood. *A.M.A. Am. J. Dis. Child.*, 92:60, 1956.



# The Respiratory System

## RESPIRATORY PHYSIOLOGY AND ITS APPLICATION TO PULMONARY DISEASE

A fundamental knowledge of respiration is essential for a proper understanding of respiratory disease. This section will deal with basic principles, some measurements of pulmonary function, and the application of such knowledge to certain respiratory conditions in infants and children. The respiratory system is made up of (1) a control system, which consists of a respiratory center in the brain stem, chemoreceptors in the carotid and aortic bodies, and peripheral nerves which are both motor (efferent) and sensory (afferent); (2) the respiratory muscles and "thorax"; (3) the lungs and the pulmonary vasculature. Any one or combination of the parts may be involved in disease processes which may contribute to pulmonary disability.

### CONTROL OF RESPIRATION

The respiratory center in the brain stem has an inherent rhythmicity which is modified by proprioceptive afferent impulses from the lungs, by various reflexes and voluntary mechanisms, and by changes in the oxygen and carbon dioxide tensions in the arterial blood. The proprioceptive impulses from the lungs are carried by the vagi; the complete cycle from proprioception to the motor response is called the *Hering-Breuer reflex*. Protective reflexes such as coughing and sneezing can alter the usual breathing patterns and act to eliminate foreign or obstructing matter from the respiratory system. Respiration is also modified during swallowing and is altered reflexly by pain, fever, and variations of blood pressure.

Oxygen lack stimulates the respiratory center principally through the carotid and aortic

\* "Thorax" in this presentation is used to include the diaphragm, rib cage, abdominal wall and abdominal contents.

body mechanisms, whereas changes in carbon dioxide tension affect the respiratory center directly. Whether carbon dioxide tension or the associated change in pH (in blood or cerebrospinal fluid) is more responsible for regulation of the respiratory center is not known, but it is recognized that respiration is very sensitive to *small* changes in the carbon dioxide tension of the blood whether secondary to respiratory or metabolic abnormalities. Both *pronounced* hypoxia and hypercapnia have a depressant effect on the respiratory center, and this is an important consideration in the management of apnea, resuscitation or chronic respiratory insufficiency. Furthermore, anesthetic agents and certain drugs such as opiates and barbiturates, hypothermia and brain injury also depress the respiratory center. The best stimulus to a depressed respiratory center is an increase in its supply of oxygen. Drugs are useful as respiratory center stimulants only as they improve the general circulation or specifically counteract a respiratory, depressant (e.g., n-allylnormorphine).

### MUSCLES OF RESPIRATION

In quiet normal breathing only the inspiratory muscles are used; expiration occurs as a result of relaxation of the respiratory muscles and the elastic recoil of the lung. The diaphragm is the most important muscle of quiet inspiration, but with increasing inspiratory effort the intercostal, spinal extensor and neck muscles become active in that order. They tend to increase the thoracic diameter and thus the volume of inspiration; the intercostal muscles also serve to stabilize the rib cage.

The abdominal muscles are the ones primarily used for a forced expiration; they are assisted by the "spinal flexors," which increase

Table 92. Normal Values for Lung Volumes and Compliance and Resistance  
(Ranges include approximately 95% of normal values; volumes in liters, BTPS)

Age (Yrs.)	Newborn	6	14	14	♂ 18	♀
Length, Ht. (Cm.)	51	115	138	160	175	163
Weight (Kg.)	3	20	32	49	63	54
Total lung capacity.....	0.180*	1.4-2.3	2.2-3.8	3.5-6.0	4.4-7.6	3.6-6.2
Functional residual capacity.....	0.080	0.6-1.2	1.0-2.1	1.6-3.3	2.2-4.3	1.7-3.4
Residual volume.....	0.040*	0.3-0.9	0.5-1.2	0.6-1.6	0.7-2.0	0.6-1.7
Vital capacity.....	0.140	1.0-1.8	1.7-2.9	2.6-4.5	3.4-6.3	2.7-4.8
RV/TLC%	?	14-34	14-34	14-34	14-34	14-34
Vital capacity (2 sec.) % total-average.....	?	90%	90%	90%	90%	90%
Maximal breathing capacity (L./min.).....	?	30-60	42-106	65-140	90-175	62-147
Lung compliance (ml. cm. H <sub>2</sub> O).....	1-10	32-96	46-142	64-194	78-245	67-204
Flow resistance (cm. H <sub>2</sub> O/L./sec.).....	4-41+	3-14#	2-9#	2-6#	1-5#	2-6#

Newborn values in supine position, all others in prone.

\* Values represent extrapolation and need further verification.

BTPS-37° C. saturated with water vapor at ambient pressure.

+ Nose-breathing.

# Mouth-breathing.

intrapulmonary pressure for coughing. The intercostal muscles also assist expiration, but here, too, they function largely to stabilize the rib cage. Patients with weakened abdominal muscles cannot cough well. Manual pressure over the abdomen after a maximal inspiration can produce a fair cough when the closed glottis is opened suddenly, but this technique is limited to patients who can cooperate.

When muscular function is diminished as with poliomyelitis or other neuromuscular disease, the forces developed may be so limited that artificial respiration is required.

## PULMONARY SUBDIVISIONS

Some of the functional subdivisions of lung volume are shown in Figure 207, A, which represents a series of tidal volumes and a vital capacity as obtained on a recording spirometer. Predicted normal values for vital capacity can be obtained from the following relationships:

	5-15 Years	16+ Years
Males.....	250 cc./yr. age	25 cc./cm. Ht.
Females.....	200 cc./yr. age	20 cc./cm. Ht.

These estimations are clinically useful, but not sufficiently accurate for research purposes. The limits of normal values for various ages are given in Table 92.

The vital capacity is made up of the inspiratory capacity and the expiratory reserve volume. The proportion of the vital capacity occupied by each of these subdivisions varies with position of the patient, although vital capacity itself changes little.

After each expiration a considerable volume of air, the functional residual capacity, remains in the lungs. It acts as a buffer to minimize changes in the partial pressure of carbon dioxide and oxygen in the alveoli and arterial blood with each breath, and tends to reduce the surface forces, since most air spaces remain open at end-expiration.

The functional residual capacity varies with changes in position, being larger in the upright than in the horizontal or recumbent position. If a person lies on his side, the lower or dependent lung has a smaller functional residual capacity than the upper lung. The volume of the functional residual capacity (the resting end-expiratory volume) is determined by the balance between the elastic recoil of the lungs and the tendency of the "thorax" to expand. The effective "thoracic" forces stem from the elastic characteristics of the rib cage, from the diaphragm and the abdominal wall, and from the hydrostatic forces of the abdominal contents. The movement of the abdominal contents is largely responsible for the changes in the functional residual capacity which occur with changes in position, and it is this movement which makes possible the use of tilting methods for artificial respiration. The functional residual capacity may be measured by means of gas dilution techniques, the simplest and easiest of which is to use helium in a closed circuit.

## MECHANICS OF RESPIRATION

The mechanical properties of the respiratory system may be divided into two components—one concerned with static or elastic forces



and the other concerned with the dynamic or flow-resistance forces. The resting end-expiratory position or functional residual capacity results from two forces—the tendency of the lungs to collapse and the tendency of the “thorax” to expand. This can be likened to the balance between two springs. Any deviation from the balance point requires work or an applied force; when the force is released, the springs return to their relaxation or balance point. In a comparable manner in normal breathing when the respiratory muscles contract, the “thorax” and lungs expand. When the muscles relax, the intrapleural pressure falls toward the resting end-expiratory pressure, and expiration occurs.

The elastic or “springlike” characteristic is called *compliance* and is expressed as milliliters or liters per centimeter of water. In the case of the lungs it represents the change in pulmonary volume for a unit change of intrapleural pressure and must be measured when there is no flow of air so that there is no flow-resistance component. The less the volume change produced by a given pressure change, the stiffer or more uncompliant are the lungs. Conversely, if the volume change for this same pressure difference is large, the lungs are said to be highly compliant or distensible.

The lungs of infants are less compliant than those of older children and adults (Table 92), but when the difference in lung size or body size is considered, they are comparable, and at all ages nearly the same transpulmonary pressure difference is required to produce the resting tidal volume. In order to measure the compliance of the lungs, one should know the intrapleural pressure

changes, but this approach has limited use. Pressure changes in the thoracic esophagus, however, may be used as an index of the transpulmonary pressure changes.

The pressure-volume relationship of the lungs and “thorax” can be related to the pulmonary compartments, as has been done in Figure 207, B. The resting end-expiratory volume has been continued as a horizontal line and also represents the pressure axis. Volume is represented by the vertical axis. Pressure changes to the right of the vertical axis are equivalent to positive airway or negative tank pressure, and pressures to the left represent negative airway or positive tank pressure. The pressure-volume relationships of the lungs and “thorax” over the vital capacity range are represented by the solid curve. There is no scale, because the values for subjects of different sizes are different; the shape of the curves, however, will be similar. In the region of the tidal volume (between A and B on the curve) the relationship of pressure to volume is essentially linear. With spontaneous respiration the strength of the respiratory muscles is an important factor in determining the magnitude of maximum volume change. In addition maximum inspiration is limited by the decreased compliance of the lungs, the rib cage, and the abdominal wall and abdominal contents at large lung volumes. Expiration, on the other hand, is limited by the compliance of the rib cage and the diaphragm.

Knowledge of pressure-volume relationship of the lungs and “thorax” is particularly important during artificial respiration. Pressures required to produce volume changes of the lungs and “thorax” are approximately twice those required for the lungs' alone.

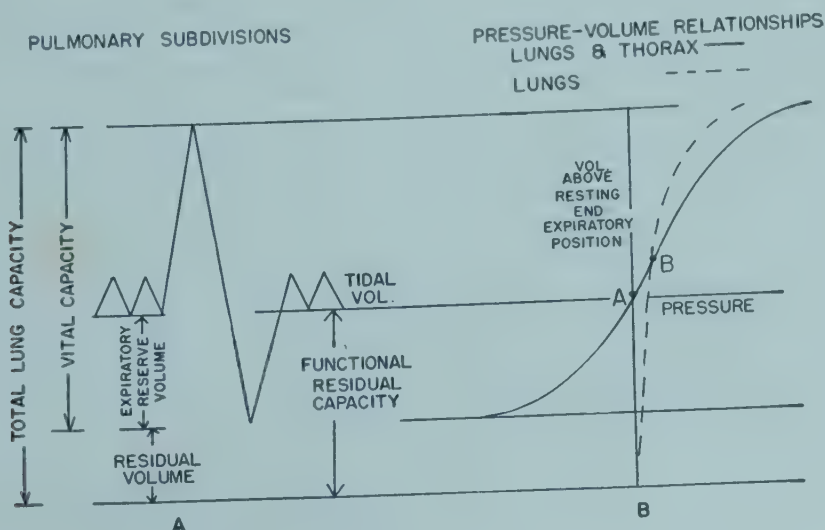


FIG. 207.

Table 93. Changes in Pulmonary Function in 6 Types of Respiratory Difficulty

	<i>Hyaline Membrane Syndrome</i>	<i>Cystic Fibrosis of the Pancreas</i>	<i>Asthma</i>	<i>Poliomyelitis with Respiratory Paralysis</i>	<i>Emphysema</i>	<i>Congestive Failure</i>
Total lung capacity	↓	↓	N or ↓	↓	↑	↓
Functional residual volume	↓	N or ↑	N or ↑	N	↑	N or ↑
Residual volume	?	↑	↑	↑	↑	↑
Vital capacity	?	↓	N or ↓	↓	↓	N or ↓
Timed vital capacity	?	↓	↓	↓	↓	↓
Maximal breathing capacity	?	↓	↓	↓	↓	↓
Lung compliance	↓	N or ↓	↓	↓	N or ↑	↓
Flow resistance	±	↑	↑	N or ↑	↑	N or ↑
Blood PCO <sub>2</sub>	↑	Late ↑	N or ↑	N or ↑	↑	±
Blood PO <sub>2</sub>	↓	Late ↓	N or ↓	N or ↓	↓	↓

Thus far the force required to maintain the lungs under static conditions has been considered. During inflation and deflation dynamic factors are also present. These are the resistance of the airway to the flow of gases and the viscous resistance of the pulmonary tissues. They are combined in the measurement of pulmonary flow resistance, which is the force or pressure difference required to produce a specific flow of air and is expressed as milliliters of water per liter per second (Table 92). In diseases such as asthma or bronchiolitis the pulmonary resistance may be increased to ten to fifteen times the normal value (Table 93). Since resistance to the flow of air through tubes is inversely related to the radius of the tube to the fourth power, inflammation or mucus (e.g., croup, bronchiolitis) is most likely to produce serious obstruction and increases in flow resistance in small infants and children.

A convenient method for indirect estimation of resistance is the rapidly expelled (timed) vital capacity. This requires the patient's cooperation, but is useful as a screening test or to assess effectiveness of therapy. Normally the patient should be able to expel at least 75 per cent of his vital capacity in the first second and 90 per cent within two seconds. If he has increased flow resistance, the percentage of vital capacity expelled in the allotted time will be decreased. The maximum breathing capacity or the greatest amount of air that can be rhythmically breathed out in a fifteen- or twenty-second period can also be used, but it requires more cooperation on the part of the patient. Furthermore, the extensive respiratory effort may be contraindicated in certain diseases such as active tuberculosis.

The respiratory muscles must have suffi-

cient work capacity to overcome the elastic and flow resistance of the respiratory system. During normal resting respiration the amount of work is small, corresponding to 1 per cent of the resting metabolism. As ventilation is increased the expenditure of energy for breathing increases more rapidly than the ventilation. Normally, except at extreme work loads, the respiratory system is able to meet the metabolic needs for oxygen consumption and carbon dioxide excretion. On the other hand, in disease resulting in stiff lungs or in an increased resistance to air flow the work required may be greatly increased. In such instances if there are also interference with transfer of gas from the alveoli to the blood, poor distribution of gas within the lungs and increased metabolic needs as with fever and anxiety, exhaustion of the respiratory muscles may result, accompanied by accumulation of carbon dioxide and eventually death.

Since the respiratory system is usually regulated to accomplish ventilation with a minimum expenditure of energy, there is a balance between the efficiency of the muscular activity and the effectiveness of the ventilation. In some diseases with stiff lungs, such as pulmonary fibrosis and the hyaline membrane syndrome (Table 93), the breathing is usually rapid and shallow in order to minimize the elastic work, but much dead space ventilation results. In asthma the breathing tends to be deep and slow, and the lower flow rates reduce the work required to overcome flow resistance.

VENTILATION

The volume of gas breathed into or out of the lungs with each breath is defined as the tidal volume (V<sub>T</sub>). This volume multiplied



by the respiratory rate ( $f$ ) gives the minute volume ( $\dot{V}_E$ ). Not all the tidal volume is effective in gas exchange; in the normal person about one third of each quiet respiration ventilates the dead space ( $V_D$ ), while the remaining portion ( $V_{Te}$ ) enters the air sacs and alveoli and participates in gas exchange. Since alveolar ventilation ( $\dot{V}_A$ ) is a function of carbon dioxide production ( $\dot{V}_{CO_2}$ ) and the partial pressure of carbon dioxide in the arterial blood ( $P_{aCO_2}$ ) or alveoli, the following expressions are useful for defining the effective or alveolar ventilation:

$$V_T - V_D = V_{Te}$$

$$V_{Te} \times f = \dot{V}_A = k \frac{\dot{V}_{CO_2}}{P_{aCO_2}}$$

Thus, as metabolism and carbon dioxide production increase, the alveolar ventilation must increase if the blood carbon dioxide partial pressure is to remain at the usual level. Conversely, if  $\dot{V}_A$  were doubled for a given  $\dot{V}_{CO_2}$ , then  $P_{aCO_2}$  would be halved. It is also apparent that when the dead space increases, secondary to disease or to the use of an anesthetic apparatus,  $V_T$  or  $f$  must increase to maintain a constant  $P_{aCO_2}$ .

The most effective way to increase alveolar ventilation is to increase the tidal volume. In this way alveolar ventilation is increased without increasing the dead space ventilation. This concept is presented in Table 94, in which tidal volume and frequency of breathing are varied while the minute volume is kept constant. Under such conditions, as the tidal volume decreases, the frequency increases and the amount of effective or alveolar ventilation decreases. As a result the alveolar  $P_{CO_2}$  would rise from a normal value of 40 mm. of mercury at the largest tidal volume to 60 mm. at the smallest tidal volume. The alveolar  $P_{CO_2}$  and arterial  $P_{CO_2}$  are considered to be essentially identical. If, on the other hand, the tidal volume increases

from a normal value of 0.125 to 0.5 liter, then alveolar ventilation increases and alveolar  $P_{CO_2}$  falls from its normal value of 40 mm. to about 27 mm. of mercury.

**Methods of Measuring Ventilation.** The adequacy of ventilation is best evaluated by measurement of alveolar or arterial partial pressure of carbon dioxide. The measurement of "alveolar" or end-tidal  $P_{CO_2}$ \* is the more practical and can be nearly continuous or at least repeated frequently. Since it provides an approximation of the arterial  $P_{CO_2}$ , it is a good index of the effectiveness of the ventilation. It is relatively easy to obtain with an infra-red carbon dioxide analyzer, but the equipment is expensive and not easily adapted for infants and small children.

The adequacy of ventilation can also be estimated by measuring the minute volume ( $\dot{V}_E$ ), by means of a recording spirometer or a ventilation meter (Fig. 209). The measured tidal volumes are then compared with the predicted values obtained from a nomogram (Fig. 208) at the observed frequency of breathing. The nomogram is based on assumptions that the arterial  $P_{CO_2}$  at sea level should be close to 40 mm. of mercury and that the lungs are relatively normal and that body weight is a good index of the person's metabolism or carbon dioxide production. Knowing the weight and the frequency of breathing, one can then predict the required tidal volume. This calculation is most applicable for regulating artificial respiration in poliomyelitis or during anesthesia. Use of the nomogram is demonstrated in the following example:

A 40-pound male child requires artificial ventilation; his temperature is 40° C., he is breathing through a tracheostomy tube, he is not in coma, and he is at an altitude of 3000 feet. Respiratory frequency is set at 20 per minute. Corrections to be

\* End-tidal  $P_{CO_2}$  is not necessarily true alveolar  $P_{CO_2}$ , but is a useful approximation.

Table 94

<i>Tidal Volume</i>	<i>Minute Volume</i>	<i>Frequency</i>	<i>Dead Space Ventilation</i>	<i>Alveolar Ventilation</i>
$V_T$ (L.)	$\dot{V}_E$ (L./min.)	$f$ /min.	$V_D$ (L./min.)	$\dot{V}_A$ (L./min.)
0.50.....	5	10	0.5	4.5
0.25.....	5	20	1.0	4.0
0.125.....	5	40	2.0	3.0

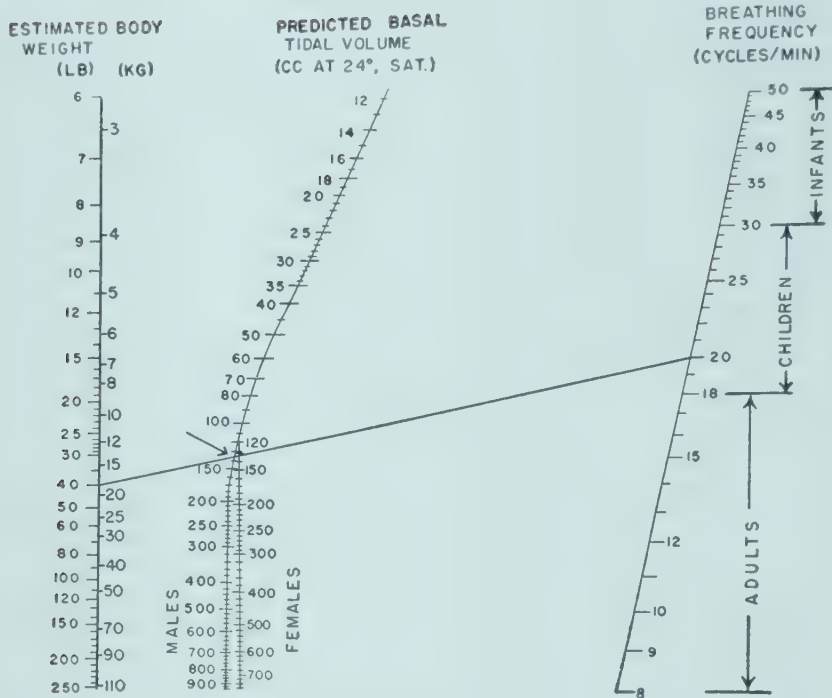


FIG. 208. Nomogram for regulation of artificial respiration.

Corrections to be applied to basal tidal volume:

For Metric System:

1. Add 10 per cent for daily activity (i.e., patient not in coma).
2. Add 9 per cent for each  $1^{\circ}$  C. above  $37^{\circ}$  C. rectal temperature.
3. Add 8 per cent for each 1000 M. altitude above sea level.
4. Subtract 1 cc./kg. weight if patient is breathing through a tracheostomy or endotracheal tube.

For English systems:

1. Add 10 per cent for daily activity (i.e., patient not in coma).
2. Add 5 per cent for each  $1^{\circ}$  F. above  $99^{\circ}$  F. rectal temperature.
3. Add 5 per cent for each 2000 ft. above sea level.
4. Subtract volume (cc.) equal to one-half body weight expressed as pounds if patient is breathing through a tracheostomy or endotracheal tube.



FIG. 209. Measuring ventilation on small child by means of mask and meter.



applied to basal tidal volume are listed on the nomogram and demonstrated below.

Basal tidal.....	135 ml.	
Awake +10%.....	14 ml.	
Fever +3 × 9 = 27.....	36 ml.	
Altitude +1.5 × 5 = 7.5%...	10 ml.	
	195 ml.	
Tracheostomy -40/2.....	-20 ml.	
	175 ml.	predicted required V <sub>T</sub> via tracheostomy tube

Predicted required minute volume is  $V_T$  times  $f$ ; i.e.,  $\dot{V}_E$  is 175 times 20, or 3500 ml. per minute.

Cyanosis is, of course, an indication of respiratory insufficiency except in patients with shock, cardiovascular disease or methemoglobinemia. If cyanosis occurs in spite of adequate ventilation as judged either by measurement of minute volume or, better still, by end-tidal  $P_{CO_2}$  measurements, then the need is for more oxygen, and not for an increase in ventilation. An increase in ventilation under such circumstances produces relatively little change in arterial oxygen saturation, but removes significant amounts of carbon dioxide from the body, lowers the  $P_{CO_2}$  and increases the pH until compensation occurs. A decreased  $P_{CO_2}$  even in the presence of a compensated pH is not a normal state and may cause personality changes in the patient.

## PARTIAL PRESSURES OF GASES

The partial pressures of gases at sea level in various physiologic media of the normal person are presented in the bar graphs in Figure 210. These are not valid at altitudes much above sea level, since the lower barometric pressure reduces the partial pressure for all gases except that of water vapor. The latter is related to the temperature of the air and remains fixed at 47 mm. of mercury at 37° C. If the patient is febrile, the vapor tension increases; an elevation of 2 to 3° C. adds about 10 mm. of mercury to the partial pressure of water vapor. The water vapor then occupies more space and displaces other gases.

Owing to the differences in the  $P_{O_2}$  of alveolar gas and arterial blood, the sum of the partial pressures in the arterial blood does not add up to the ambient barometric pressure. In normal persons most of this difference is due to a small venous admixture or "shunt" into the arterial system and very little to a

diffusion gradient from the alveoli to the red blood cell. When there are abnormal ventilation (alveolar)-perfusion (blood flow) relationships, "shunted blood" may be considerable. Thus if a part of the lung is underventilated in relation to its perfusion, the blood exposed to these underventilated alveoli may approximate venous blood, and in effect this blood is shunted. If an area is overventilated and receives relatively little blood, the result is the same as an increase in the dead space. Even if perfused alveoli are hyperventilated, the blood is not able to take up much more oxygen and cannot compensate for blood that is unsaturated. The explanation lies in the shape of the oxyhemoglobin dissociation curve, which is sigmoid and flattens out near 100 mm. of mercury. When the arterial  $P_{O_2}$  is about 95 mm. of mercury, the hemoglobin is about 97 per cent saturated, and a further increase in the  $P_{O_2}$  by hyperventilation adds little oxygen to the blood. On the other hand, the mixture of 5 per cent venous blood to arterialized blood produces a significant fall in the oxygen tension because such unsaturated blood is on the steep part of the dissociation curve where considerable amounts of oxygen can be taken up for small changes in partial pressure.

The sum of the partial pressures in the mixed venous blood is much less than in the

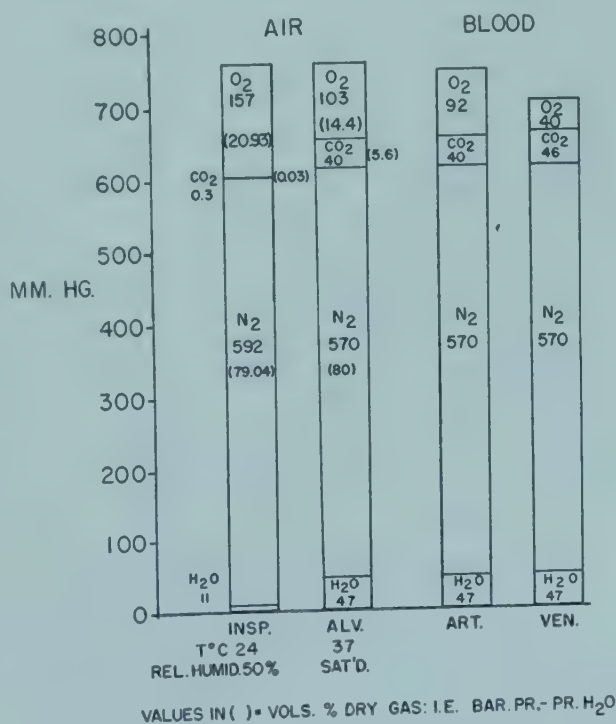


FIG. 210. Partial pressures of gases in various physiologic media at sea level (Barometric pressure, 760 mm. Hg.).

arterial blood. Again this is largely due to the decrease in venous  $\text{Po}_2$ . There is only a small increase in the venous  $\text{PCO}_2$  because the blood can carry large amounts of carbon dioxide with little change in partial pressure of carbon dioxide. The difference between the alveolar  $\text{Po}_2$  and the venous  $\text{Po}_2$  is large (40 to 60 mm. of mercury) and acts as the initial driving force to deliver oxygen from the alveoli into the blood.

Measurements of the diffusing capacity of the lungs can be made by using carbon monoxide as the indicator gas. In infants and small children they are technically difficult, and particularly so in disease states.

## INITIATION OF RESPIRATION

The onset of respiration is the most critical adjustment required of the infant. Thus it is not surprising that most neonatal deaths are related to failure of respiration. Although before birth the lungs have no obvious function, there is ample evidence that there are rhythmic respiratory-like movements of the fetus in utero. The resultant movement of amniotic fluid into the lungs may facilitate their expansion at birth.

Extrapolations to the human fetus from the experimental observations of Barcroft in fetal lambs suggest that the onset of respiration is usually produced by sensory stimuli (tactile or thermal). When central nervous system depression exists, chemical changes may act as an emergency mechanism to stimulate the respiratory center. But the apneic infant is already hypoxic and acidotic, and the administration of carbon dioxide may only lead to further depression.

With the first breath certain forces must be overcome to expand the lungs and permit adequate ventilation. Under normal circumstances the greatest force opposing expansion of the fetal lung is surface tension, but, in addition, there is their elastic recoil as well as flow resistance. Measurements by Karlberg of the first few respirations have demonstrated that the transpulmonary pressures required to expand the normal lung may be 20 to 50 cm. of water. Although these high pressures normally are produced by the infant himself, alveolar rupture may occur either spontaneously or as a result of artificial respiration. Thus positive pressure, when indicated, must be used with caution.

The respiratory mechanism at birth is most likely to fail as the result of (1) central

nervous system depression or (2) abnormalities within the lungs. Drugs, intrauterine hypoxia and trauma may all depress the respiratory center. Unless morphine antagonists are indicated, little can be done to improve the responsiveness of the center except to supply it with oxygen and to remove excess carbon dioxide. Good obstetric and anesthetic procedures should greatly reduce the incidence of this type of respiratory failure.

Expansion of the lungs may be limited because of obstruction which can be removed if it is in the larger air passages. If the obstruction is in the smaller air passages, as may occur with aspiration of meconium-containing amniotic fluid or with plugging of alveolar ducts with hyaline-membrane material, the lungs may be resistant to expansion. The latter type of respiratory distress is the greatest single cause of death in the newborn period.

Congenital malformations such as diaphragmatic hernias, lung cysts, intrathoracic tumors and tracheo-esophageal fistulas may also be a cause of respiratory difficulty in the newborn period and may at times simulate conditions which have less specific therapy.

## ARTIFICIAL RESPIRATION

Although obvious technical and quantitative differences exist, the basic principles of artificial respiration are the same for all ages. These are as follows:

1. Maintenance of an adequate airway by:
  - a. Prone position for drainage
  - b. Extension of neck with forward traction on mandible
  - c. Gentle suction
  - d. Intubation or tracheotomy
2. Institution of adequate ventilation as quickly as possible
3. Avoidance of injury to the patient

Severe hypoxia of only a few minutes may lead to irreversible damage, especially to the brain. Fortunately the newborn infant can tolerate hypoxia better than older persons, but, since the duration and severity of intrauterine hypoxia are impossible to gauge accurately, one should not delay resuscitative procedures even in the newborn. Oxygen administration is a useful adjunct, but is no substitute for adequate ventilation.

The methods of producing artificial respiration are (1) manual methods, (2) positive pressure applied to the airway, or negative pressure about the body, (3) rhythmic rock-



ing of the patient, (4) electrical stimulation of the phrenic nerve.

**Newborn Infant.** The normal newborn infant should not require resuscitation. If respiration has not started by thirty to sixty seconds after birth and is not fully established by one to three minutes, the central nervous system is probably depressed. Initially a free airway should be established. For this purpose an oral airway is usually adequate, although under special circumstances, and when an experienced person is available, tracheal intubation may be useful. When intubation is used by unskilled persons, however, more harm than good may be done.

If not expanded, the lungs may most practically be inflated by positive pressure applied by a mask or through the endotracheal tube. The magnitude of the pressure necessary and its duration are variable for each infant. Available data suggest that transpulmonary pressures up to 20 cm. of water are usually safe, but in many instances pressures of 30 to 50 cm. may be necessary for adequate expansion. If such pressures are necessary for expansion of the lungs, even higher pressures will obviously be required for expansion of both the lungs and the chest. Certainly high pressures, if used at all, should be used with caution and for brief periods only (probably for less than 0.5 second). Furthermore, high pressures should be applied only to infants with unexpanded or incompletely expanded lungs.

Pressures may be applied and controlled by a variety of machines and with practice and experience by mouth-to-mouth or mouth-to-tube resuscitation. The latter techniques have the disadvantage that there is a chance of cross infection between the patient and the physician, and pressure is difficult to gauge or control. Since hypoxia causes depression of the respiratory center itself, supplemental oxygen should be supplied in all instances until spontaneous respiration is established. In the newborn particularly, but in anyone subjected to artificial respiration, the effectiveness of the procedure should be checked not only by observation of the excursion of chest and abdomen and auscultation of the lungs, but also, when possible, by measurements of the ventilation.

For the infant whose lungs have never expanded, rocking will accomplish little; subsequently the effectiveness of rocking is in direct proportion to the size of the infant. Hence rocking is of little direct use in small infants as a ventilating maneuver. Central

nervous system stimulants (other than oxygen) are of little or no use and in some instances may be harmful. Tubbing, spanking, jackknifing and manual compression of the thorax are all dangerous and ineffective. Phrenic nerve stimulation produces a more natural type of breathing, but has limited practical use because of the need for special equipment and a trained operator.

**Infants and Older Children.** Since the lungs of older infants and children have already been expanded, other techniques are applicable. Positive pressure (e.g., mouth-to-mouth) is useful once a free airway has been established. In addition, manual compression and expansion of the thorax as in the back pressure-arm lift method or back pressure-hip lift method can produce an adequate ventilation provided there is no respiratory obstruction. Electrical stimulation of the phrenic nerve is more practical than it is in the newborn infant. For more prolonged artificial ventilation the tank type of respirator, endotracheal positive pressure, the rocking bed and special chest-type or cuirass respirators can be used. The cuirass respirators have limited usefulness in infants and small children because the chest is compressed and ventilation may be insufficient. When mechanical artificial ventilation is required for a prolonged period, the patient should be given deep breaths at regular intervals in order to minimize the development of atelectasis.

The effectiveness of various types of ven-

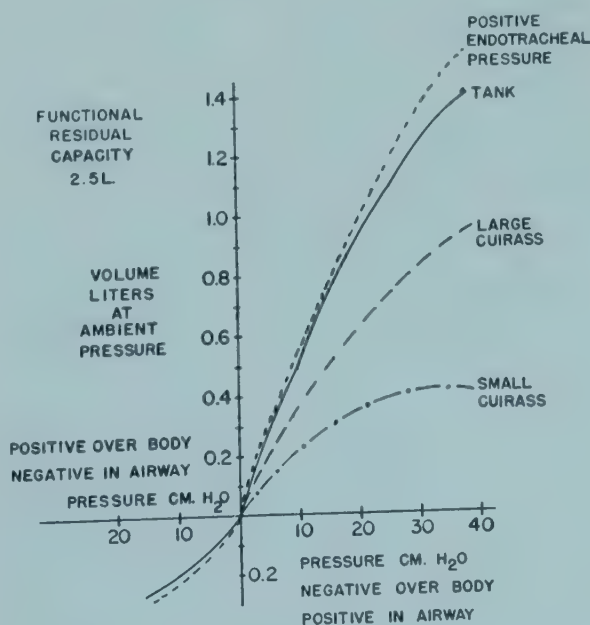


FIG. 211. Effectiveness of breathing machines.

tilating devices is presented in Figure 211. The endotracheal positive pressure technique produces the greatest tidal volume, owing to the compression of the gas within the lungs. The effectiveness of the cuirass respirators varies with the amount of the body that is enclosed within them and the freedom of motion allowed. The rocking beds are not included since there is great variation with the size of the patient.

There is no special pressure that should be used for different age groups. The pressure or degree of tilting should be set so that the required tidal volume or an end-tidal  $P_{CO_2}$  of 40 mm. of mercury is obtained. This requires measuring the tidal volume and comparing it with the predicted values from the nomogram (Fig. 208) or measuring the end-tidal  $P_{CO_2}$ . If the device is unable to produce sufficient pressure at a given frequency, adequate ventilation may be obtained by increasing the frequency, which in turn usually increases the pressure developed. A new calculation from the nomogram will be necessary, since the predicted tidal volume will be different.

## INHALATION THERAPY

Besides oxygen, the most frequently used agents for inhalation therapy are water, antibiotics and bronchodilators, which are administered in compressed air or oxygen.

**Oxygen Therapy.** The therapeutic use of oxygen is not without danger. Inhalation of oxygen in concentrations greater than 60 per cent for a period of days is toxic in animals and human beings. In premature infants concentrations of oxygen over 30 per cent increase the incidence of retrolental fibroplasia. These potential dangers do not, however, preclude the use of oxygen for infants with respiratory distress when it is specifically indicated to prevent severe hypoxia.

A less well appreciated effect of oxygen therapy occurs when patients suffering from chronic underventilation are given oxygen to combat cyanosis. These patients may stop breathing and die because the drive to breathe, which came from the low blood oxygen tension, is removed. Owing to chronic underventilation, blood carbon dioxide tension may be high and the respiratory center no longer responsive to carbon dioxide. If the carbon dioxide is high initially ( $P_{aCO_2}$ ), about 80 mm. of mercury, a further increase may reach narcotic levels, and the patient will become comatose. In such a situation artificial respiration may be necessary.

**Water.** The administration of air or oxygen supersaturated with water has long been used when there is evidence of increased or tenacious secretions and narrowing of the larger air passages (as with laryngitis or tracheobronchitis). Similarly, inhalation of water vapor is important in the management of patients breathing through a tracheostomy tube, when the normal humidifying action of the upper respiratory system is bypassed.

The use of vaporized water in peripheral pulmonary disease is less certainly effective. The air from the lower part of the trachea to the periphery of the lung is normally saturated with water at body temperature, whereas air saturated with water at room temperature (24° C.) is only 50 per cent saturated when raised to body temperature. Thus a saturated atmosphere does not necessarily supply saturated gas to the peripheral air passages. The effect, if any, of water vapor on peripheral pulmonary disease of all age groups needs further critical study. When used, water vapor is best administered as a cool mist.

**Antibiotics.** Inhalation of antibiotics in compressed air or oxygen (aerosols) is occasionally useful in the control of severe, diffuse pulmonary disease, (e.g., cystic fibrosis of the pancreas). In most instances, however, the same agents may be as effective and more easily administered orally or parenterally. Furthermore, the distribution of ventilation, as well as the droplet size, the growth of the droplets, the polarization of the particles, and possibly other factors determine the penetration of an aerosol into the smaller pulmonary units and thus impose limitations on aerosol therapy.

**Bronchodilators.** A number of bronchodilators can be effectively administered by inhalation. This route has the physical advantage that it is easy for the patient and the psychologic advantage that it is a means of treating directly the bronchoconstriction and thus the patient's symptoms. The disadvantage of this route is the difficulty in controlling dosage.

BENJAMIN GREELEY FERRIS, JR.  
CHARLES DAVENPORT COOK

## REFERENCES

- Barcroft, J.: *Researches on Pre-Natal Life*. Springfield, Ill., Charles C Thomas, 1947.
- Colville, P., Shugg, C., and Ferris, B. G., Jr.: *Effects of Body Tilting on Respiratory Mechanics*. *J. Applied Physiol.*, 9:19, 1956.



- Comroe, J. H., Forster, R. E., DuBois, A. B., Briscoe, W. A., and Carlsen, E.: *The Lung*. Chicago; Year Book Publishers, Inc., 1955.
- Day, R., Goodfellow, A. M., Apgar, V., and Beck, G. J.: Pressure-Time Relations in Safe Correction of Atelectasis in Animal Lungs. *Pediatrics*, 10:593, 1952.
- Engstrom, I., Karlberg, P., and Kraepelien, S.: Respiratory Studies in Children. I. Lung Volumes in Healthy Children, 6-14 Years of Age. *Acta paediat.*, 46:277, 1956.
- Ferris, B. G., Jr., Mead, J., Whittenberger, J. L., and Saxton, G. A.: Pulmonary Function in Convalescent Poliomyelitis Patients. III. Compliance of the Lungs and Thorax. *New England J. Med.*, 247:390, 1952.
- Ferris, B. G., and Smith, C. W.: Maximum Breathing Capacity and Vital Capacity in Female Children and Adolescents. *Pediatrics*, 12:4, 1953.
- Ferris, B. G., Whittenberger, J. L., and Gallagher, J. R.: Maximum Breathing Capacity and Vital Capacity of Male Children and Adolescents. *Pediatrics*, 9:659, 1952.
- Gilson, J. C., and Hugh-Jones, P.: Measurement of the Total Lung Volume and Breathing Capacity. *Clin. Sc.*, 7:185, 1949.
- Helliesen, P. J., Cook, C. D., Friedlander, L., and Agathon, S.: Studies of Respiratory Physiology in Children. I. Mechanics of Respiration and Lung Volumes in 85 Normal Children 5 to 17 Years of Age. *Pediatrics*, 22:80, 1958.
- Karlberg, P.: in Transactions of the second (1957) Macy Conference on "Physiology of Prematurity." To be published.
- Mead, J., McIlroy, M. B., Selverstone, N. J., and Kriete, B. C.: The Measurement of Intraesophageal Pressure. *J. Applied Physiol.*, 7:491, 1955.
- New York Medical Society: Resuscitation of New-born Infants. *J. Obst. & Gynec.*, 8:3, 1956.
- Otis, A. B., and others: Mechanical Factors in Distribution of Pulmonary Ventilation. *J. Applied Physiol.*, 8:427, 1956.
- Radford, E. P., Jr., Ferris, B. G. Jr., and Kriete, B. C.: Clinical Use of a Nomogram to Estimate Proper Ventilation during Artificial Respiration. *New England J. Med.*, 251:877, 1954.

## AGE AS A FACTOR IN RESPIRATORY DISTURBANCES

Respiratory disturbances constitute one of the major problems of pediatric practice. Some of these disorders are confined to the very young infant, and others occur most frequently in that age group. Furthermore, the clinical patterns of most respiratory diseases are influenced by the patient's age.

**Newborn Period.** Respiratory difficulties may appear at birth (p. 297); though they are largely mechanical or chemical (anoxic) in origin, they may be infectious. Pneumonic infection may occur in utero during prolonged labor, especially when there has been premature rupture of the membranes, or may be acquired during or soon after birth. In some instances pneumonic infections are secondary to disturbances in pulmonary mechanics, as, for example, those resulting from aspiration of large amounts of debris in amniotic fluid or inadequate respiratory excursions in weak, premature or cerebrally damaged infants. Establishment of infection may also be facilitated by congenital anomalies of the upper respiratory tract or of the lungs.

Mechanical disturbances are produced principally by conditions which result in obstruction of the respiratory tract or in depression of the respiratory center. Completely obstructive *malformations* of the respiratory tract are rare; those which cause partial obstruction and may produce laryngeal stridor are not common. One of the infrequent causes of obstruction is *aspiration* of amniotic fluid containing debris such as meconium, epithelial cells and vernix caseosa during the

process of birth. Probably infants aspirate amniotic fluid without ill effect, but when there is asphyxia during prolonged labor, there does appear to be a relation between the pathologic changes and the inhalation of foreign material in the amniotic fluid. The *pulmonary hyaline membrane syndrome* (p. 324) is an important but inadequately understood cause of death in the newborn, especially in premature infants and those of diabetic mothers. *Depression of the respiratory center* may result from direct injury in the area of the medulla or from anoxia (p. 321). Either factor may raise the threshold of stimulation of the respiratory center, resulting in weak and irregular respirations, often with relatively long periods of apnea.

*Atelectasis* is frequent in the newborn infant. Its persistence or secondary occurrence may be facilitated by such conditions as weak respiratory excursions and blockage of the bronchial tree by aspirated material.

**Infancy.** Disturbances of the neonatal period may persist, but this is not particularly common except in cases of congenital laryngeal stridor and of chronic pneumonitis. A pneumonitis which originates within the first few weeks of life and persists should be thoroughly studied for the primary or underlying disturbance. This may be (1) mechanical disturbances related to birth, (2) pulmonary changes associated with cystic fibrosis of the pancreas, (3) stasis secondary to obstructive anomalies within or without the respiratory tract, (4) aspiration of foreign material

such as foreign bodies, food and lipid substances, or (5) a viral infection with secondary bacterial infection.

After the newborn period infection becomes the most important etiologic factor, although it must not be forgotten that this is the age period when aspiration of foreign bodies, of lipid substances and of zinc stearate is at its peak. The common cold takes on added importance because of the frequency of systemic manifestations, the attendant difficulties in nursing due to nasal obstruction, and the high incidence of otitis media and of secondary pneumonia. Throat infections are relatively less frequent than in older children, but the complication of retropharyngeal abscess occurs more frequently. Laryngeal infections more readily cause serious obstruction than in older children, and congenital laryngeal stridor is to a considerable extent limited to the period of infancy.

Pneumonia in infants is a different clinical entity than in children beyond the age of three or four years. The incidence in infants is high; the mortality was excessively so before the introduction of the sulfonamides and antibiotics and is still considerably greater than in older children. During infancy even pneumococcal pneumonias often have a lobular or disseminated distribution in contrast to the frequency of lobar involvement in older children and adults. Pulmonary infections, particularly in infants, can be divided into two groups on the basis of the clinical response. In one the principal clinical manifestation is toxicity; in the other the disturbance is primarily respiratory embarrassment. Both factors, of course, may be and frequently are present in the same infant. The bacterial pneumonias are more liable to produce toxic symptoms in excess of those of respiratory embarrassment; whereas the acute condition variously designated as interstitial pneumonia, bronchiolitis or capillary bronchitis tends, especially in its earlier stages, to cause a disproportionate amount of respiratory embarrassment. Owing to the effectiveness of the

antimicrobial drugs against most of the pathogenic bacteria of the respiratory tract, the incidence and severity of bacterial pneumonias have been greatly decreased. The exception to this situation is the increasing incidence and severity of pneumonia caused by antibiotic-resistant strains of *Staphylococcus aureus* (pp. 344 and 792).

Acute bronchiolitis, asthma, aspiration of amniotic fluid or zinc stearate powder, pulmonary infection associated with cystic fibrosis of the pancreas, and chronic passive congestion secondary to cardiac lesions, as well as widely disseminated bacterial infections, can be responsible for obstructive emphysema and patchy atelectasis. Secondary bacterial infections are frequent complications.

**Childhood.** Respiratory infections gradually take on different characteristics during childhood and eventually, in the preadolescent years, tend to assume the clinical pattern characteristic of the particular infection in adults. The incidence of the common cold increases with entrance to school, but there is less ear involvement and fewer systemic symptoms; even fever becomes relatively uncommon in the latter part of childhood. Throat infections become more frequent, and the tonsil and adenoid problem comes to the fore. The clinical syndromes of acute laryngotracheobronchitis and of acute bronchiolitis are uncommon after three or four years of age; when they do occur, they are clinically less severe. Childhood is the "safe age" of pneumococcal pneumonia; between the ages of four and twelve years the total mortality rate without treatment is only about 5 per cent, and with antimicrobial therapy it is less than 1 per cent. In the latter part of childhood there is a significant increase in the incidence of chronic suppurative lesions, especially of sinobronchitis and, to a less extent, of bronchiectasis. As puberty is approached, the problem of tuberculosis becomes more important, in part because of the stress that physiologic adjustments make upon the growing child.

## THE UPPER RESPIRATORY TRACT

### THE NOSE

#### MALFORMATIONS OF THE NOSE

Congenital anomalies, in contrast to acquired malformations, are uncommon. Such gross anomalies as an accessory nose or complete

absence of the external nose are extremely rare. There may be narrowing of the nasal passages, and occasionally there is complete obstruction of the anterior or posterior nares, more frequently of the latter. Rarely, super-



numery teeth may occur in the nose, or teeth may grow in from the maxilla and be absent from their usual site.

*Choanal atresia* may be unilateral or bilateral; though usually membranous, it may be bony. If it is bilateral, there is difficulty or inability on the part of the infant to suck, and the mouth is constantly open. There may be constant dyspnea, presumably because the infant cannot accommodate to mouth breathing. When the obstruction is unilateral, it may pass unnoticed until infection develops and persists on the affected side with drainage only anteriorly. The obstruction is demonstrated by passing a sound or probe. Bilateral obstructions should be relieved as promptly as possible. Perforation of the membranous obstruction may be performed with direct vision through a nasoscope, but bony obstructions require a more extensive surgical procedure. When the obstruction is unilateral, it is desirable to postpone the operation until the infant is in a satisfactory physical condition and is gaining weight adequately.

*Deviation of the nasal septum* is more often an acquired than a congenital condition and is not common in young children. If at all possible, operation should be deferred until the child is fourteen or fifteen years of age. If operative correction seems imperative before this age, a method should be used which preserves the septal tissues, since, otherwise, external deformities of the nose may result. Perforation of the nasal septum is more likely to be due to such infections as syphilis or tuberculosis than to congenital defects. Malformations of the septum, of the floor of the nose and even of the external nose are frequently associated with harelip and cleft palate.

An *encephalocele* protruding through a defect in the cribriform plate into the nasal cavity is a rare anomaly, but should be differentiated from polyps and tumors of extracranial origin.

## FOREIGN BODIES IN THE NOSE

Foreign bodies of various sorts such as peas, cherry stones and beads are frequently introduced into the nose in early childhood. Larvæ of flies are occasionally deposited in the nose. The foreign body is situated at first well forward, but unskillful efforts of the patient or others to remove it may push it farther inward. The early symptoms are obstruction to respiration, pain and, perhaps, sneezing from the local irritation. If the object is

smooth and hard and not liable to swell by absorption of liquid, it may remain for weeks or months without producing other symptoms. Generally, however, evidences of increasing irritation soon develop, with swelling of the mucous membrane, increasing obstruction and a purulent bloody discharge. The fact that the discharge and other symptoms are unilateral strongly suggests the presence of a foreign body, and examination with a speculum or nasoscope is indicated. forcible blowing of the nose with the unaffected nostril compressed is sometimes effective if the object has been present for only a short time. When the foreign body is more securely lodged, the nasal cavity should be sprayed with a local anesthetic before removal under direct vision is attempted.

## NEOPLASMS OF THE NOSE

The most frequent nasal growths are polyps (see *encephalocele*, above). They produce obstructive symptoms and are often associated with chronic nasal discharge and allergic rhinitis. Treatment consists in their removal and in attention to the chronic rhinitis and/or any allergic factor. Neoplasms are rare in early life and are described on page 1347.

## EPISTAXIS

**Etiology.** Nosebleed is rare in the neonatal period and in infancy, is common in childhood, and decreases in incidence after puberty. Rhinitis, foreign bodies, polyps, external trauma, forcible blowing and picking of the nose may be inciting causes. A persistent, bloody, purulent nasal discharge is a characteristic manifestation of nasal involvement in syphilitic and diphtheritic infections. Adenoid overgrowths may be associated with congestion which incites nasal bleeding. Varicosities or telangiectases of the mucous membrane of the septum, at times associated with a small area of ulceration, are frequent factors in recurrent bleeding. The strain of physical exercise or mental excitement in children with a local nasal lesion may be sufficient to instigate nasal bleeding. Any condition (cardiac, vascular, renal or emotional) which causes elevation of the blood pressure may be responsible for nasal hemorrhage; during the active phase of rheumatic fever there is frequently epistaxis with or without hypertension. Nasal bleeding may occur in association with any of the blood

dyscrasias, and occasionally is associated with a variety of infectious diseases such as typhoid fever, diphtheria, scarlet fever, measles, influenza and malaria. Near the age of puberty it is not infrequent in girls, when it may constitute vicarious menstruation.

**Clinical Manifestations.** Usually the hemorrhage comes without warning, and the blood flows slowly from one nostril or sometimes from both. Exceptionally, it may be in large amount, especially in some of the systemic hemorrhagic diseases, and it may even be fatal. When it occurs at night, the blood may be swallowed and the diagnosis made only from the vomiting of blood or its passage in the stools or by rhinoscopic examination. Generally an attack of epistaxis stops spontaneously.

**Treatment.** The child should be kept as quiet as possible in a semi-erect position, have the clothing around his neck loosened, and be cautioned against blowing his nose. An ice bag may be applied over the bridge of the nose. A few drops of a solution of epinephrine (1:1000), with or without 1 per cent cocaine added, may be applied to the nasal mucous membrane with a cotton applicator. It may be possible to detect the bleeding area and to cauterize it with silver nitrate. Packing the nares is necessary in more severe instances; Gelfoam may be used. Blood transfusion may be indicated if much blood has been lost. Rarely it becomes necessary to ligate the internal maxillary arteries or even the carotid. An attempt should be made to determine the underlying factor.

## ELONGATED UVULA

Persistent enlargement of the uvula is rare; it may be congenital or may result from a chronic upper respiratory tract infection. The long uvula coming into contact with the base of the tongue produces an annoying cough and a constant desire to clear the throat.

These symptoms tend to be exaggerated when the child is lying on his back. Enlargement associated with chronic infection may disappear with eradication of the infection. Otherwise, amputation of the tip of the uvula may be indicated.

## INFECTIONS OF THE UPPER RESPIRATORY TRACT

### GENERAL CONSIDERATIONS OF ACUTE INFECTIONS

Infections of the upper respiratory tract constitute a major segment in the illnesses of infants and children. The epidemiologic aspects are more important in acute infections than in chronic ones. Acute infections tend to be widespread in a group, be it family, school or community. Understanding of a specific acute infection is related to identification of the etiologic agent, when possible, its means of spread, and the variations in its clinical patterns. By contrast, the problems of chronic respiratory disease are to a much greater extent centered in the individual patient and include such factors as susceptibility to infection, anatomic abnormalities of the nasopharynx, allergy, and perhaps other factors related to chronic involvement of tonsils, adenoids and sinuses.

Acute infections may be caused by viruses or bacteria; nearly all the acute infections of the nose and nasopharynx are caused by viruses. Although bacteria are more fre-

quently responsible for pharyngeal and laryngeal infections, most of the acute infections in these areas are also of viral origin.

### ETIOLOGIC CONSIDERATIONS OF NEWLY ISOLATED VIRUSES

More new viruses are being associated with infections of the respiratory system than there are well defined clinical and epidemiologic entities with which to match them. In recent years at least nine viruses or groups of viruses other than influenza have been reported as possible causes of respiratory tract disease. These include the large group of adenoviruses, the group A Coxsackie viruses, certain miscellaneous viruses such as the respiratory syncytial virus, "2060" virus, JH virus and an ECHO virus, "JV-1," as well as the following myxoviruses: the croup-associated virus, the hemadsorption viruses and Sendai virus (newborn pneumonitis virus, hemagglutinating virus of Japan or influenza D). All these



agents have been recovered from the respiratory tracts of children or adults during respiratory infection. However, more is known about some than about others in their etiologic relation to respiratory tract illness.

The adenoviruses, for example, are extremely common inhabitants of the respiratory tract; the group includes the cytopathogenic agents which were originally isolated from tonsils and adenoids, and other related viruses which have subsequently been found in cases of conjunctivitis and pharyngitis and from fecal material and certain tissues at necropsy. There is good evidence that one of the adenoviruses, type 3, causes so-called *pharyngoconjunctival fever*, an acute illness characterized by fever, pharyngitis, conjunctivitis and posterior cervical lymphadenopathy. Adenoviruses types 4 and 7 have been established as causes of an acute febrile disease of the respiratory tract in military recruits characterized by fever, chills, headache, generalized aches and pains, hoarseness and irritation of the throat. The clinical pattern is considered relatively specific by those dealing with military personnel. Types 4 and 7 viruses have rarely been isolated from children. Apparently adenoviruses types 1, 2, 3, 4, 5 and 7 may cause pharyngitis, but sufficient cases have not been reported to allow a full clinical description. These viruses, particularly types 1, 2 and 5, have been found in up to 90 per cent of tonsils and adenoids removed surgically in several parts of the world. This observation permits the speculation that after an acute infection with adenoviruses a person may harbor the virus in a "latent" state for an indefinite time.

The clinical relation of group A Coxsackie viruses to a particular type of vesicular pharyngitis in children, herpangina (p. 528), is now well accepted.

Two myxoviruses, hemadsorption virus, types 1 and 2, have recently been identified, and controlled studies strongly suggest that they may be common causes of respiratory tract disease in children. In one study up to 33 per cent of infants with a "croup syndrome" were infected with type 2 hemadsorption virus.

Clinical and epidemiologic studies on the other viruses mentioned have not been of an order to permit definitive deductions about the frequency with which they cause respiratory tract disease. The croup-associated agents have been isolated in several parts of the world from children with croup as well as

from children with other manifestations of respiratory tract illness. In one survey 90 per cent of adults had hemagglutination inhibition antibodies against these viruses. Sendai virus has been found in association with pneumonitis in infants, a meningitis-like syndrome in infants, and an influenza-like illness in adults. This agent is serologically related to hemadsorption virus, type 2, by complement fixing, but not by hemagglutination inhibition and antibody neutralization tests. Limited data suggest that the respiratory syncytial virus, identical with a causative agent of coryza in chimpanzees, may be a causative agent of bronchopneumonia. Similarly, ECHO virus, JV-1, has been related to mild respiratory illness. In two different outbreaks the "2060" virus was recovered from naval recruits with mild respiratory illness, and sixteen of forty-seven affected patients showed a rise in neutralizing antibody to this virus in their serums after the illness. The prevalence of antibody to "2060" virus increases with advancing years. JH virus has been described in association with symptoms of low grade fever, malaise, coryza, sore throat and a cough; 20 per cent of serums from persons over the age of eight years contained neutralizing antibodies to this virus. There is some evidence to suggest that the "2060" virus and JH virus are serologically related to each other.

It would appear that a number of newly isolated viruses may affect the upper respiratory tract in a common way. A great deal of combined clinical, laboratory and epidemiologic study is necessary before the clinical patterns produced by these recently identified viruses, as well as by those yet to be identified, can be adequately defined.

In spite of the frequency and importance of acute infections of the upper respiratory tract, it is impossible to identify many of them as distinct clinical entities. This is not surprising, since the tissues of the nose, pharynx and larynx, as well as those of the tracheobronchial tree, are in direct continuity, and they connect with the paranasal sinuses and middle ear. Further, all these structures have limited ways in which they can respond to noxious agents of any sort. Although some infecting agents tend to have a predilection for certain portions of the respiratory tract, most of them tend to produce symptoms in the several anatomic divisions of the upper respiratory tract, often in descending order.

For clinical purposes it is deemed advisable

to classify respiratory infections on the basis of their principal location as rhinitis, nasopharyngitis, pharyngitis or laryngitis.

### ACUTE NASOPHARYNGITIS

(THE COMMON COLD, UNDIFFERENTIATED ACUTE RESPIRATORY DISEASE AND OTHER VIRAL INFECTIONS)

The designation "acute nasopharyngitis" is used principally as a substitute for the clinical designation "the common cold." This infection, which characteristically involves the nasal accessory sinuses as well as the nasopharynx during the acute phase, is the most frequent one of infants and children. Its importance in pediatric practice depends not only upon this factor, but also upon the frequency with which serious complications result. The clinical pattern of the "common cold" in infants and small children is quite different from that in older children and adults.

**Etiology.** It seems likely from the work of Dochez and others that the common cold is a specific contagious disease caused by a filtrable virus or a group of viruses responsible for the initial catarrhal symptoms and for transmission of the disease. The characteristic secondary purulent stage is, in turn, produced by bacterial invaders. Though this latter phase may be a means for dissemination of pathogenic bacteria, the infective period of the cold, *per se*, is apparently limited to some hours before and to only a day or two of the initial phase.

Secondary bacterial invaders are apparently responsible for the purulent stage of the common cold, and perhaps to a large extent for the complications in the sinuses, ears, mastoids, lymph nodes and lungs. The more frequent bacterial invaders are the Pneumococcus, the hemolytic Streptococcus, *H. influenzae* and the Staphylococcus, the last especially in small infants.

**Contributory Factors.** A number of factors appear to have contributory roles in the development of colds, but their relative importance is not clear. There appears to be a variation in *susceptibility* even in infants. But often what appears to be an increased susceptibility may represent frequent exposure to infection or acute exacerbations of a chronic infection.

Age is a factor in severity and complications, but the evidence of its relationship to susceptibility is less definite. It has been stated that there is an insusceptibility to colds

in the neonatal period and that not until four to six months of age does the infant have a high susceptibility. It may be that the low incidence among newborn infants mainly reflects the relative infrequency of their exposure; infection does occur at this age.

The state of *nutrition* would appear to be a greater factor in determining severity or the development of complications than in affecting susceptibility to infection.

Dust or other *irritants*, including specific allergens, may produce sneezing and a copious watery nasal discharge, but this is not to be confused with the common cold.

**Chilling** of the body, exposure to cold and dampness, and wet feet have long been associated with nasal disturbances. They do have a vasomotor effect and reduce the temperature of the nasal mucous membrane by several degrees. Initially there is a vasoconstriction followed by a period of vasodilatation. Under such circumstances many persons have such symptoms of nasal irritation as sneezing and serous discharge, and those with chronic infections might well have exacerbations. If the "cold" virus were a recent invader, the effects of exposure would most likely be distinct contributory factors.

**Fatigue** and *emotional disturbances* may also temporarily lower resistance.

**Epidemiology.** There is practically universal susceptibility to acute nasopharyngitis, and it has been estimated that the incidence in children is three to six attacks a year. Infections tend to occur in cycles with several peaks of incidence during the year. The first of these occurs shortly after the opening of school in September and October, another in January and February, and a third in April and May. The incidence is highest during periods of increased housing and the school term.

**Pathology.** Initially there is only edema of the submucosa, quickly followed by infiltration with leukocytes which are principally mononuclear at first, with polymorphonuclear cells predominant by the second or third day. There is separation and sloughing of the epithelial cells, with the result that practically the entire nasal epithelium is destroyed. After the acute phase the remaining epithelium proliferates, and the epithelial surface is renewed.

**Clinical Manifestations.** The clinical pattern in infants and small children differs from that in older children and adults. In the first two or three years of life, except perhaps in the first month or two, fever is a



prominent symptom, whereas in older children, especially after eight to ten years of age, the clinical course simulates that of adults and is usually afebrile, or at most there is only a low grade fever. Young children are also more prone to complications, especially otitis media and pneumonia, so that the "cold" problem is a serious one in the first few years of life. Persistent infection of the sinuses is, however, more frequent in older children than in infants.

**In older children.** Characteristically, the initial symptoms are dryness and irritation in the nose and, at times, in the pharynx. This is followed within a few hours by chilly sensations, muscular aches, sneezing and a watery nasal discharge. Headache, general malaise, anorexia and low grade fever in varying combinations may be present. Within one to three days the secretions become thicker, and eventually purulent. The discharge is irritating and reddens the edges of the nostrils and the upper lip. The nasal obstruction makes mouth breathing compulsory, and the drying effect on the throat increases the sensation of soreness. The duration of the acute phase varies from one to two weeks.

**In infants.** The onset in the infant is usually characterized by fever, in which the temperature may be 102° to 104° F., and by irritability and restlessness. The local manifestations are similar to those described for the older child with the addition of vascular congestion of the eardrum in most instances during the first day or two whether or not there is otitis media subsequently. Interference with sucking becomes a problem because of the nasal obstruction. Fever may be present only at the onset, or may last two or three days and return again if there are purulent complications. Vomiting is not uncommon, and mild diarrhea may be a manifestation. In the newborn infant the general manifestations, especially the fever, may be less marked.

**Differential Diagnosis.** The principal conditions to be considered in the differential diagnosis are the initial phases of certain of the acute contagious diseases, influenza, acute exacerbations of chronic upper respiratory tract infections, allergic rhinitis, vasomotor responses to cold and exposure, and, in young infants, syphilis.

The initial manifestations of *measles* and *pertussis* in particular and, to a less extent, of *poliomyelitis* are those of nasopharyngitis. *Scarlet fever* and *pharyngeal diphtheria* are less likely to be confused with "the common cold," since their respiratory symptoms are

predominantly pharyngeal. When there is a persistent nasal discharge, bloody or otherwise, in the first few months of life, the possibility of *congenital syphilis* must be considered, and that of *nasal diphtheria* at any age.

The milder cases of viral *influenza* of the respiratory type may be indistinguishable from other forms of nasopharyngitis, although as a rule influenza is attended with a degree of prostration out of proportion to the respiratory symptoms.

**Allergic rhinitis** should always be considered when there are frequent "colds." If the nasal discharge does not proceed to the purulent stage, an allergic etiology is likely, but the possibility of allergy is not eliminated even when there are frequent or persistent attacks of purulent rhinitis. The demonstration of large numbers of eosinophilic cells in the nasal secretions and a distinct pallor of the nasal mucous membrane are suggestive evidence in favor of allergy, but the proof rests in the detection of the specific allergen and improvement following its removal or antiallergic treatment.

**Complications.** The principal complications occur by direct extension from the nose with involvement of the accessory sinuses, ears, mastoids, throat, larynx, bronchi and lungs. Slight enlargement of the cervical lymph nodes is common; less often it is extensive, when there may be suppuration. *Middle ear infection* of some extent occurs with a high degree of regularity in infants and small children, but is less frequent in older children. Direct visualization of the eardrum is an essential part of the examination of the infant with the common cold, especially when the fever continues high after the first day or two or when there is a recurrence of it. *Bronchitis* and *pneumonia* not only occur more frequently in infants than in older children, but are also more serious. In children who have a tendency to spasmodic laryngitis acute nasopharyngitis is an effective trigger mechanism. The *paranasal sinuses* are probably involved in all nasal infections; persistence of the infection in them after the acute phase is not common, but is more frequent in older children than in infants.

**Prevention.** There is no adequate means for the prevention of epidemic nasopharyngitis other than that of avoidance of contact with an infected person. In older children and adults such prevention is practically impossible. Some degree of isolation can be provided for the infant, however, and every

effort should be made to lessen his chances for infection, owing to the relative severity of the infection in this age group. Vaccines are of no value, nor is there any evidence that so-called hardening processes are effective.

**Treatment.** Treatment is symptomatic. There is no need for antimicrobial therapy except when complications develop, and their use otherwise is not advisable.

Rest in bed is advisable during the febrile period. Sleep, especially in infants and small children, may be disturbed by the fever and by nasal obstruction. Aspirin is often helpful in reducing the restlessness of infants as well as the aching and malaise of older children. It may be prescribed in doses of 60 mg. (1 grain) per year of age up to five years with doses of 0.3 gm. (5 grains) in older children, two or three times a day, for the first day or two of the infection. Excessive and protracted use should be avoided, especially in infants, owing to the danger of salicylate intoxication. A barbiturate to induce sleep is rarely necessary if the nasal obstruction is relieved.

Though nasal instillations have been much abused, they do have merit. The provision of a patent nasal airway not only decreases the restlessness, but makes it possible for the child, and especially the infant, to eat more satisfactorily. Ephedrine in aqueous solution, preferably a buffered one, or one of the many commercial ephedrine or ephedrine-like nasal solutions may be given. Solutions of one-half to one-quarter the strength for adults should be prescribed for infants and small children. Oily vehicles should be scrupulously avoided, owing to the danger of lipoid pneumonia; preparations containing sulfonamides and/or antibiotics are not recommended. Instillation of the drops should be done only when there is obstruction, not oftener than every three hours, and such frequency should not be continued for more than two or three days. A good plan is to instill the drops fifteen to twenty minutes before feedings and at bedtime. Often a single instillation produces shrinkage of the mucous membrane only in the anterior part of the nasal cavity; if a second instillation is made within five or ten minutes, it may increase the effectiveness by shrinking the posterior part. When the edema of the mucous membrane is marked, better results may be obtained by introducing the shrinking solution as far as the nasopharynx on a cotton-wrapped flexible metal applicator which is permitted to remain in position for a few minutes. Care should be taken that the

cotton extends beyond the anterior nares when the applicator is completely inserted. The Proetz or Parkinson displacement techniques may be used in older children. Bottles containing nose drops should not be used for more than one person, nor for more than one infection, since they may become contaminated with bacteria and be a source of secondary infection. Older children may use inhalers if their frequent and prolonged use is avoided.

Nasal drainage is a problem in infants, since they cannot "blow their noses." Best drainage is provided by placing the infant on his abdomen, provided this position does not tend further to embarrass respiration. Raising the head of the bed facilitates anterior drainage somewhat, but increases the likelihood of pulmonary aspiration and hence of pneumonia; for this reason it is preferable to raise the foot of the bed. Various types of suction apparatus, both intranasal and extranasal (with suction cups), have been used, but they are annoying to the infant, not very effective and not without danger. The humidity of the air should be maintained at a high level, preferably 80 to 90 per cent.

Both infants and children tend to have some loss of appetite and should be permitted to determine the amount of food taken and, to a considerable extent, the type. Attempts to force food at such times are a frequent cause of persistent feeding difficulties. Purgation is to be condemned, and cathartics are to be prescribed only when definitely indicated. Fluids, including fruit juices, should be offered frequently, but forcing them has no merit. The intake of water-soluble vitamins should be maintained at usual levels.

A convalescent period of a few days after the acute phase is to be commended, but unfortunately is not common practice. Isolation of the child is important not only to protect others, but also to lessen the chances of secondary infection of the child himself. The treatment of such complications as otitis media, sinusitis and pneumonia is discussed under their respective headings.

## ACUTE PHARYNGITIS

### BACTERIAL AND NONBACTERIAL (VIRAL)

Acute infections of the throat are not common in the first year or so of life, but occur frequently thereafter. Though there is some degree of throat involvement in all acute upper respiratory tract infections, including "the common cold," the various grippal infec-



tions and most of the acute contagious diseases, the conditions under discussion here are those in which the principal involvement is in the throat. Because they are discussed in detail elsewhere, diphtheria, scarlet fever, herpangina and infectious mononucleosis are not described here.

**Etiology.** In the past acute throat infections were considered to be bacterial in origin, with members of group A hemolytic *Streptococcus* responsible for most of them. Clinical, bacteriologic and epidemiologic studies now indicate that nonbacterial agents, presumably viruses, are responsible for the majority of pharyngeal infections. Clinically, certain distinctions between bacterial and nonbacterial throat infections have been described, but they do not permit an etiologic diagnosis. When, however, a preponderance of a pathogen such as the beta hemolytic *Streptococcus*, group A, the *Pneumococcus* or type b *H. influenzae* is demonstrated in a bacterial culture early in the course of the disease, and when the clinical findings are compatible and there is a polymorphonuclear leukocytosis, an etiologic diagnosis is justified. Except for group A Coxsackie viruses in herpangina, adenovirus type 3 in pharyngoconjunctival fever and adenovirus types 1, 2, 3 and 5 in some cases of pharyngotonsillitis, viral agents have not been identified, and the evidence that they may be responsible for exudative lesions of the pharynx and tonsils is indirect.

**Clinical Manifestations.** *Nonbacterial exudative tonsillitis and pharyngitis* is generally a mild disease of short duration. In contrast to the typical case of bacterial pharyngitis, the onset tends to be gradual, the more common early complaints being feverishness, headache and anorexia. Sore throat, hoarseness and cough, often productive, are present in the majority of patients and tend to be at their peak by the third or fourth day of illness. Evidences of inflammation are not severe as a rule. There are moderate degrees of vascular injection and often a follicular type of exudate, in which the individual lesions usually do not coalesce. The exudative lesions may be situated on the individual lymphoid follicles on the posterior pharyngeal wall as well as on the faucial tonsils. Cervical lymphadenopathy may occur, but suppuration does not unless there is secondary bacterial infection. Pulmonary involvement is not common. Leukocyte counts are usually below 10,000 per cubic millimeter with normal differential distributions. Fever usually does not exceed 101° to 102° F. and declines

by lysis, the total duration of the febrile course being three to five days. Complications are infrequent.

In contrast, the onset of *bacterial pharyngitis and tonsillitis* is generally acute, and initially there may be only fever, which tends to be high (102° to 105° F.). Throat symptoms and signs are frequently absent for the first twelve to twenty-four hours, and commonly the complaints or physical findings at this time are inadequate to provide a clue to the diagnosis. There may be headache and vomiting and frequently a general grippal sensation. If the tongue is coated and the papillae are swollen, as they frequently are at this stage, it is impossible to differentiate an acute pharyngitis from the prodromal stage of scarlet fever. Initially, there may be a feeling of dryness in the throat, but actual pain is inconstant. Pharyngeal pain is usually noted by the end of the first day, but its degree varies considerably. It may never be mentioned, or it may be so excruciating that swallowing and speaking are affected. In general, the systemic manifestations tend to become less marked as the throat signs become apparent. In the milder cases the temperature returns to normal within one to three days, and the local manifestations do not persist much longer, but in the severe cases the course may extend for a week or two. The appearance of the throat varies from a moderate inflammatory injection of the tonsils or tonsillar fossae, the pharynx and soft palate to a fiery redness and swelling of these tissues with exudative lesions. The latter may consist of many small areas of exudates (follicular tonsillitis), or there may be one or more relatively large membranous areas. Cervical lymphadenopathy is present in most instances.

The term *streptococcosis*, coined by the Yale group in the 1940's, although not widely adopted as a diagnostic term, does imply descriptions of streptococcal disease in childhood which are worthy of perpetuation. In general it is suggested that infection with the beta hemolytic *Streptococcus* in a manner somewhat analogous to tuberculous infection has its clinical manner of expression altered by an initial invasion of the individual host. Since effective contact with this organism is so frequent, it is postulated that the first infection is most likely to occur within the first few years of life. Subsequent to this first infection (sensitization), the clinical reactions to streptococcal disease tend to be localized, particularly in the throat, with acute manifes-

tations of relatively short duration ("strep throat"). Scarlet fever with its expression of the erythrogenic toxin is included in this secondary infectional pattern, and glomerulonephritis and rheumatic fever are considered systemic manifestations of it. The obvious question in this hypothesis is whether initial infection with one strain of beta hemolytic *Streptococcus* group A will alter the reaction pattern to subsequent infections with other strains.

The following is the description of the clinical patterns by Powers and Boisvert:

In the simplest form, the infant under 6 months shows irregular fever, under 102° F., a thin mucoserous nasal discharge causing some excoriation and crusting around the nostrils and some pharyngeal injection. There may be slight vomiting and diarrhea early in the course and loss of appetite. The acute episode may last less than a week and except for persisting nasal discharge the patient may seem only somewhat peaked and slightly indisposed for . . . five or six weeks. Sometimes the disease, like primary tuberculosis, is almost asymptomatic with little or no complaint.

In the form most frequently demanding medical attention . . . the patients are children between 6 months and 3 years of age; they are more severely ill than those just described. The early symptoms and signs are those of coryza with postnasal discharge, a diffusely reddened pharynx, fever, vomiting, and loss of appetite. For a few days the temperature curve shows elevations of from 100 to 103° F. and continues, in typical cases, to be irregular for . . . four to eight weeks gradually becoming normal. Within a few days of onset the cervical glands begin to enlarge; they are usually modest in size and moderately resistant in consistency, there is some tenderness and pain when the mouth is opened. The course of the adenopathy follows roughly the fever with subsidence in about six weeks in the typical case. This is one of the several "glandular fevers" and "catarrhal fevers." However, marked swelling, reddening, softening, and suppuration may occur at any time in the six weeks' course; this complication is usually unilateral. Catarrhal otitis media, like persisting cervical adenopathy, is so frequently an accompaniment of streptococcal upper respiratory infections in infants that the conditions in some form may be regarded . . . as integral parts of the disease rather than as complications.

These patients have a pasty pallor and are anorectic; they lose weight and are unhappy and querulous; convalescence is slow and return to health often a matter of months. The four to eight weeks' subacute febrile illness and prolonged convalescence constitute outstanding clinical characteristics of the disease.

**Diagnosis.** Bacterial and nonbacterial tonsillitis and pharyngitis cannot be distinguished except as indicated under Etiology by bacterial cultures and other findings. The presence of an epidemic of a particular type of

infection is of course of some benefit in evaluation of the individual patient. The response of the disease to antibacterial therapy is also of limited value in differential diagnosis. Ideally, a throat culture should be obtained in each instance, but this is not practical. When there is a membranous exudate, a culture is necessary in order to eliminate the possibility of diphtheria. Though the onset of acute nondiphtheritic pharyngitis is characteristically more abrupt, the fever higher, and the pseudomembrane more likely to be limited to the tonsillar area, the clinical impression should be supported by bacteriologic data. The throat in infectious mononucleosis may also have a similar appearance. Scarlet fever presents the greatest difficulty, and, until the rash appears, it may be impossible to make a distinction. In herpangina there are characteristically many vesiculoulcerative lesions with an erythematous areola on the anterior pillars, fauces and soft palate.

**Complications.** The inflammation of the cervical and retropharyngeal nodes may proceed to abscess formation. Uncommonly there is an agranulocytosis associated with ulcerative and gangrenous throat lesions (*agranulocytic angina*). Especially in malnourished and debilitated children, there may be secondary and prolonged ulcerative throat lesions from which fusospirochetal organisms may be obtained in large numbers; whether they have a pathogenic role is not established. Peritonsillar abscess is an occasional complication, as are pneumonia, sinusitis, otitis media and meningitis. Acute streptococcal throat infections are the precipitating cause of acute glomerulonephritis and of initial and repeat attacks of rheumatic fever. For this reason the urine should be examined weekly for three weeks after the acute phase of the throat infection, and the child should be observed for manifestations of rheumatic fever. Acute mesenteric adenitis with symptoms of abdominal pain and vomiting is an occasional complication and, when the pain is in the right lower quadrant, may simulate appendicitis.

**Treatment.** For nonbacterial infections the treatment is symptomatic. In proved or suspected bacterial infections, most of which are caused by group A beta hemolytic streptococci, penicillin is the drug of choice and should be given for about ten days. Ideally, the child should be kept in bed during the acute phase and should be isolated. Either hot or cold compresses or ice or hot water bags may be placed about the neck, the choice



(usually cold) depending upon the child's preference. Aspirin is a satisfactory drug for the relief of pain and general discomfort. Dosages may be calculated on the basis of 60 mg. (1 grain) per year of age. Adequate fluid intake should be maintained, but no effort need be made to force the child to eat. The diet should be soft, and chilled or hot substances are as a rule more easily swallowed than those at room temperature.

There are no practical measures for prevention of pharyngeal infection other than isolation and avoidance of contact with known active cases. Sulfonamide or penicillin prophylaxis, however, is justified for children who have had rheumatic fever.

### RETROPHARYNGEAL ABSCESS

This infection is a suppurative lesion in one or more of the retropharyngeal lymph nodes, which is usually secondary to a nasopharyngeal infection. Retropharyngeal abscess is relatively uncommon after the first few years of life. Its incidence has decreased in recent years along with that of other suppurative lesions secondary to respiratory infection. Rarely, the infection may be introduced by a penetrating foreign body, as, for example, a fish bone.

**Clinical Manifestations.** In the well developed case the manifestations are fairly characteristic. The onset is more or less abrupt, following an acute upper respiratory tract infection. There is difficulty in swallowing, and the infant lies with his head retracted or to one side and his mouth open. Respirations are noisy, often gurgling. Fever is usually high, and prostration is likely to be marked. On visual examination the bulge of the posterior pharyngeal wall is apparent if it is situated high in the pharynx.

Digital examination provides more definite information and usually reveals the mass to be greater on one side; the tongue is gently depressed with a tongue blade, and the finger is inserted from the angle of the mouth onto the base of the tongue and into the pharynx. A gag is not necessary. The infant rarely has teeth in the lateral portions of the gums during the age when retropharyngeal abscess is common, and introduction of the finger into the pharynx reflexly keeps the mouth open. The entire procedure should be performed quickly and gently, since not only is the child disturbed by the examination, but also serious damage can be done.

Infrequently the pus may burrow down the

vertebral column, and the bulge of the abscess is then sufficiently low that it is shown only on a lateral roentgenogram. The mass in the pharyngeal area is also demonstrated on a lateral roentgenogram. The roentgenogram does not, of course, provide any indication of whether suppuration has taken place. Non-fluctuant lymphadenitis in the retropharyngeal area may produce shadows similar to those of suppurative lesions. Retrogression of nonsuppurative adenitis is not unusual, and the decision for drainage can be based only on the presence of fluctuation revealed by digital examination.

Suppressive antimicrobial therapy may alter the course significantly. One case with abscess formation of a month's duration has been reported in which the principal complaints were pain on swallowing and stiffness of the neck.

*Cervical caries* may be responsible for a retropharyngeal abscess. Although this is uncommon in infancy, it must be considered in the differential diagnosis. In such cases the onset is less abrupt, the course is longer, the abscess is more medial, there is greater stiffness of the neck, and there are likely to be other signs of spinal involvement.

**Course and Prognosis.** If the abscess is incised as soon as fluctuant, and appropriate antibacterial therapy is given, the prognosis is good. The abscess may rupture externally on the side of the neck or into the esophagus, mediastinum or auditory canal; facial paralysis results from the last complication. The majority of deaths occur in previously unrecognized cases, and sudden death may be caused by edema of the glottis, pressure upon the larynx, rupture into the larynx, or erosion of blood vessels with severe hemorrhage. Other causes of death are pneumonia and pulmonary abscess. When the abscess is secondary to cervical caries, the course is slower, and after operation reaccumulation of pus is likely. There is also greater tendency to burrow, but less danger of asphyxia.

**Treatment.** Antibiotic therapy should be prescribed immediately. If the child is seen before suppuration has occurred, retrogression is often obtained without abscess formation. When the abscess becomes fluctuant, it should be opened, preferably without general anesthesia. After the child has been wrapped firmly in a sheet a gag should be inserted and the head of the operating table lowered to prevent aspiration of the discharging pus. A puncture incision is made where the abscess is pointing, and the pus is removed by suc-

tion. When the abscess has been evacuated, the incision may be lengthened slightly to permit proper drainage. Suction of the pharynx should be carried out frequently after the operative procedure. Should the incision close and an abscess form again, it will have to be reopened. Before the incision is made, however, the fluctuant mass should be aspirated to make sure that hemorrhage has not occurred from erosion of one of the branches of the carotid artery. Incision in such a case might well result in a fatal hemorrhage. When there is active bleeding, the carotid artery, in spite of the possibilities of serious cerebral sequels, may have to be ligated.

### PERITONSILLAR AND RETROTONSILLAR ABSCESES

In contrast to retropharyngeal abscess, peritonsillar and retrotonsillar abscesses (quinsy) are uncommon during infancy and less common during childhood than in young adulthood. The term *peritonsillar* abscess is used for suppurative lesions situated mesial to and in front of the tonsil and usually adjacent to the upper pole, so that the tonsil is pushed backward and the uvula is displaced to the opposite side; the *retrotonsillar* abscess, which is directly behind the tonsil, pushes the tonsil outward into the throat and makes it more prominent. Any of the common pyogenic bacteria may be causative, but the hemolytic *Streptococcus* is the most frequent one. Only rarely do such abscesses occur in children whose tonsils have been removed. Repeated attacks may occur if the tonsils are not removed.

**Clinical Manifestations.** The abscess usually occurs with or follows closely an acute tonsillitis or pharyngitis. If the initial fever has subsided, there is a secondary elevation of temperature ( $103^{\circ}$  to  $105^{\circ}$  F.), and the subsequent course is septic. The pain in the throat is severe and out of proportion to that usually observed in acute throat infections. Difficulty in opening the mouth is a characteristic symptom of peritonsillar abscess, and swallowing and speaking are usually impaired. The pain may radiate to the ear of the affected side, and there may be torticollis with the head turned toward the side of the abscess. Inspection during the early stage shows little except a unilateral prominence in the tonsillar region, but palpation reveals a hard, swollen and tender mass. As the process advances, the affected tonsillar area becomes more prominent, the mucous mem-

brane is red and swollen, and the edematous uvula is displaced to the opposite side of the throat. After several days or a week the abscess points, and fluctuation is demonstrable generally in the region of the anterior faucial pillar. The inflammation may subside without abscess formation when effective antibacterial therapy has been started early. When there is an abscess, spontaneous rupture occurs if it is not incised. Complications are not common, although severe hemorrhage, edema of the glottis and extension of the suppurative process into the neck have been observed.

**Treatment.** Before suppuration has occurred, treatment consists in the local use of an ice bag or hot compresses, hot water bottle or a heating pad, depending upon the preference of the child; such analgesic drugs as aspirin and/or codeine, and full dosage of penicillin or a broad-spectrum antibiotic. When suppuration is present, the abscess should be incised. It is preferable to open the abscess rather than allow it to rupture spontaneously, but one should await definite fluctuation before making the incision. After the abscess has ruptured or has been incised, warm saline irrigations may aid in keeping the oral cavity clean and provide some relief from the discomfort. Three or four weeks after the inflammation has subsided the tonsils should be completely removed in order to prevent subsequent attacks. At this time the prophylactic administration of an antibiotic is indicated.

### SINUSITIS

The maxillary antrums and the anterior and posterior ethmoid cells are present at birth and are usually of sufficient size to harbor infection. Each of the frontal sinuses develops from an anterior ethmoid cell. Though invasion of the frontal bone and pneumatization of the sinuses are demonstrable some time during the first two to four years of life, the frontal sinus is rarely a site of significant infection until the sixth to the tenth year. When there is severe ethmoidal disease in the first few years of life, the development and pneumatization of the frontal sinuses may be curtailed or even completely prevented. The sphenoidal sinus is present at birth; though there are variations in its development, it usually does not assume clinical significance until the third to the fifth year of life.

It can be assumed that the paranasal sinuses are involved in practically all acute nasal infections, but, as a rule, the sinus in-



involvement does not persist after the nasal infection has subsided unless there has been a pre-existing sinus infection. The incidence of both acute and chronic sinus infections increases in the latter part of childhood.

#### ACUTE SINUSITIS

In addition to the general involvement of the sinuses during acute nasal infections, there may be acute empyema of one or more sinuses of sufficient severity to dominate the clinical picture. Serious sinus involvement may occur during acute nasal infection or follow it closely.

**Clinical Manifestations.** The symptoms of acute sinusitis, in addition to those of rhinitis, are fever, localized pain, tenderness or a sense of fullness, headache and, at times, edema over the affected sinus. So-called sinus headaches, which tend to involve the region of the affected sinus, may assist in localization. In sphenoidal sinusitis the headache may be in the suboccipital region; in anterior ethmoidal sinusitis, in the region of the temples and over the eyes; and in posterior ethmoidal sinusitis, over the distribution of the trigeminal nerve, especially over the mastoid area. Unless the sinusal ostia are obstructed, there is a purulent discharge which can be observed directly through a nasoscope. Pus in the middle meatus suggests involvement of the maxillary, frontal or anterior ethmoid sinuses; in the superior meatus, of the sphenoid or posterior ethmoid cells.

In acute ethmoiditis, especially in infants and small children, periorbital cellulitis with edema of the soft tissues and redness of the skin is a common manifestation.

**Diagnosis.** The roentgenogram will reveal an opaque shadow when a frontal or maxillary sinus is filled with pus, but a similar appearance may also be produced by thickening of the lining membrane. Transillumination is not helpful in young children, but in older ones it is, although it has greater limitations than the roentgenographic examination. It is rarely necessary in children to puncture a sinus simply to establish a diagnosis. Clouding of the ethmoid cells may be demonstrated on the roentgenogram in acute and chronic ethmoiditis. Serious complications are otitis media, meningitis, cavernous sinus thrombosis, optic neuritis, orbital cellulitis and abscess, and nephritis.

**Treatment.** Treatment is essentially that of the rhinitis. Shrinkage of the nasal mucous membranes will often facilitate drainage from the sinus. Gentle suction or aspiration may be

used, but may be more of an annoyance than a help, especially in infants. Drainage of a sinus is rarely necessary, but, if there is persistence of local and systemic manifestations, it may be justified. Appropriate antimicrobial therapy should be used in full dosage.

#### CHRONIC SINUSITIS

Chronic infection of the paranasal sinuses should always suggest the possibility of a local or generalized disturbance which facilitates persistence of the infection. Search should be made for nasal deformities and infected and hypertrophied adenoids which might cause obstruction, for infected teeth as a source of maxillary sinusitis, and for such general disturbances as allergy and nutritional and thyroid deficiencies. The incidence of sinusitis is said to be greater in children who have had their tonsils and adenoids removed.

**Clinical Manifestations.** Symptoms of chronic sinusitis vary considerably. Fever, when present, is low grade, and there is frequently malaise, easy fatigability, difficulty in mental concentration, anorexia and malnutrition. Nasal discharge, which may be bilateral or unilateral, varies from day to day, and may be greater during a certain portion of the day. Postnasal discharge or drip is common and, in the absence of infected adenoids, is practically diagnostic. Headaches are frequent, and pain or tenderness to palpation or percussion is helpful in localization. There are frequent attacks of sneezing; when there is an associated watery, nasal discharge, the possibility of allergic rhinitis must be considered.

Sinus disease should be suspected when there is persistent mouth breathing, not otherwise explained, and constant pharyngeal irritation. Any of the complications mentioned under Acute Sinusitis may occur with chronic sinusitis, but probably the most frequent one is chronic bronchial infection. The term "sinobronchitis" is used frequently to designate the relationship.

**Treatment.** Attention should be given to the general health of the child, and the diet should be corrected as necessary. Locally obstructive nasal deformities should be corrected, if possible, and infected or hypertrophic adenoid tissue should be removed. Shrinkage of the mucous membranes by ephedrine or other related compounds with the head in such a position as to facilitate entrance of the solution into the sinuses may be of some benefit. Either the so-called displacement method of Proetz or the lateral head-low posture of Parkinson may be used.

In the latter the child lies on his side with the shoulder elevated by a firm pad such as a folded blanket, and the head is bent down to a dependent position. The nasal solution which is then instilled can be expected to have contact with the various sinusal ostia on both sides. The child should breathe through the mouth to prevent drawing the medication into the pharynx. The position is maintained for five to six minutes, and the face is then turned downward for a few moments to permit drainage of the nasal contents, or the child may sit up and place the head down between the knees.

Nasopharyngeal cultures and antibiotic susceptibility tests should be obtained as a guide in selection of antibiotic agents. Such therapy should be continued for about two weeks. Continued use of nasal solutions should be discouraged.

Every effort should be made to avoid operative procedures; but when there is persistence of chronic purulent sinusitis in spite of all nonoperative measures, surgery is indicated. At times removal of the child to a warm, dry climate is beneficial.

## GENERAL CONSIDERATIONS OF CHRONIC INFECTIONS OF THE UPPER RESPIRATORY TRACT

### THE PROBLEM OF CHRONIC COLDS

One of the disturbing problems of pediatric practice is that of the child with persistent or recurring upper respiratory tract infection with or without associated chronic bronchial involvement. By no means can all children with such chronic infections be placed in the same category; rather, each must be studied to determine, if possible, the underlying factor or factors.

In general, the age of greatest incidence of respiratory infections is from the latter part of the first year of life to six or seven years. During this time it can be expected that the average child will have three to six "colds" a year. However, recovery should occur after each attack, and the child should appear healthy in the meantime. In the so-called chronic cases the child seems to recover from one acute attack, only to enter another, or there is more or less persistent rhinitis, cough and a general failure to do well. Such patterns may reflect what appears to be a familial or individual susceptibility or repeated exposure to respiratory infection within the home. Often there is some underlying disturbance in the child. Specifically included in the "chronic respiratory group" are chronic rhinitis, sinusitis, infected adenoids and tonsils,

chronic otitis media, chronic bronchitis, bronchiectasis, tuberculosis, allergy and hypogammaglobulinemia.

### CHRONIC RHINITIS

Chronic rhinitis as evidenced by a chronic nasal discharge, with or without a tendency to acute exacerbations, is usually a reflection of some particular underlying disturbance, such as infected adenoids, nasal polyps, chronic sinusitis, allergy, foreign bodies, deviated septum, various congenital malformations, nasal diphtheria, or syphilis. Chronic rhinitis should be considered merely a symptom, and the differential diagnosis should include the various disturbances enumerated. In addition, the possibility of a chronic debilitating infection or some nutritional or metabolic deficiency (as of the thyroid) must also be considered.

**Clinical Manifestations.** Symptoms vary with the individual case, but chronic nasal discharge is common to all. In the persistent cases the odor may be foul, and there may be excoriation of the anterior nares and upper lip. Bloody discharge is likely to be present in syphilitic and diphtheritic lesions and in association with foreign bodies, but may also occur in other conditions, especially if there are excoriations from persistent picking of the nose. Disturbances of taste and smell are frequent. During exacerbations or superimposed infections, fever is common, but otherwise is usually absent. Chronic sinusitis, otitis media, pharyngitis and bronchitis are frequently associated.

*Nasal polyps* are most frequently associated with allergy or sinusitis, and often produce symptoms predominantly unilateral. Their presence is determined by direct examination. They should be removed and the underlying disturbance treated (see *encephalocele*, p. 745).

Persistent *hypertrophic rhinitis* is also most often associated with chronic sinusitis or allergy. Especially in the latter condition the mucous membrane tends to be pink or pale in contrast to the usual red color. The soft tissues are swollen and resistant to pressure. Nasal obstruction may occur in a cyclic pattern.

*Atrophic rhinitis* is uncommon in children and is rare before late childhood. It is said to be more frequent in girls. It is usually associated with some general debilitating condition, or it may be a sequel to long-continued nasal infection. The sense of smell



is impaired. There may be little or no discharge, but there is likely to be considerable crusting and a sense of dryness in the nose and throat. In other instances there is a profuse, excessively foul nasal discharge (*ozena*). Direct examination shows abnormally wide nasal passages with atrophy of the mucous membrane and even of underlying structures.

**Treatment.** Treatment must be directed toward the underlying disturbance, so that each patient must be thoroughly studied. Particular emphasis must be placed upon eradicating foci of infection in sinuses, ears, adenoids or tonsils and upon the removal of all known allergens or upon desensitization to them. Attention should be given to such factors as nutritional status, rest and prevention of exposure to reinfection. In an attempt to provide symptomatic relief it is often difficult to avoid the use of such mucosal shrinking solutions as ephedrine and related compounds. It must be borne in mind, however, that their use is not without danger and they may cause further damage. There is no substantial evidence to justify the use of local antiseptics, including the silver salts and antibiotics. Systemic administration of antibacterial agents is, however, indicated in selected cases.

### CHRONIC PHARYNGITIS

Chronic pharyngitis is essentially a secondary condition resulting from such chronic infections as those of the sinuses, adenoids and tonsils, although on occasion there is no other evidence of infection than that of the hypertrophied lymphoid tissue on the posterior pharyngeal wall and on the base of the tongue. The latter type of involvement occurs with frequency only in children whose faucial tonsils have been removed, some of whom have infected tonsillar tags.

**Clinical Manifestations.** There are likely to be repeated acute exacerbations; in the intervals there are complaints of discomfort in the throat such as dryness and a raspy irritation. There are frequent efforts to clear the throat, and an irritative type of cough is common. The mucous membrane is usually inflamed, though on occasion it is pale, and the blood vessels are prominent. The pharyngeal wall is frequently covered with a mucopurulent secretion, and the lymphoid tissue is often hypertrophied and has a pebbled appearance.

**Treatment.** Treatment should be directed toward any disturbance in the sinuses, nose

(deformities), adenoids or tonsils. Attention should also be given to the general nutrition and hygiene of the child.

### TONSILS AND ADENOIDS

The term "tonsils" is used in its commonly accepted sense of indicating the two faucial tonsils; the term "adenoids," as synonymous with hypertrophy of the pharyngeal tonsil. The tonsils and adenoids are part of the lymphoid tissues which circle the pharynx and is known collectively as Waldeyer's ring. This consists of the lymphoid tissue on the base of the tongue (lingual tonsil), the two faucial tonsils, the adenoids (pharyngeal tonsil) and the lymphoid tissue on the posterior pharyngeal wall. This tissue naturally serves as a defense against infection; when its defense mechanism is overcome, it may become a site of acute or chronic infection.

The principal disturbances are infection and hypertrophy. The latter is in most instances secondary to infection. The most important factor from a medical standpoint is the decision as to their removal. Though both tonsils and adenoids are usually removed at the same operation, there are good reasons for making the decisions for tonsillectomy and adenoidectomy separately, especially in children under four or five years of age.

### NEOPLASMS OF THE TONSILS

Neoplasms of the tonsils are rare, although papilloma, lipoma, angioma, teratoma, fibroma, plasmocytoma and lymphosarcoma have been reported.

### ACUTE TONSILLITIS

Acute infections of the tonsils are considered in the same category as acute pharyngitis and are discussed on page 750; for peritonsillar abscess, see page 754.

### CHRONIC TONSILLITIS

(CHRONICALLY HYPERTROPHIC AND INFECTED TONSILS)

The "tonsil problem" is of particular concern in pediatric practice, not only because of the frequency of chronic tonsillar involvement, but also because of its distortion by physicians and laity who have been too ready to attribute all sorts of complaints and ills to tonsillar involvement and have not been sufficiently critical in recommending or asking for tonsillectomy. A more critical attitude is developing. Tonsillar disturbances are not com-

mon during infancy, but become more frequent during childhood.

**Clinical Manifestations.** These vary considerably, but the more significant ones are recurrent attacks of sore throat or a more or less persistent one, and obstruction to swallowing or breathing; the last is more often due to adenoids. There may be a sense of dryness and irritation in the throat, and the breath may be offensive, although neither of these is diagnostic. Constitutional symptoms are neither characteristic nor, as a rule, marked. Occasionally there is low grade fever, fatigue, underweight and poor appetite. One should, of course, be certain that such symptoms are not due to other disturbances.

**Indications for Tonsillectomy.** Decision for removal of tonsils should be based so far as possible on symptoms and signs related to the tonsils; tonsillectomy should not be recommended as a possible panacea for unrelated disturbances. In general, the conditions for which tonsillectomy is considered are (1) factors directly related to the tonsils, (2) disturbances in closely related structures, and (3) systemic disturbances.

*Local indications* for removal are of two types, chronic infection and marked hypertrophy. True hypertrophy is usually the result of infection, acute or chronic, but may occur independently. Many tonsils considered to be hypertrophic actually are normal in size; the misinterpretation results from failure to appreciate that tonsils are normally relatively larger during childhood than in later years. On the other hand, infection does not always produce hypertrophy, and chronically infected tonsils may be small and embedded behind the faucial pillars. In the evaluation of chronic infection, history of repeated or essentially constant sore throat is of more value than examination. There is no certain way to demonstrate by direct observation whether tonsils are harboring chronic infection. The consistency or size of the tonsil and the presence of cheesy material within the crypts are not reliable guides. Persistent hyperemia of the anterior pillars is a more reliable sign, and enlargement of the cervical lymph nodes is supporting evidence. Persistent enlargement of the node just below and slightly in front of the angle of the jaw is especially significant. In contrast to the difficulty in determining the presence of chronic infection, hypertrophy such as to obstruct swallowing or breathing is readily detectable. Such tonsils practically meet in the midline when the throat is examined without gagging

the patient. Tonsils of average size are projected toward the midline when the child is gagged and may be interpreted by the physician who is unaware of the relatively large size of the tonsil during childhood as being hypertrophic. Before tonsillectomy is recommended it should be ascertained that the hypertrophy is chronic and not the result of a recent acute infection. Tonsils can increase in size greatly during an acute infection and recede after its subsidence.

Removal of tonsils and adenoids may be recommended for persistent carriers of diphtheria bacilli (p. 418).

Among the *disturbances in adjacent tonsillar structures*, peritonsillar (and retrotonsillar) abscess is the only definite indication for tonsillectomy. Other indications are less clear cut. There are differences of opinion as to the value of tonsillectomy for sinusitis. When there are symptoms directly referable to the tonsils, as there frequently are, there is adequate justification for their removal. The physician who recommends removal before other treatment for the sinusitis is not to be condemned, but he will be wise if he does not promise relief from the sinusitis. In many instances removal of the adenoids is more likely to be indicated than is tonsillectomy. This is also true in cases of chronic otitis media and of middle ear deafness. Suppurative cervical adenitis, when the focus of infection is not traceable to structures other than the tonsils, may also be considered an indication for tonsillectomy. There is no evidence to indicate that the removal of tonsils is justified for infections in the lower respiratory tract, although such conditions are not a contraindication if there are other reasons for tonsillectomy.

No *systemic disturbance* in itself is an indication for tonsillectomy. The decision should be based on local indications in all instances. This applies to children with rheumatic fever or glomerulonephritis as well as to those with other infections in which the tonsils may be removed in a blind search for a focus of infection or as a remedy for undernutrition.

**Tonsillectomy in relation to age of the child.** Rarely it seems advisable to recommend tonsillectomy for children two or three years of age. Every attempt should be made, however, to postpone the operation. Frequently when the operation is postponed for reasons of age, the apparent need for tonsillectomy disappears within the next year or so. Actually, in the first few years of life the indica-



tions for adenoidectomy, though infrequent, are present more often than those for tonsillectomy. Neither procedure should be performed as a prophylaxis against the common cold at any age.

***Tonsillectomy in relation to season of the year.*** Formerly it was customary to postpone elective tonsillectomy until the summer months in order to avoid the secondary dangers incident to the seasons with a high rate of respiratory infection as well as to avoid absence from school. It has been shown, however, that children who have recently had a tonsillectomy are more liable to have bulbar involvement if they acquire poliomyelitis than children who have not had such an operation. Further, the introduction of effective antibacterial agents has decreased the danger of secondary bacterial infections after tonsillectomies. For these reasons, tonsillectomies have been performed electively in the winter and spring months rather than in the summer and early fall ones (the poliomyelitis season). What effect the changed epidemiologic pattern due to the Salk vaccine will have on the choice of time of operation is not yet apparent. Whatever policy is adopted, it should be recognized that no season is ideal for tonsillectomy, and that the physician should at all times be critical in his recommendation for operation.

***Tonsillectomy in relation to active infection.*** So far as possible, tonsillectomy should be postponed until two or three weeks after subsidence of an infection. This, however, is not always possible; an occasional child seems never to be free of infection in and about the tonsils. In such a case it is justifiable to perform the operation if a sulfonamide or antibiotic is administered for a day or two before and two or three days after the operation. In rheumatic fever and glomerulonephritis, tonsillectomy should also be postponed until after the acute phase has subsided. In all instances, irrespective of the evidence of active infection, penicillin and/or a sulfonamide should be administered before and after tonsillectomy in children with a history of rheumatic infection.

***Type of Operation.*** Though this is not the place to discuss operative procedures, certain generalizations are indicated. Careful removal by dissection should be carried out to ensure that all the tonsillar tissue is removed without destruction of adjacent tissues. Too frequently small amounts of tonsillar tissue are allowed to remain which later become infected and hypertrophied, or there is removal

of adjacent tissue from the lateral pharyngeal wall, from the soft palate and even at times from the uvula. Aspiration of the throat during the operation will lessen the chances of pulmonary abscess or pneumonia. Bleeding should be completely controlled, and the child should not leave the operating room until he has dry tonsillar fossae. Radiologic treatment, which causes shrinkage of the tonsils, should be recommended only when surgery is contraindicated, as in hemophilia.

***Preoperative Preparation.*** This consists in a medical history which includes questions related to recent infection, to exposure to contagious diseases and to bleeding tendencies in the patient or his family; and a thorough physical examination should include observation for loose or carious teeth, which should be removed or repaired before tonsillectomy. Bleeding and clotting times are usually obtained, but it would seem that a careful history of bleeding tendencies is apt to be a more effective screening process. The child should be told of the operation and the procedure explained, preferably by informed parents. There should be adequate preoperative sedation with one of the barbiturates and atropine. Though food is withheld for several hours before the operation, feeding should be adequate up to this time. In children who are undernourished or are readily susceptible to ketosis, the preoperative and, if needed, postoperative intravenous administration of glucose solution is indicated.

***Postoperative Care.*** This is usually not complicated. The child should be kept in bed for the remainder of the day and at rest for several more; it is wise to encourage eating and drinking as soon as the nausea from the anesthetic has disappeared. Rinsing the mouth with an alkaline solution has certain esthetic advantages. Aspirin may be prescribed when there is considerable discomfort. Avoidance of contact with infection is of the greatest importance. The membrane which forms at the operative site is at times interpreted as being diphtheritic. Fusiform bacilli (Vincent's organisms) may be cultured from it with a high degree of regularity, but this by itself is not an indication for treatment. (See Tonsillectomy in Relation to Active Infection for suggestions as to antibacterial therapy.)

***Complications.*** Complications are not particularly frequent, but postoperative hemorrhage, lung abscess, pneumonia and septicemia do occur. Hemorrhage is, of course, the most frequent one, and should be controlled

by packing or, in the case of severe bleeding, by ligation. Extensive bleeding will be responsible for severe anemia, leukocytosis, fever, and even dilatation of the heart. Transfusion is indicated in such cases.

**Results to Be Expected from Tonsillectomy.** No reduction in the incidence of epidemic respiratory infections is to be expected. The incidence of persistent throat infections may be decreased. Obstructive symptoms due to hypertrophied tonsils can be relieved. Otitis media and sinusitis are rarely benefited by tonsillectomy; the incidence of sinusitis may even be increased. Nasal allergy is not affected, nor is the incidence of laryngitis. Pulmonary infections are not decreased, and may even be increased. The incidence of initial attacks of rheumatic fever appears to be somewhat decreased, but recurrences are not affected. The incidence of diphtheria is less in tonsillectomized children, and the carrier state may be controlled by the operation. The incidence of cervical lymphadenitis is decreased. In some instances nutrition is improved after tonsillectomy. In part this may be due to psychologic factors, but it is reasonable that general benefit should accrue when a focus of infection is removed. Care should be taken, however, in making predictions in this respect.

Follow-up studies of tonsillectomized and nontonsillectomized children for whom the operation had been recommended do not reveal striking differences in favor of the tonsillectomized group. In one large group surveyed by Dey, which consisted of children for whom tonsillectomy and/or adenoidectomy had been recommended and then deferred for at least eighteen months, it was concluded that there was no longer a need for the recommended operation in more than one third of the children.

## ADENOIDS

### (HYPERTROPHY OF THE PHARYNGEAL TONSIL)

Disturbances of the lymphoid tissue of the nasopharynx (adenoids) tend to parallel those of the faucial tonsils. Hypertrophy and infection may occur separately, but usually occur together, infection, as a rule, being primary. The soft adenoid structure, which is normally widespread in the nasopharynx, especially on the posterior wall and the roof, undergoes hypertrophy, and masses of varying size, reaching even that of a walnut, are formed. These masses may almost fill the

vault of the nasopharynx and interfere with the passage of air through the nose and obstruct the eustachian tubes.

**Clinical Manifestations.** Mouth-breathing and more or less persistent rhinitis are the most characteristic symptoms. Mouth-breathing may be present only during sleep, especially when the child is on his back, and in this position snoring is also likely to occur. In decided adenoid hypertrophy the mouth is kept open during the day as well, the mucous membranes of the mouth and lips are dry, and the child's facial expression is dull or stupid. Alteration in the shape of the nose is common, the nostrils being small and narrow, although sometimes the upper portion of the nose appears unduly broad. Chronic nasopharyngitis may be constantly present or recurs frequently. The voice is altered, developing a nasal, muffled quality. The breath is offensive, and taste and smell are impaired. A harassing cough may be present, especially at night, resulting from irritation of the larynx by inspired air which has not been properly warmed and moistened by passage through the nose. Deafness is common and may become permanent unless the obstruction of the eustachian tube has been relieved before chronic changes occur in the middle ear, which may be the seat of pyogenic infection. Chronic otitis media, with persistent or recurrent purulent drainage, may be associated with infected, hypertrophied adenoids.

Permanent bony deformities have been attributed to faulty nasal breathing, but are probably more likely the result of other factors. These deformities include a high and narrow arching of the palate, a forward projection of the upper jaw, prominent eyes, and a keel-shaped chest with lateral depression of the lower portion of the thorax.

Stunting of growth, anemia and other general effects have been attributed to adenoid hypertrophy, but in most instances are probably due to other causes. The facial expression may, as stated, be stupid, but there is no direct effect of adenoid hypertrophy on mental development except that related to deficient hearing. It would not appear that adenoid hypertrophy has any etiologic connection with such conditions as stammering, enuresis, or grinding of the teeth.

The *diagnosis* can be confirmed by direct digital palpation, examination of the vault of the pharynx by pharyngeal mirror, or roentgenographic examination. Otherwise the presence of adenoid hypertrophy can be suspected from such symptoms as mouth-breathing.



snoring and persistent rhinitis with or without chronic otitis media.

**Suppurative Adenoiditis.** A recent description by Goldbloom (original source, Libman) of an abscess in the adenoid tissue as a cause of protracted fever is of interest. The characteristic clinical pattern described is as follows: throat infection of several days' duration four to six weeks previously is followed after a few symptom-free days by resumption of the fever with daily temperatures to 102° F. or higher. The lymph nodes under the sternocleidomastoid may or may not be enlarged. The child usually has no symptoms, including none of the nasopharynx, but occasionally may complain of headache, often occipital in location. The white blood cell count is indicative of a purulent infection. The clinical course is terminated by expressing pus from the enlarged boggy adenoids with the finger. Subsequently, adenoidectomy is advised.

**Treatment.** Surgical removal is indicated when there are symptoms such as persistent mouth-breathing, "nasal" speech, repeated attacks of otitis media, deafness and persistent or recurring nasopharyngitis. Improvement occasionally results from change in climate or with appropriate antibiotic treatment administered for ten to fourteen days; operation can then be deferred, especially in young infants. It is customary to remove the adenoids when tonsillectomy is performed, although there are occasions, particularly in young children, when only adenoidectomy should be recommended. The same precautions for complete removal and control of bleeding points as recommended for tonsillectomy should be observed; for this reason, removal under direct vision is preferable to the use of the adenotome. If impaired hearing persists after adenoidectomy, radiation therapy may be considered.

ROBERT H. PARROTT  
WALDO E. NELSON

## REFERENCES

### *Nasopharyngeal Infections*

Chanock, R. M., and Finberg, L.: Recovery from Infants with Respiratory Illness of Virus Related to Chimpanzee Coryza Agent (CCA). *Am. J. Hyg.*, 66:291, 1957.

- Chanock, R. M., and others: Newly Recognized Myxoviruses from Children with Respiratory Disease. *New England J. Med.*, 258:207, 1958.
- Cramblett, H. G., and others: Respiratory Illness in Six Infants Infected with a Newly Recognized ECHO Virus. *Pediatrics*, 21:168, 1958.
- Hilding, A.: The Common Cold. *Arch. Otolaryng.*, 12:133, 1930.
- Ishida, N.: Discussion, Part II, Viruses in Search of Disease. *Ann. New York Acad. Sc.*, 67:299, 1957.
- Parrott, R. H.: Newly Isolated Viruses in Respiratory Disease. *Pediatrics*, 20:1066, 1957.
- Paul, J. H., and Freese, H. L.: Epidemiological and Bacteriological Study of the "Common Cold" in an Isolated Arctic Community (Spitsbergen). *Am. J. Hyg.*, 17:517, 1933.
- Pelon, W., Mogagbab, W. J., Phillips, I. A., and Pierce, W. E.: A Cytopathogenic Agent Isolated from Naval Recruits with Mild Respiratory Illnesses. *Proc. Soc. Exper. Biol. & Med.*, 94:262, 1957.
- Powers, G. F., and Boisvert, P. L.: Age as a Factor in Streptococcosis. *J. Pediat.*, 25:481, 1944.
- Price, W.: The Isolation of a New Virus Associated with Respiratory Clinical Disease in Humans. *Proc. Nat. Acad. Sc.*, 42:892, 1956.

### *Retropharyngeal Abscess*

Townsend, E. H., Jr.: Retropharyngeal Abscess. *A.M.A. Am. J. Dis. Child.*, 92:308, 1956.

### *Tonsils and Adenoids*

- Dey, D. L.: A Survey of 681 Children Awaiting Tonsillectomy and the Indications for Operation in Children. *M. J. Australia*, 1:510, 1952.
- Goldbloom, A.: Suppurative Adenoiditis. *Pediat. Clin. North America*, 5:323, 1958.
- Kaiser, A. D.: The Tonsil and Adenoid Problem; in McQuarrie, I., ed.: *Brennemann's Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 2, Chap. 40.

### *Nose*

Ingraham, F. D., and Matson, D. D.: Spina Bifida and Cranium Bifidum. IV. An Unusual Nasopharyngeal Encephalocele. *New England J. Med.*, 228:1, 1943.

### *Ears*

- Altmann, F.: Malformations of the Auricle and External Auditory Meatus; Critical Review. *Arch. Otolaryng.*, 54:115, 1951.
- Gottschalk, G. H.: New Middle Ear Aspirator for Treatment of Otitis Media with Effusion. *Arch. Otolaryng.*, 56:532, 1952.
- Pattee, G. L.: Improved Hearing in Congenital Auricular Malformation; A Review of the Results Obtained by Surgical Methods. *Am. Acad. Ophth. Otol.*, 56:465, 1952.

# THE EAR

## MALFORMATIONS

The majority of malformations of the ear are congenital in origin. They include abnormalities of the auricle, external auditory canal, middle ear and inner ear. The abnormalities of the auricle are varied, owing to its complex embryologic development; they include aplasia, hypertrophy, partial development, and variations in size and shape. Aplasia of the auricle may be partial or complete. The external auditory canal may be present, though covered by the deformed auricle, but more often abnormalities of the external auditory canal, tympanic membrane, middle and inner ear accompany the congenitally deformed auricle. There may be absence or fusion of the ossicles.

In the female child with a unilateral auricular deformity nothing need be done; when there are bilateral deformities, correction to improve hearing is a necessity. In the male child operations to improve both function and appearance are indicated.

Instead of attempting to reproduce a new external auditory canal, the auricle is mobilized, and the mastoid excavated and lined with skin grafts. The auricle is shifted over the mastoid cavity, which serves as the new canal. Additional hearing improvement is obtained by fenestrating the external auditory canal. After the hearing has improved, a new auricle may be constructed. At times prosthetic devices are used, an auricle of plastic material being held in place with adhesive.

Congenital outstanding ears, or lop ears, are often a source of great embarrassment. Correction should be done before the child starts school. Restraining devices are of little benefit, since the anomaly is due to absence of the antihelix fold. The operation is usually effective.

Small preauricular fistulas, which are remnants of the first branchial cleft, are common and often extend into the temporomandibular joint. If they become infected, there is liable to be persistent purulent drainage, and surgical resection is indicated. To secure a successful result, the entire fistulous tract must be dissected and removed. Methylene blue is injected into the tract, and dissection is carried to its depth.

A traumatic lesion of the auricle may re-

sult in a hematoma and in deformity if untreated. The hematoma should be evacuated immediately by aspiration or incision, and a tight bandage applied to prevent further infiltration, fibrosis and ultimately a "cauliflower ear." *Abscess of the auricle*, secondary to perichondritis or chondritis, can usually be treated adequately by antibiotic therapy. If fluctuation occurs, prompt incision and drainage are indicated.

## FOREIGN BODIES

Various animate or inanimate foreign bodies may be introduced into the external auditory canal. Unless they are visible, within easy reach, and the child is cooperative, it is best to remove the object under general anesthesia. Irrigation of organic particles should be avoided, since absorption of water may increase their size. Occasionally, if the foreign body is tightly impacted, a postauricular incision may be needed for removal.

Cerumen may become inspissated and impacted. A small mass of cerumen may be removed by gentle and careful extraction with a hook or curette. Large masses should be softened with oil or a detergent soap solution and then removed by irrigation with warm water. A 20-cc. glass syringe to which is attached a piece of a no. 8 French soft rubber catheter makes a good irrigating apparatus and will avoid injury.\*

## OTITIS EXTERNA

Otitis externa may occur at any age. It may follow trauma or swimming in contaminated waters. Sometimes it is due to mechanical probing in an attempt to clean the external auditory canal, a procedure which is rarely necessary and should never be performed by an inexperienced person.

*Symptoms* are pain, redness and swelling of the external canal and auricle and at times of the postauricular area. There is pain on motion of the auricle and on pressure over

\* The deVilbiss Company makes an excellent irrigating device which is operated by compressed air; it provides a steady stream of water without the necessity of filling a syringe or pushing a plunger, thus avoiding trauma to the canal in an uncooperative child.



the tragus. The temperature may be elevated if the cellulitis is diffuse.

*Treatment* consists of hot packs of Bur-ow's solution and broad-spectrum antibiotic coverage, systemically and locally (ear wick). The infection is frequently ascribed to a fungus, but it is usually bacterial in origin, often being caused by *Pseudomonas* organisms. Resolution usually occurs, and incision and drainage are seldom necessary.

*Vesiculation* of the auditory canal may be due to viral infection such as that of herpes simplex or influenza. This infection may be accompanied by severe pain in the canal and over the mastoid area and by fever. The so-called *Ramsay Hunt syndrome* is a herpes zoster infection of the geniculate ganglion, with dermal lesions of the auricular region, at times with a facial paralysis.

Hemorrhagic blebs may fill the ear canal and cover the tympanic membrane in viral infections, especially influenzal ones. Relief may be obtained by rupturing the blebs with a cotton-tipped applicator.

## THE TYMPANIC MEMBRANE

The normal drum is gray and translucent, the short process of the malleus, the umbo and the cone of light being easily visible.

Diseases of the tympanic membrane include otitis externa, otitis externa hemorrhagica bullosa and herpes zoster oticus. In the early stages of otitis media the drum membrane is red and injected (acute myringitis). The appearance of the drum head usually reflects the inflammatory processes within the middle ear.

Perforations of the ear drum occur as the result of trauma as well as of infection of the middle ear. Trauma is most often indirect, such as a blow with the open palm over the auricle, severe head injuries and concussion from an explosion.

The perforation is followed immediately by bleeding, pain and hearing impairment. Otoscopic examination reveals the extent of the damage. The canal should be kept closed with sterile cotton, and an antibiotic should be administered to prevent infection. No liquid (drops) should be put in the canal. The perforation will often heal spontaneously, but healing may be hastened by touching its edges with trichloroacetic acid or silver nitrate, or freshening them with a myringotomy knife. The perforation may be covered with cellophane or Cargile membrane, which may act as a bridge for epithelization.

## OTITIS MEDIA

### ACUTE OTITIS MEDIA

Acute otitis media is usually secondary to an upper respiratory infection, especially a nasopharyngitis, and is often a sequel of measles or scarlet fever. The incidence is greater in the young infant, supposedly because the eustachian tube is shorter and wider, and because the infant is supine most of the time. Actually, infection may spread through the subepithelial pathways and lymphatics from the nasal mucosa or by direct extension from the nasopharyngeal area. The first stage is due to closure of the eustachian tube, which is followed by congestion, serous exudation and infection.

In the untreated case the *symptoms* are pain in the ear, which increases in intensity as exudation occurs, and an elevated temperature. The young infant may cry fretfully and rub the affected ear. The pain becomes intense as the fluid pressure of the middle ear increases. Occasionally there may be nausea and vomiting and signs of meningeal irritation. Inspection of the tympanic membrane reveals a red and congested ear drum with loss of the normal landmarks in the early stage; later there may be edema and bulging of the membrane.

**Clinical Course and Treatment.** In untreated cases the temperature and pain may persist until spontaneous rupture occurs. If the drum is red and congested, but the normal landmarks are still visible and there is little fullness, appropriate antibacterial therapy will usually result in resolution. Nasal treatments should also be carried out, when indicated. If, after therapy for forty-eight hours, there are no signs of resolution and the appearance of the drum suggests the presence of fluid, myringotomy under local or general anesthesia or aspiration of the middle ear (as described under Serous Otitis Media) should be performed. If bulging is present at the first examination, myringotomy should be performed immediately and antibacterial therapy started. A culture should be made from the myringotomy knife, and antibiotic sensitivity tests obtained for any pathogenic organism isolated, as a further guide to therapy. No harm will result from a well performed myringotomy, but delay or failure to perform it may result in an attenuated (chronic) infection, impaired hearing or an acute exacerbation when the antibiotic is discontinued.

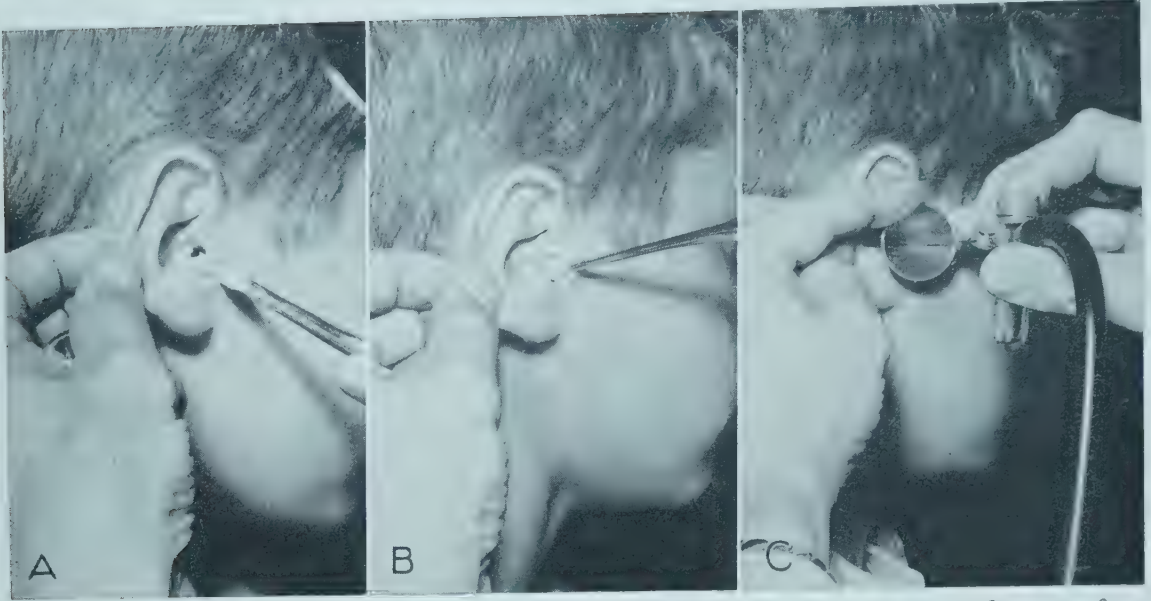


FIG. 212. Aspiration of middle ear for treatment of serous otitis media. A and B, Application of topical anesthesia; the pack is allowed to remain *against* the drum for 10 to 15 minutes. C, After the fine needle has perforated the anterior-inferior quadrant of the drum mild suction is applied. Note the aspirated fluid in the tube. The device illustrated is the Gottschalk apparatus; it can also be used with oral suction.

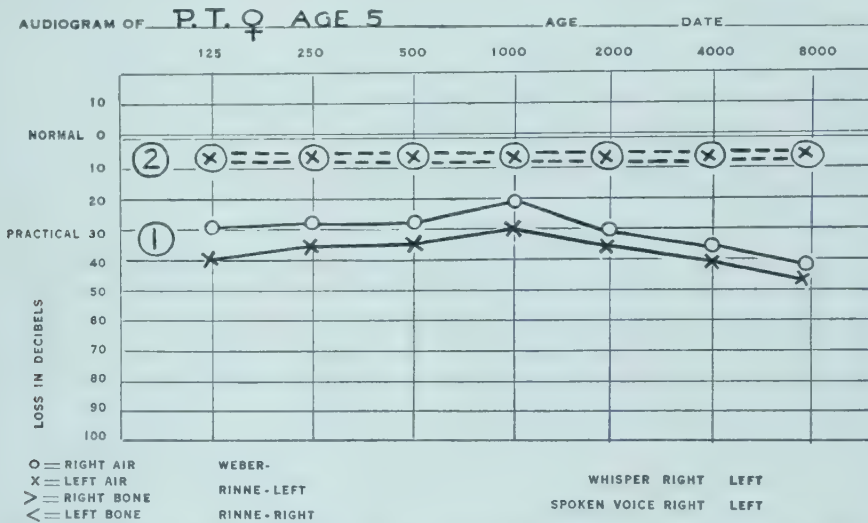


FIG. 213. Audiometric studies of a patient with serous otitis media. 1, Unbroken lines indicate hearing loss before treatment, which consisted of needle aspiration and systemic administration of antihistaminic and antibiotic drugs. The second audiogram (2, broken lines) shows the immediate improvement in hearing after aspiration of the serous fluid.

Antibacterial therapy should always be given in full dosage and for a sufficient time to ensure complete resolution.

Complications are rare and are usually the result of inadequate (suppressive) therapy. They include acute mastoiditis, chronic otitis media, chronic mastoiditis, lateral sinus thrombophlebitis or thrombosis, septicemia, meningitis, cerebral or cerebellar abscess, labyrinthitis, petrositis and facial paralysis.

#### SEROUS OTITIS MEDIA

Serous otitis media is a condition in which fluid is present in the middle ear. The fluid

may be clear, mucoid or purulent. The etiology may be on an allergic basis, or the cause may be a partially attenuated middle ear infection.

The child complains of a fullness in the middle ear and impaired hearing. There is usually no real pain or fever, but there may be a sensation of something moving about in the ear. Otoscopic examination reveals a gray membrane, which at first glance seems normal, but on closer inspection the drum is opaque, a yellowish reflex is present, and there is some fullness. On occasion a fluid level may be seen. The audiometric test re-



veals an obstructive type of deafness. The diagnosis is confirmed by the aspiration of fluid (Fig. 212), which also relieves the symptoms; the hearing is improved immediately.

*Treatment* consists in repeated aspirations with a fine needle. If the child is uncooperative, a myringotomy with suction aspiration should be performed under general anesthesia. Local anesthesia may be obtained by placing a piece of cotton saturated with a solution of cocaine and aniline, U.S.P. (10 to 90 parts, respectively), against the drum. When the fluid is very viscid, a myringotomy followed by aspiration with a fine suction tip is required. Subsequently any existing allergic or infectious condition should be treated appropriately. When hypertrophied adenoid tissue is a factor, its removal may be indicated; if an adenoidectomy has previously been performed, radiation therapy may be considered. Such therapy is not without danger and should be used advisedly and only by an experienced person. Inflation of the middle ear by the Polit-

zer technique may aid in hastening resolution.

### CHRONIC OTITIS MEDIA

Chronic otitis media is now relatively rare, owing to the effectiveness of antibacterial agents for the prevention and treatment of acute otitis media. When a middle ear infection persists for three to six weeks after adequate drainage and antibacterial therapy, a roentgenogram of the mastoid should be obtained. When there is evidence of mastoiditis, a "complete mastoidectomy" is indicated. It should result in resolution of the middle ear infection and prevent chronic otitis media and deafness.

Chronic otitis media accompanied by perforation of the drum in Shrapnell's region and by clinical and roentgenographic evidence of cholesteatoma should be treated by a so-called mastoido-atticotomy or Bondy operation, which may be accomplished postauricularly or endaurally. It should result in a dry ear with preservation of the tympanic membrane and ossicles as well as hearing.

## DISTURBANCES OF THE INNER EAR, MENINGES, LATERAL SINUS AND FACIAL NERVE

Chronic tuberculous otitis media and mastoiditis should be treated by mastoidectomy and intensive antibacterial therapy.

*Labyrinthitis* may be secondary to acute or chronic otitis media and/or mastoiditis. Acute purulent labyrinthitis is accompanied by signs of meningeal irritation, nystagmus, deafness, nausea and vomiting. Spinal puncture reveals an increased number of cells. There is usually evidence of mastoiditis. The treatment of choice is mastoidectomy with appropriate antibacterial therapy. Severe or complete deafness in childhood may be the result of unrecognized labyrinthitis, which may be due to inadequate antibiotic therapy. Though the clinical manifestations are suppressed, the disease progresses, and total deafness occurs. Ménière's labyrinthitis of allergic origin may occur in childhood, as may toxic labyrinthitis involving the vestibular or cochlear portion of the endolabyrinth, during viral infections, especially mumps, and bacterial infections.

Deafness and loss of the vestibular function of equilibrium are the most serious of the toxic reactions to streptomycin.

*Otitic meningitis* is now relatively uncommon. When it occurs, removal of the suppurative focus in the middle ear and mastoid

must be prompt and complete; otherwise antibacterial therapy is likely to be ineffective.

*Phlebitis or thrombosis of the lateral sinus* is now a rare complication of otitic infections. The characteristic symptoms are likely to be modified or masked by the antibacterial therapy being administered. There may be no directly referable symptoms, the only evidence being that of a persistent infection. The classic pattern includes chills, a high septic type of fever, a positive blood culture, a positive Ayer-Tobey test and thrombotic phenomena.

*Facial paralysis* occurring early in the course of acute otitis media is usually toxic in origin and will disappear with proper treatment of the middle ear infection. When the paralysis occurs late in the course of an otitis media, it may indicate a mastoiditis, and a mastoidectomy is necessary.

### MASTOIDITIS

The incidence of purulent mastoiditis has been reduced by antibacterial treatment of acute otitis media so that it is now relatively rare. When "surgical" mastoiditis does occur, it is usually because the child has had no

or inadequate antibacterial therapy or because there has been inadequate drainage of the middle ear infection. The symptoms include postauricular pain, fever, fullness of the ear drum, occasional edema of the postsuperior portion of the external auditory canal and roentgenographic evidence of mastoiditis.

In rare instances, when there is pneumatization and cellular formation of the zygomatic process of the temporal bone, an infection in the mastoid may extend to involve these cells. The osseous and soft tissue involvement may result in swelling and inflammation over the temporo-mandibular region.

DAVID MYERS

## REFERENCES

### *Nasopharyngeal Infections*

- Commission on Acute Respiratory Diseases: Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter-Passing Agents. *J. Clin. Investigation*, 26:957, 974, 1947.
- Cowan, D. W., Diehl, H. S., and Baker, A. B.: Vitamins for the Prevention of Colds. *J.A.M.A.*, 120:1268, 1942.
- Denny, F. W., Wannamaker, L. W., and Hahn, E. O.: Comparative Effects of Penicillin, Aureomycin and Terramycin on Streptococcal Tonsillitis and Pharyngitis. *Pediatrics*, 11:7, 1953.
- Diehl, H. S., Baker, A. B., and Cowan, D. W.: Cold Vaccines: A Further Evaluation. *J.A.M.A.*, 115:593, 1940.
- Dingle, J. H.: Common Virus Infections of the Respiratory Tract. *J.A.M.A.*, 136:1084, 1948.
- Dochez, A. R., Mills, K. C., and Kneeland, Y., Jr.: Filtrable Viruses in Infection of the Upper Respiratory Tract. *J.A.M.A.*, 110:177, 1938.
- Gafafer, W. M.: Hardening Processes and Upper Respiratory Diseases (Common Cold). *Am. J. Hyg.*, 16:233, 1932.
- Hilding, A.: The Common Cold. *Arch. Otolaryng.*, 12:133, 1930.
- Jones, P. H., Brigham, R. S., and Manning, P. R.: Use of Antibiotics in Nonbacterial Respiratory Infections. *J.A.M.A.*, 153:262, 1953.
- McCurby, R. S., and Neter, E.: Effects of Penicillin and Broad Spectrum Antibiotics on the Emergence of a Gram-Negative Bacterial Flora in the Upper Respiratory Tract of Infants. *Pediatrics*, 6:572, 1950.
- Moulton, F. R., ed.: *Aerobiology. A Symposium*. Washington, D. C., American Association for the Advancement of Science, Publication 17, 1942.
- Paul, J. H., and Freese, H. L.: Epidemiological and Bacteriological Study of the "Common Cold" in an Isolated Arctic Community (Spitsbergen). *Am. J. Hyg.*, 17:517, 1933.
- Powell, H. M., Sparks, A. L., and Clowes, G. H. A.: Further Inoculation-Experiments with the Common Cold Virus. *J. Immunol.*, 38:309, 1940.

### *Tonsils and Adenoids*

- Aycock, W. L.: Tonsillectomy and Poliomyelitis; Epidemiologic Considerations. *Medicine*, 21:65, 1942.
- Dey, D. L.: A Survey of 681 Children Awaiting Tonsillectomy and the Indications for Operation in Children. *Med. J. Australia*, 1:510, 1952.
- Hardy, M. C.: General Health at Maturity of Tonsillectomized and Nontonsillectomized Children. *J. Pediat.*, 12:463, 1938.
- Kaiser, A. D.: The Tonsil and Adenoid Problem; in McQuarrie, I., ed.: *Brennemann's Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Co., Inc., 1948, Vol. 2, Chap. 40.

### *Nose*

- Ingraham, F. D., and Matson, D. D.: Spina Bifida and Cranium Bifidum. IV. An Unusual Nasopharyngeal Encephalocele. *New England J. Med.*, 1:228, 1943.

### *Ears*

- Altmann, F.: Malformations of the Auricle and External Auditory Meatus; Critical Review. *Arch. Otolaryng.*, 54:115, 1951.
- Gottschalk, G. H.: New Middle Ear Aspirator for Treatment of Otitis Media with Effusion. *Arch. Otolaryng.*, 56:532, 1952.
- Pattee, G. L.: Improved Hearing in Congenital Auricular Malformation; A Review of the Results Obtained by Surgical Methods. *Am. Acad. Ophth. Otolaryng.*, 56:465, 1952.

## IMPAIRED HEARING

Impaired hearing is a complex problem and requires well planned and coordinated teamwork for its solution. This team includes the child, his family, the child's physician, the otologist, the audiologist, the speech therapist and often the psychologist and/or psychiatrist. There is little value in discovering hearing losses unless something is done about them.

### CONGENITAL DEAFNESS

Congenital deafness may be complete or partial; it may be due to a lack of development, or to disease, in the organ of Corti. Although the entire labyrinth may be involved, usually the vestibular apparatus retains normal function.

It is difficult to detect hearing loss accurately in infants. The deaf infant at two or three months of age coos with pleasure or cries with pain just as a hearing one does, but when the hearing infant reaches the age of six or seven months, he usually begins to respond to the sounds made by others, whereas the deaf infant does not. At twelve to sixteen months of age the noises made by



the hearing child begin to be recognizable as words, but the deaf child by this age may have almost ceased to vocalize. Conditioned psychogalvanic skin reaction tests may give some information as to presence or absence of hearing. The auropalpebral reflex or other reflex reactions to sound elicited by striking a C-4 or C-5 tuning fork or other type of noisemaker near the side of the head may give useful information about the hearing. Noisemakers such as whistles, drums or bells may be calibrated in terms of the sound pressure levels they produce. Such relatively crude hearing tests often are of considerable diagnostic value. A determination of the degree of deafness in infants and young children may necessitate a series of examinations.

A child of eighteen months who makes no attempt at verbal response must be suspected of being deaf. Because it is often difficult for parents to believe that the random noises the child is making are not attempts at speech, but merely reflexive movements of the oral mechanism, the child may be three or four years of age before he is taken to a physician for diagnostic appraisal. A child with impaired hearing who is deprived of any means of communication may become physically aggressive and in many respects almost unmanageable.

In contrast to their lack of auditory ability, these children may be otherwise alert. They learn the performance of various physical means of expression quickly, and often are remarkably dexterous. They become highly conditioned to family routine, and develop spontaneously the ability to read the lips of their parents so accurately that parents are convinced they can hear.

A child with a serious hearing impairment does not learn speech in the usual way. He must be taught by special methods to utilize any hearing he may have and to make use of his visual and kinesthetic senses in acquiring speech. This training can best be started when the child is two and one-half to three years of age, at a time when the normally hearing child is learning to talk. These early hearing losses usually are not progressive, nor do they respond to any known form of medical treatment. It is important that physicians inform parents that the congenitally deaf child can achieve a satisfactory means of communication. Special instruction is available for the parents as well as for the children.

## ACQUIRED DEAFNESS

The problem is quite different when the child has developed speech and then acquired a hearing loss, even a severe one. He has developed a cortical speech pattern which, under favorable circumstances, can be kept alive. The muscles involved in speech have attained a certain degree of development, and the child has known the rhythm and physical sensation of vocalized sounds.

Since some residual hearing is present in most cases, these children can benefit by auditory training with the assistance of electronic amplification. They can also profit from lip-reading instruction, speech training and psychological guidance. Acquired deafness may be caused by middle ear infections and their sequels and also by toxic effects of infectious diseases and of certain drugs upon the inner ear and/or the eighth cranial nerve. Severe and permanent deafness may follow meningitis, encephalitis, scarlet fever, measles, typhoid fever, influenza, mumps, and the like. Streptomycin is an example of a drug with high toxicity; it affects mainly the vestibular function, whereas dihydrostreptomycin tends to impair the cochlear function. Middle ear infections are usually amenable to treatment, so that an impairment can be avoided or at least can be ameliorated in a high percentage of cases. However, there is no known cure for cochlear or eighth nerve degeneration following any of the infectious diseases named above.

## DETECTION OF HEARING IMPAIRMENT

The prime requisite is early diagnosis, irrespective of age or cause. But mere demonstration of hearing loss is not sufficient; its extent and nature must also be established.

**In the Preschool Child.** Techniques for the quantitative measurement of the auditory acuity of preschool children leave much to be desired, because the child's cooperation is essential. It is usually necessary for the child to have sufficient speech and language development to understand the instructions for the test and to have some capacity for attention and concentration. In the evaluation of any child whose speech development is delayed or who develops unintelligible speech, the possibility of a hearing loss must be considered until an accurate quantitative evaluation of his hearing can be obtained.

If the child is unable to repeat simple words or sentences at various intensity levels

or to respond to the tones produced by a pure-tone audiometer, it is customary to observe his reactions when noises of graduated intensity are produced near him, but out of his range of vision. Calling his name, clapping the hands, blowing a police or referee's whistle and striking a Koenig rod are noises used for testing purposes. Noises of exceedingly high intensity levels stimulate the threshold of feeling to which children with total loss of hearing respond. If a child shows no reaction to any of the sounds mentioned, his response to floor vibration when an object is dropped behind him will indicate that he probably has a hearing impairment.

Dix and Hallpike devised a hearing test by means of which preschool children can be conditioned to respond to pure tones of different intensity levels, and Ewing and Ewing described several tests based on observation of the child's behavior or response during play periods. Keaster developed a quantitative test which indicates the intensity levels at which the child can identify simple pictures; it can be used only for children who have sufficient speech to indicate that they recognize the objects.

**In the School-Age Child.** It is possible to obtain accurate quantitative measurements of the auditory acuity of children five years of age and older with pure-tone and speech audiometers. The tuning fork, watch tick, coin click and direct whispered or spoken voice tests, as usually administered, are grossly inaccurate as compared to the audiometer tests.

The pure-tone audiometer measures the acuity in calibrated steps of frequency (pitch) and intensity (loudness). Frequencywise, test signals are provided in octave and/or semi-octave intervals within a range of 64 to 12,000 cycles per second (cps). Intensitywise, steps are provided in intervals of 5 decibels (db), since steps of that magnitude are easily recognized even by persons unfamiliar with audiometric tests. Since the decibel is a relative measure, absolute calibration of intensity is achieved in the following manner. Zero decibel represents the intensity level at which a given tone is barely perceived by young adults (persons under thirty years of age) with normal hearing acuity in quiet rooms. (Normal hearing in this respect has a range of plus or minus 5 decibels around the mean value.) This threshold intensity level differs from frequency to frequency, the ear being most sensitive within the range of 3000 to 4000 cycles per second. The intensity range

of audiometers, in terms of hearing loss, extends from -10 (better than normal) to approximately 100 decibels, the latter value varying somewhat with frequency.

This method of calibration permits measuring hearing losses for any frequency in terms of the decibel ratio in relation to the normal threshold value. For reasons of convenience the zero decibel level is plotted as a straight line near the top of the audiogram blank. The audiometer and the audiogram blank now make available, respectively, a standardized instrument for the testing of hearing and a standardized method of recording the results of hearing tests.

**Interpretation of Audiograms.** Criteria which can be used in the localization of pathologic changes within the ear are the severity of the hearing impairment at different frequency levels, the relationship between air and bone conduction acuity, and the ability to understand speech above threshold intensity levels. As a rule, patients with involvement of the inner ear have greater losses in acuity for high frequency tones than for low frequency ones, and those with involvement of the middle ear have equal losses for all tones over the audiometric frequency range. Patients with involvement only of the middle ear never have a complete loss of hearing, usually not exceeding 60 decibels. It is about at this latter value that vibrations which sound sets up in the entire skull are transmitted to the inner ear, even when the middle ear pathway is entirely blocked, for example by an atresia of the external auditory canal. Patients with lesions of the inner ear may have any degree of impairment, including total loss of auditory function.

The relationship between air and bone conduction acuity in different types of hearing impairment can be summarized as follows: (1) When there is a hearing deficit by air conduction and none by bone conduction, the lesion is in the middle ear. (2) When the patient has an equal loss for both air- and bone-conducted sound, or possibly a slightly greater loss for bone conduction, the involvement is in the inner ear (usually the history and physical examination contraindicate middle ear involvement in these cases). (3) When there are losses for both air and bone conduction, but a greater loss for air conduction, there is involvement of both the middle and inner portions of the ear.

A further means of differentiation is provided by the so-called recruitment phenomenon: this is the sensation of loudness which



increases at a rate faster than normal when the intensity of the test signal is raised. Recruitment is displayed by persons with inner ear involvement, whereas in persons of middle ear involvement the rate of increase of loudness follows the pattern of normal ears. Pure-tone audiograms alone do not provide adequate clues for differentiation of lesions of the inner ear from those of central origin. Here examination of the patient's ability to synthesize sounds above threshold, e.g., in the perception of speech signals, has proved helpful. Walsh and Silverman and also Davis described the differences in reception of speech above threshold levels by the impaired ear. Briefly, the reception of speech by persons with disease of the middle ear increases to the normal or near-normal value if the intensity of the speech is increased sufficiently. By contrast, in persons with disease of the inner ear the intelligibility of speech does not increase to the same extent no matter how high the intensity level is raised. This failure of synthesizing speech is especially marked in central disturbances of the auditory function. The term "phonemic regression" is used to describe this condition, which is conspicuous in that a given loss of hearing for pure tones is associated with a relatively severe loss for speech perception. As a further means of differentiation, there is no recruitment in hearing losses of central origin.

From the foregoing, it is evident that persons with middle ear involvement benefit maximally from sound amplification provided by hearing aids, whereas persons with inner ear or central types of hearing losses obtain only limited help from these devices. If a hearing loss exceeds about 30 decibels, a person is socially handicapped as far as his verbal communication ability is concerned. A person with approximately 80 decibels hearing loss has a complete loss of serviceable hearing for speech, and usually receives limited help from the use of hearing aids.

**Labyrinthine Examination.** All children with a hearing loss should have an examination of the static labyrinth. Vastine said: "As goeth the labyrinth, so goes the cochlea." The reverse could also hold true. Caloric and turning tests as well as nerve electrical stimulation tests of vestibular function should be carried out whenever possible.

#### CONSERVATION-OF-HEARING PROGRAMS

Effective treatment of hearing impairment is dependent upon early detection. The two most important methods of detection are

routine testing of the hearing of school children and of preschool children as a part of their regular health examinations. School children should all be examined at least every three years; those who are known to have borderline hearing impairment, speech defects or acquired ear trouble should be examined promptly.

A complete hearing clinic requires the services of otologists, audiologists, speech pathologists, pediatricians, psychologists, psychiatrists, special education experts and social workers to evaluate and assist the hard-of-hearing child. A number of such clinics have been established by educational institutions and foundations.

Hearing-testing programs for school children should be sponsored by each state and should have the support and cooperation of the state and county medical societies as well as the local school authorities. Each county medical society should appoint an otologist to examine children found to have definite hearing losses. Parents should be present during these examinations and, if treatment and further examinations are necessary, should be advised to take their children to private otologists or clinics. The school nurse or some other staff member should follow through on each case to see that the children with hearing impairment secure proper treatment.

All children with speech defects which appear to be due to a hearing loss and those whose better ear has an impairment of 25 decibels or more at 500, 1000 or 2000 cycles, which does not improve with medical care within six months, should be referred for speech training and lip reading. Hearing aids should be considered for children whose hearing shows an impairment of 30 decibels or more at 500, 1000 or 2000 cycles and does not improve within six months with medical care. Children with average intelligence quotients who fail repeatedly in their schoolwork because of impaired hearing, in spite of assistance of medical treatment, lip reading and hearing aids, should be referred to a school for the deaf.

Prevention of hearing losses is of first importance. Preventive methods include (1) immunization of children against contagious diseases which may endanger hearing; (2) avoidance of swimming by children with dry perforations of the ear drum and by all children during acute upper respiratory tract infections; (3) appropriate management of acute upper respiratory tract infections; and (4) prompt and adequate treatment of purulent

otitis media. Additional measures which may be of value in preventing hearing losses are the removal of wax in the external canal, prompt treatment of external otitis, removal of infected lymphoid tissue in the nasopharynx, treatment of sinus infections, control of allergy, treatment of metabolic disorders and avoidance of drugs which damage the eighth nerve.

Serous otitis media is common, especially among smaller children, and in this age of the antibiotics often considered harmless. Although antibiotic treatment will prevent complications, such as purulent otitis media and mastoiditis, it frequently fails to resolve the infection, which continues at a low, sub-clinical level. Eventually the exudate is organized, scar tissue is formed in the middle ear, and function is permanently impaired. This sequence of events makes it imperative to drain accumulations of fluid of the middle ear through myringotomy, repeatedly if necessary, and to apply suction in order to remove the tenacious secretions (see p. 765).

Careful audiometry is essential not only for the diagnosis of hearing loss, but also for evaluation and guidance of therapy. It is entirely improper to continue therapy of any kind unless measurable improvement is manifested by repeated audiometric measurements.

Every child with a permanent or irreversible hearing loss should be evaluated from many aspects in relation to his educational, economic and social future. His speech de-

velopment, intelligence, school achievement, personality adjustment and his parents' understanding of his problems must be known and evaluated.

DEAN M. LIERLE

## REFERENCES

- Davis, H.: The Articulation Area and the Social Adequacy Index for Hearing. *Laryngoscope*, 58:761, 1948.
- Dix, M. R., and Hallpike, C. S.: The Peep-Show (A New Technique for Pure-Tone Audiometry in Young Children). *Brit. M.J.*, 2:719, 1947.
- Ewing, I. R., and Ewing, A. W. G.: The Ascertainment of Deafness in Infancy and Early Childhood. *J. Laryng. & Otol.*, 59:309, 1944.
- Fowler, E. P.: A Method for the Early Detection of Otosclerosis: A Study of Sounds Well above Threshold. *Arch. Otolaryng.*, 1936, 24:731, 1936, *Tr. Am. Otol. Soc.*, 1936, pp. 26, 275.
- Gaeth, J. H.: A Study of Phonemic Regression in Relation to Hearing Loss. Doctoral Dissertation, Northwestern University, XVI, 1948.
- Keaster, J.: Quantitative Hearing Test for Young Children. *J. Speech Disorders*, 12:159, 1947.
- Lierle, D. M., and Reger, S. N.: Correlations between Bone and Air Conduction Acuity Measurements over Wide Frequency Ranges in Different Types of Hearing Impairments. *Laryngoscope*, 56: 187, 1946.
- Newhart, H., and Reger, S. N.: Syllabus of Audiometric Procedures in the Administration of a Program for the Conservation of Hearing of School Children. Rochester. Minn., American Academy of Ophthalmology and Otolaryngology, 1945.
- Walsh, T. E., and Silverman, S. R.: Diagnosis and Evaluation of Fenestration. *Laryngoscope*, 56: 536, 1946.

## THE LARYNX

Symptoms referable to disturbances of the larynx are dyspnea, stridor, wheezing, hoarseness and aphonia. Dyspnea may be due to other causes, but the dyspnea of laryngeal obstruction is characteristically associated with inspiratory indrawing at the suprasternal notch and supraclavicular spaces, as well as with stridor. However, not all inspiratory indrawing at the suprasternal notch is the result of high obstruction; it also occurs when the accessory muscles of respiration are brought into play as in generalized obstructive emphysema (see p. 806). Wheezing of laryngeal disease occurs in the inspiratory phase in contrast to that of asthma and other bronchiolitic disturbances, which is predominantly in the expiratory phase.

The only method of examining the larynx

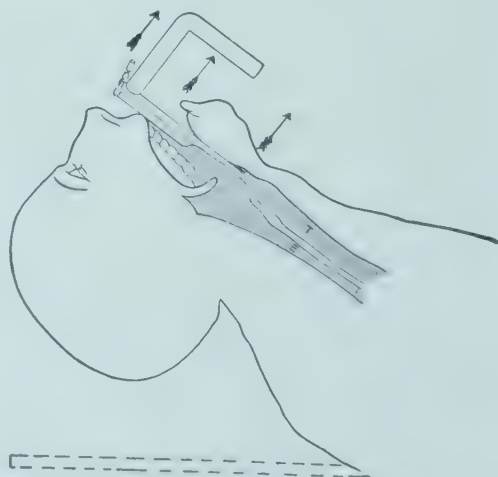


FIG. 214. Direct laryngoscopy affords the only means of objective examination of the larynx in an infant or a child under 6 years of age.



of a child under six or seven years of age is by direct laryngoscopy (Fig. 214). Direct laryngoscopic examination is therefore indicated in the presence of the symptoms mentioned and may afford a means of treatment as well as of diagnosis. Thorough physical examination, appropriate roentgenographic examination and bacteriologic studies are also essential for the appraisal of laryngeal disease.

## CONGENITAL MALFORMATIONS

### CONGENITAL LARYNGEAL STRIDOR

Noisy, crowing respiratory sounds, usually associated with inspiration, are relatively common in the neonatal period and during the first year of life. Some infants merely have noisy breathing, whereas others have a laryngeal "crow," hoarseness or aphonia, dyspnea, and inspiratory retractions in the supraclavicular, intercostal and subcostal spaces. If inspiratory retractions are severe, deformity of the thorax may result. Infants with severe dyspnea frequently have difficulty in nursing, so that undernutrition is common. Cyanosis is rarely observed. Respiratory infections tend to exaggerate all the symptoms.

In the first few days of life it may be difficult to distinguish between congenital disturbances of the larynx and transient disturbances such as the laryngospasm of tetany of the newborn or laryngeal edema secondary to trauma or aspiration of irritant substances at birth. The history of aspiration at birth, hoarseness or aphonia and laryngoscopic examination establish the presence of post-natal laryngeal edema.

Stridor persisting or appearing after the first few days of life usually results from disturbances in or adjacent to the larynx. The most common of these is congenital deformity or flabbiness of the epiglottis and supraglottic aperture. Developmental malformations may be present, or there may merely be an exaggeration of the normal "omega" shape of the infantile epiglottis. Anomalies of the larynx

include malformations of the laryngeal cartilages, intraluminal webs, and malformations or duplication of the vocal cords. At times generalized chondromalacia of the larynx and trachea may be observed. In such instances the larynx and trachea tend to collapse with inspiration and to expand with expiration. Congenital tumors such as fibromas of the larynx are rare. Mucous retention cysts, branchial cleft cysts and thyroglossal duct remnants are other infrequent causes of stridor. Birth trauma must also be considered in the differential diagnosis.

Stridor may also be produced by extralaryngeal causes. Hypoplasia of the mandible permits the base of the tongue to interfere with the epiglottis. Macroglossia from hypertrophy of the muscles, hemangioma, lymphangioma or cysts may have the same effect. Compression of the larynx by congenital goiters has been reported. Congenital vascular anomalies (p. 877) may also cause stridor. Enlargement of the thymus is rarely, if ever, responsible for stridor.

**Diagnosis.** Most cases of congenital laryngeal stridor can be diagnosed only by direct laryngoscopy. Abnormalities of the epiglottis, the vocal cords and the larynx can be visualized by this examination.

Extralaryngeal causes of stridor can often be diagnosed without the aid of direct laryngoscopy. The stridor associated with macroglossia or hypoplasia of the mandible can be relieved by pulling the tongue and mandible forward. Vascular anomalies which partially occlude the trachea and esophagus can often be detected by fluoroscopic observation during a "barium swallow" (p. 877).

**Treatment.** The most common cause of laryngeal stridor, "flabby" epiglottis, rarely requires treatment. The condition is seldom serious, and symptoms gradually become less severe, generally disappearing by about one year of age. Cysts, webs, tumors and malformations of the larynx require various specialized procedures, such as excision, dilata-

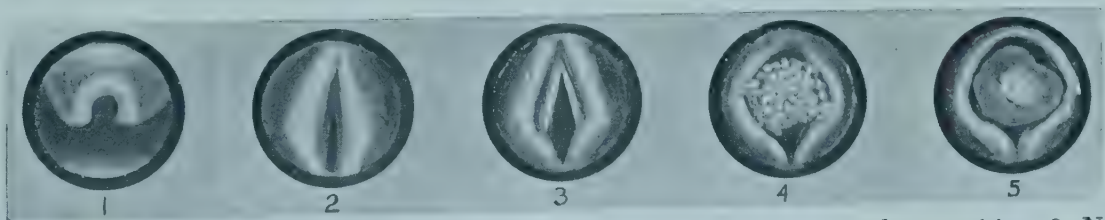


FIG. 215. 1, Epiglottis of child as seen by direct laryngoscopy in the recumbent position. 2, Normal larynx spasmodically closed, as is usual on first exposure without anesthesia. 3, Same on inspiration. 4, Supraglottic papillomas as seen on direct laryngoscopy in a child of 2 years. 5, Cyst of the larynx in a child of 4 years, seen on direct laryngoscopy without anesthesia.

tion, laryngoplasty or tracheotomy. The treatment of the various extralaryngeal causes of stridor is discussed elsewhere with the descriptions of the various clinical entities.

Particular attention must be given to the feeding of infants with stridor. Aspiration is an ever-present danger. Moreover, the respiratory efforts preclude normal sucking and swallowing in some infants. Slow, careful feedings from a small nipple or by dropper or glass are usually adequate. Feeding by gavage or even gastrostomy is occasionally necessary.

Infants with stridor must be protected from respiratory infections.

### CONGENITAL WEB

This condition is not common, but its immediate diagnosis is essential. If the web is complete or almost complete, the newborn infant will quickly become asphyxiated. A few cases are on record in which such a web was perforated or removed with sufficient promptness to save the infant's life. Often the web is only sufficiently obstructive to cause stridor and mild dyspnea.

**Diagnosis and Treatment.** Direct laryngoscopy affords the means for both diagnosis and treatment. In some instances it may be necessary to insert a tracheotomy tube while a series of dilatations is carried out. If the web is incised instead of dilated, care should be taken to incise it along one cord, and subsequently to prevent the cut edges from growing together.

## TRAUMA OF THE LARYNX

### BIRTH TRAUMA

Injury of the larynx during birth is not infrequent. It may result in *dislocation of the cricothyroid or cricoarytenoid articulations*. Such an injury will result in hoarseness and at times in wheezing or fluttering respiratory sounds. The *diagnosis* is made by direct laryngoscopic examination. *Treatment* by direct laryngoscopic manipulations, using a laryngeal dilator, may be effectual, but tracheotomy should be done when there is evidence that the infant is not getting enough air.

*Unilateral or bilateral recurrent laryngeal paralysis* may also be produced by birth trauma, especially during instrumental delivery. When only one cord is paralyzed, there may be only hoarseness and a slight stridor. There is usually no dyspnea. In bilateral paralysis there is dyspnea and stridor. Direct laryngoscopic examination will establish the

diagnosis. When there is bilateral paralysis, tracheotomy is usually necessary. A valvular cannula may be worn, and later a laryngoplasty may be done to permit decannulation, unless breathing through the larynx has improved spontaneously.

### POSTNATAL TRAUMA

Any trauma such as that brought about by a fall against a hard object may produce acute or chronic stenosis of the larynx. *Diagnosis* and *treatment* are those of stenosis from too high tracheotomy or from too prolonged intubation. Immediate tracheotomy is required in the acute stage if there are signs of high obstruction.

## LARYNGEAL STENOSIS

### ACUTE LARYNGEAL STENOSIS

Acute stenosis may result from any of the acute infections, diphtheritic or nondiphtheritic, which are responsible for edema of the subglottic region, from inflammation secondary to the inspiration of a vegetal foreign body such as a peanut, and especially after instrumentation in the removal of such an object, from noninflammatory edema resulting from allergic factors or cardiorenal disease and from a foreign body lodged in the larynx.

**Treatment.** This consists in immediate provision of an airway by intubation or tracheotomy, after which appropriate medical treatment can be instituted.

### CHRONIC LARYNGEAL STENOSIS

Chronic laryngeal stenosis is a frequent sequel of high tracheotomy, i.e., a tracheotomy in which the first tracheal ring or the cricoid cartilage has been damaged. It is a rare complication of tracheotomy when care is taken to keep these two structures intact. The various laryngeal diseases which may be responsible for chronic stenosis include laryngeal diphtheria, acute laryngitis, syphilis, tuberculosis, burns by roentgen rays or radium, and external trauma.

**Pathology.** Scarring and stenosis develop in the subglottic region, and at times there is necrosis of cartilage.

**Clinical Manifestations.** These are generally limited to inability to decannulate the tracheotomized patient or to extubate the intubated patient. When neither intubation nor tracheotomy has been done, there will be dyspnea with audible stridor and indrawing



at the suprasternal notch and at the supraclavicular and intercostal spaces.

**Diagnosis.** Diagnosis is by direct laryngoscopy, supplemented by palpation of the larynx and by roentgenographic examination. The *prognosis* for eventual cure is good, though many patients require treatment for months or years.

**Treatment.** Treatment depends upon the severity of the condition. In the milder cases replacement of the tracheotomic cannula by a smaller one, and occlusion of this tube with a cork (at first a partial occlusion and then a complete one), will re-educate the patient to breathe through the mouth and permit removal of the cannula. If this is not successful, dilatation through a direct laryngoscope may accomplish the desired result. Such dilatation should not be done at too frequent intervals, and each series of dilatations should be followed by a period of rest. When neither of these methods has sufficed to re-establish adequate breathing through the larynx, laryngostomy must be done.

## NEOPLASMS OF THE LARYNX

### BENIGN TUMORS

#### PAPILLOMA

This is the most common benign tumor of the larynx in children. The lesions may grow profusely from any portion of the larynx, though usually from the vocal cords. The tumor rarely, if ever, becomes malignant, and often disappears after puberty. Initially, the only *symptom* is hoarseness; but if the condition is allowed to persist, there is likely to be dyspnea; asphyxia has occurred in unrecognized cases. The *diagnosis* may be made by direct laryngoscopy during the stage of hoarseness, even in an infant. The lesions are pinkish, warty tumors, which scalp off easily when grasped with forceps. The diagnosis should be confirmed by histologic examination.

The best *treatment* is superficial removal of the tumors by forceps through the direct laryngoscope. Care should be taken not to damage normal tissues. Cure will ultimately be obtained, even though at first there is usually rapid recurrence. The disease is self-limited, and eventually the tendency to recurrence will cease. If recurrence is too rapid to be kept under control by this method, and asphyxia threatens, a tracheotomy should be done; the tracheotomic cannula should be left in place while the tendency to recurrence

persists. More extreme therapeutic measures such as radical surgical excision or intensive irradiation are absolutely contraindicated.

#### FIBROLIPOMA

This is a rather rare tumor of the larynx which, though histologically benign, may cause death by asphyxia unless it is removed while still small. In one of the author's patients a large tumor of this kind had so deformed the larynx that chronic stenosis persisted, though the patient's life was saved by tracheotomy. The tumor was extirpated without damage to the larynx.

#### VOCAL NODULES

These are small tumors which occur in children at the junction of the anterior and middle thirds of the vocal cords. They are generally bilateral. They have been called "screamer's nodes" or "singer's nodes." The only *symptom* is slight hoarseness. The nodules may be removed by a small cupped forceps under direct laryngoscopic view.

### OTHER BENIGN NEOPLASMS

During childhood, angiomas and adenomas, as well as various "benign tumors of inflammatory origin" such as hematomas and cysts, may occur in the larynx.

#### MALIGNANT TUMORS

Malignant tumors of the larynx are rare in childhood; epithelioma and sarcoma occasionally occur. *Treatment* is the same as in adults, namely, radical surgical excision or irradiation, the method depending upon the location and extent of the process.

## FOREIGN BODIES IN THE LARYNX, TRACHEA AND BRONCHI

The air passages of children are frequent sites for the lodgment of many kinds of exogenous foreign bodies; the carelessness of adults is the most important contributory factor.

**Pathology.** The changes produced by foreign bodies depend upon their character and upon the degree of obstruction of the air passage. A sharp or irritating object lodged in the larynx will produce severe edema and later suppurative perichondritis. In the bronchus a nonobstructive foreign body may produce little pathologic change, whereas an ob-

structive object will produce atelectasis and later bronchiectasis, pulmonary abscess or empyema. On the other hand, a vegetal object, such as a peanut, may produce immediately a generalized inflammatory condition involving not only the portion of the tracheobronchial tree obstructed, but also the entire respiratory tract. Pneumonia, contrary to popular opinion, does not as a rule occur as the result of lodgment of a foreign body in the air passages.

**Clinical Manifestations.** The initial symptoms of a foreign body in the air passages are choking, gagging, wheezing or cough. After the initial period there is often a symptomless interval which may last for hours, days or weeks. By the time symptoms reappear the initial ones may have been forgotten. The secondary symptoms usually give a clue to whether the foreign body is lodged in the air or food passages, and may indicate the level of lodgment. On occasion, however, dysphagia may occur from the swelling which results from lodgment of a foreign body in the region of the larynx, and foreign bodies in the upper esophagus may cause symptoms referable to the air passages by compression or by the overflow of food or secretions into the larynx. The symptoms localizing a foreign body to the larynx, trachea or bronchi are discussed below.

#### LARYNGEAL FOREIGN BODY

**Clinical Manifestations.** A foreign body in the larynx causes hoarseness, a cough which soon becomes croupy, and aphonia. Hemoptysis, dyspnea with wheezing, and cyanosis may occur. Obstruction resulting from the foreign body or the combination of it and the inflammatory reaction to it may prove fatal if the signs of high respiratory tract obstruction are not promptly recognized and appropriate treatment given.

**Diagnosis.** Roentgenographic and direct laryngoscopic examinations reveal the presence of a foreign body in the larynx. An opaque foreign body in the neck will be clearly demonstrated on a lateral roentgenogram. When it is lodged anteriorly, it is obviously in the larynx; when it is behind the soft tissue shadows of the larynx, it is in the hypopharynx or the cervical esophagus. The plane in which the foreign body lies is another differential point in its localization. If it lies in the sagittal plane, it is in the larynx. If it is in the coronal plane, it is probably in the food passage. Even if the foreign body is nonopaque, indirect evidence of its presence

may be afforded by the roentgenographic examination. Films should always be taken from both the lateral and the anteroposterior projections, although the lateral projection is generally the more useful. In some instances administration of a small amount of opaque material will also be helpful. Direct laryngoscopy will confirm the diagnosis and provide access for instrumental removal of the foreign body. When there is a severe degree of dyspnea, it may be advisable to do a tracheotomy prior to the laryngoscopic examination.

#### TRACHEAL FOREIGN BODY

Though a foreign body in the trachea may be responsible for cough, hoarseness, dyspnea and cyanosis, the characteristic signs are the audible slap, the palpatory thud and the asthmatoïd wheeze. The *diagnosis* of tracheal foreign body may occasionally be made from the symptoms, physical signs and roentgenogram of the chest, but in most instances a definite diagnosis can be made only by bronchoscopy.

#### BRONCHIAL FOREIGN BODY

**Clinical Manifestations.** The initial symptoms are usually similar to those of foreign bodies in the larynx and trachea. Cough, blood-streaked sputum, and metallic taste in the case of metallic foreign bodies, are other symptoms which may be produced by bronchial foreign bodies. The degree of obstruction produced by a bronchial foreign body is a determining factor in the symptomatology as well as in the pathologic changes. A *non-obstructive* foreign body may produce few symptoms even after prolonged sojourn. An *obstructive* foreign body quickly produces symptoms and signs and pathologic changes. When there is only a slight obstruction, a wheeze will be noted. When obstruction is of greater degree, obstructive emphysema or obstructive atelectasis will be produced; if either is allowed to persist, chronic bronchopulmonary disease is liable to be a sequel. When both main bronchi are obstructed, there will be severe dyspnea and even asphyxia. If the foreign body is vegetal, as, for example, a peanut, a severe condition known as *vegetal bronchitis*, or *arachidic bronchitis*, will result. This is characterized by cough, a septic type of fever, and dyspnea. Chronic pulmonary suppuration may be expected when a bronchial foreign body has been present for a long time.

**Diagnosis.** In the diagnosis of a bronchial foreign body the symptoms will depend upon



the stage in which the patient is seen. The possibility of a foreign body as an etiologic factor must be considered in every child with an acute or chronic pulmonary lesion regardless of whether there is a history of a foreign body accident. The physical signs of bronchial obstruction from foreign bodies include limited expansion, decreased vocal fremitus, impaired (atelectasis) or hyperresonant (emphysema) percussion note and diminished breath sounds distal to the foreign body. When there is complete obstruction, with a so-called drowned lung or with atelectasis, there is absence of vocal resonance and vocal fremitus, which may lead to an erroneous diagnosis of empyema. Varying degrees of tympany may be noted over areas of obstructive emphysema, which may persist for a time. Rales are more likely to be on the uninvaded side, but may also be present on the invaded side.

In order to understand the physical signs and the roentgenographic appearance of bronchial obstruction it is necessary to think of the fundamental principles of hydraulics, and to recognize the analogy between the types of valvular obstruction produced by foreign bodies and the different types of valves used in pipes (Fig. 216). What is considered a *first-degree* obstruction may be compared to a bypass valve, which allows passage of air or fluid in both directions, with only slight interference. In such cases a *wheeze* will be produced. In a *second-degree* obstruction there is sufficient interference with the passage of air to permit it to go in one direction only. A "check-valve" action of this sort in the bronchial

tree depends primarily upon the physiologic expansion of the bronchus on inspiration and its contraction on expiration. If the lumen is obstructed by an object which is of just the right size to cause complete obstruction in the expiratory phase, but to allow air to pass in the inspiratory phase, air will enter the distal portion of the lung on inspiration, but little or none will escape during expiration. This type of obstruction produces *obstructive emphysema* (Fig. 217). If blockage of the bronchus is complete, either by complete corking of the bronchus by the object itself or by an obstruction produced by the foreign body in combination with the inflammatory swelling of the bronchial mucosa, a stop-valve obstruction results, and the air in the distal portion of the lung is soon absorbed, leaving an area of *obstructive atelectasis* (Fig. 218). These phenomena are most readily appreciated by observation under the fluoroscopic screen. In a bypass valve obstruction there is little or no roentgenographic evidence produced by a non-opaque foreign body.

When there is a check-valve type of obstruction, the presence of *obstructive emphysema* makes it possible to localize a bronchial foreign body. The obstructed lung will remain expanded during expiration, while the heart and mediastinum will shift to the opposite side as the unobstructed lung empties. The diaphragm is low, flattened and fixed on the obstructed side, while its excursion will be free and even exaggerated on the unobstructed side. The differences between the two lungs are much more evident on expiration than on inspiration. If a permanent record is desired, two films should be taken, one on full inspiration and one at the end of expiration.

When there is complete obstruction of the bronchus, producing *obstructive atelectasis*, the heart and mediastinum are drawn toward the obstructed side and remain there during both phases of respiration.

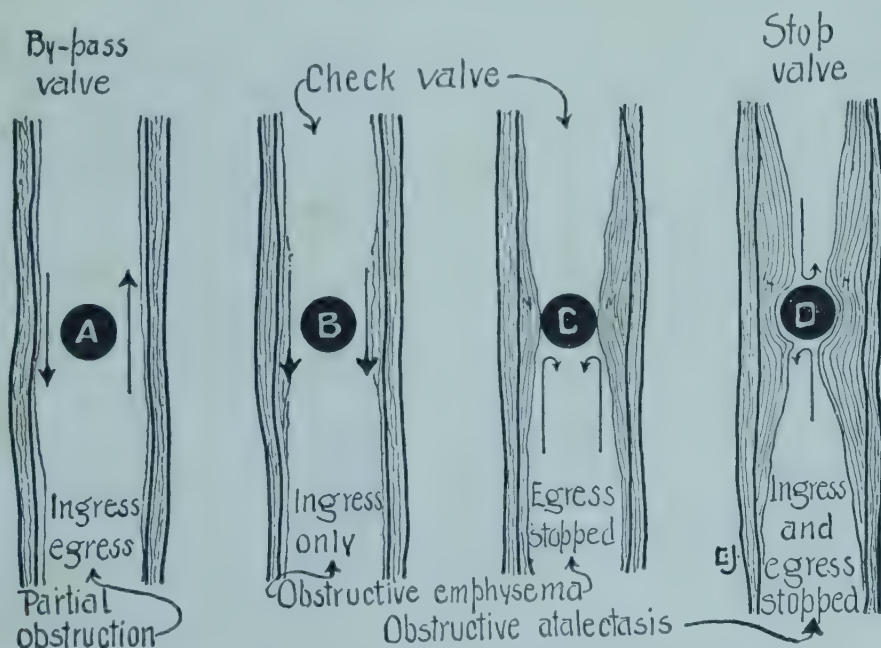


FIG. 216. Schema showing mechanism of production of obstructive emphysema and obstructive atelectasis by a bronchial foreign body.

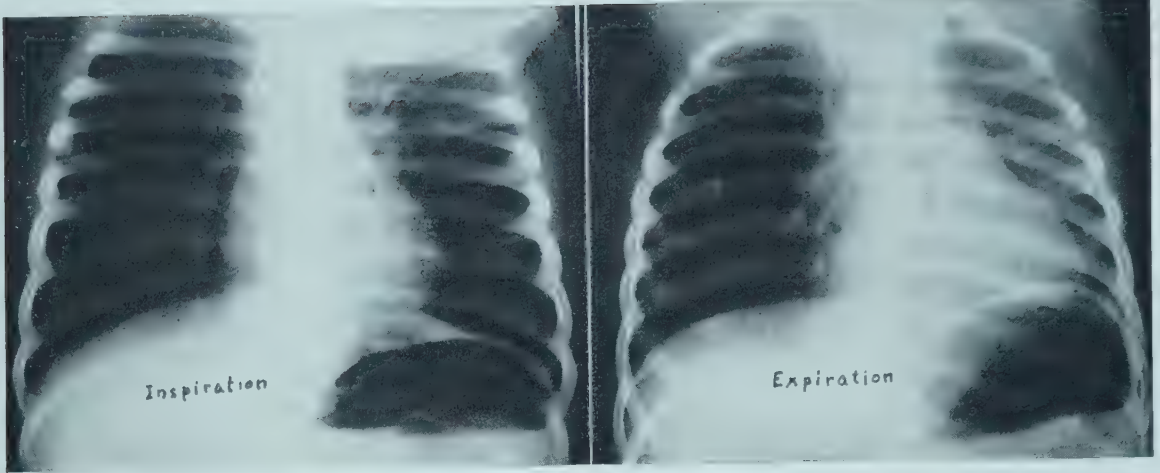


FIG. 217. Obstructive emphysema produced by a vegetal foreign body in the right bronchus of a child 15 months of age. Note that the emphysema is best demonstrated by the film taken on expiration.

The diaphragm on the obstructed side remains high, while that on the unobstructed side moves normally. Films taken at the end of inspiration and of expiration will show only the slight difference resulting from the filling and emptying of the unobstructed lung. After the physician has observed these phenomena under the fluoroscope and has come to appreciate the principles of the valvular mechanisms, it is much easier for him to understand the physical signs produced.

Opaque foreign bodies are clearly revealed on the roentgenogram. It is necessary to take films from both the anteroposterior and the lateral positions, with a sufficiently heavy exposure in the anteroposterior view to show a foreign body behind the heart.

**Prognosis.** Foreign bodies in the air passages which are not removed are sooner or later fatal in the majority of instances. Only 2 to 4 per cent of foreign bodies are coughed up spontaneously. About 99 per cent of them can be removed safely by the skilled bronchoscopist, and at least 98 per cent of patients so treated should recover completely when the foreign body is removed.

**Prevention.** Much can be done to avoid foreign body accidents. If small objects are kept out of the reach of children, if children too young to masticate are not given candy containing nuts, and if toys which contain small parts loosely attached are not given to children, many serious cases of foreign body in the air passages will be prevented. Beads, the button box and coins should not be given to children as playthings. Safety pins should not be left near the baby's crib; if they are left within reach, they should always be closed. The closed safety pin is not a dangerous foreign body, but the open one is among

the most dangerous, and the most difficult to remove safely. Adults should not set a bad example by holding pins or other objects in the mouth. The impulse to imitate is strong in a young child; frequently foreign body accidents occur because a baby or young child has imitated an adult by putting foreign objects in his mouth.

**Treatment.** The treatment of foreign body in the air passages consists in removal by direct laryngoscopy or bronchoscopy, with due consideration for the mechanical problem involved in the particular case. In some instances treatment of complicating conditions may be of equal importance. Removal

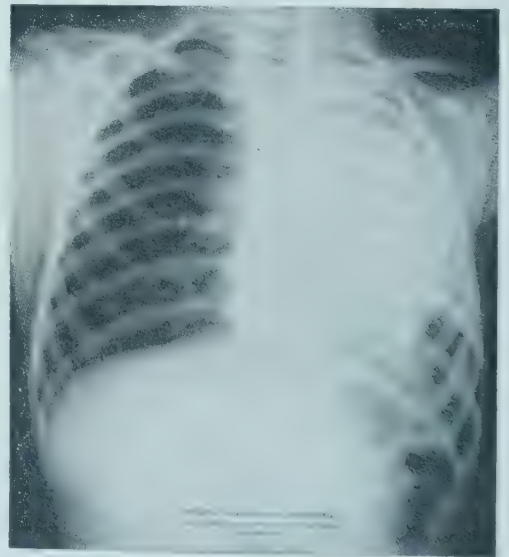


FIG. 218. Foreign body lodged in left main bronchus, producing atelectasis of entire left lung. Note that the heart is drawn completely into the left chest.



of opaque foreign bodies lodged in the peripheral bronchi should be performed under the biplane fluoroscope. Any secondary infection should be treated with appropriate antimicro-

bial agents as indicated by laboratory sensitivity tests of the pathogenic organism.

CHEVALIER L. JACKSON

## ACUTE INFECTIONS OF THE LARYNX

### GENERAL CONSIDERATIONS

Acute infections of the larynx are of relatively greater importance in infants and small children than in older children. This is true in part because of a somewhat greater incidence in the younger age group, but principally because the younger child has a relatively smaller airway which predisposes to greater respiratory distress.

Acute infections of the larynx are rarely isolated lesions, but are usually associated with some involvement of the adjacent portions of the respiratory tract. However, when there is sufficient involvement of the larynx to produce symptoms, the laryngeal part of the clinical picture is likely to overshadow other manifestations, owing to the severe effects upon vocalization and breathing.

Presumably any of the bacterial and viral pathogens of the respiratory tract can be responsible for laryngeal infection (see Etiologic Considerations of Newly Isolated Viruses, p. 746). None of them, including the diphtheria bacillus, produces a sufficiently characteristic lesion to permit an etiologic deduction from clinical examination alone. The manifestations of hoarseness, aphonia, stridor and inspiratory dyspnea, characterized by suprasternal, substernal, subcostal and intracostal respiratory retractions, are common to infections of whatever etiology. An absolute diagnosis can be established only by laryngoscopic and bacteriologic examinations.

Although an exact classification of acute laryngeal infection is not possible, there are several clinical varieties which, because of etiologic and therapeutic differences, would seem to justify the following classification:

- Acute diphtheritic laryngitis (p. 415)
- Acute spasmodic laryngitis
- Acute nondiphtheritic infections
  - Laryngitis
  - Epiglottitis
  - Laryngotracheobronchitis

### ACUTE SPASMODIC LARYNGITIS

#### (CROUP DIATHESIS)

Acute spasmodic laryngitis, or spasmodic croup, is a self-limited, but usually recurrent,

catarrhal inflammation in which the severity of the laryngeal spasm is out of proportion to that of the infection. The laryngeal involvement comes on suddenly, almost invariably during the night, and is, as a rule, preceded by a mild upper respiratory tract infection. Certain children seem to be especially predisposed to spasmodic laryngitis, and in some instances there is a familial predisposition. The "nervous type" of child is more often affected than is the phlegmatic type. Spasmodic laryngitis is uncommon after five or six years of age and is relatively common only between the ages of two and four years.

**Clinical Manifestations.** Symptoms of the attack may be preceded by moderate coryza and hoarseness for several hours, or the child may have been put to bed apparently entirely well. Less frequently laryngitis, accompanied by fever and a somewhat croupy cough, precedes the spasmodic symptoms. Early in the night, either after gradually increasing dyspnea and some cough or suddenly, the child awakens with a characteristic barking, metallic cough and noisy inspirations. He sits up in bed, struggling for breath, obviously frightened, and often grasps at his throat because of the feeling of oppression and impending suffocation. His face is congested, his expression anxious, his lips and extremities may be cyanotic, and his alae nasi and accessory muscles of respiration move with each stridulous inspiration. The voice is hoarse, the pulse accelerated and the skin moist. There may be little elevation of temperature, usually not over 101° F., but prostration is present. The dyspnea increases with excitement or without discoverable reason. After several hours the severity of the spasm and of the other symptoms diminishes, although more than one attack may occur during the night. By the following morning the evidence of laryngospasm has disappeared, and only slight hoarseness and loose cough remain; the child does not otherwise appear to be seriously ill. Another, but usually less severe, attack may occur upon the next night and occasionally upon the third night unless they are prevented by treatment.

The foregoing description is of severe cases.

In milder ones there may be only a croupy cough and a moderate degree of laryngospasm and dyspnea.

The prognosis is good.

**Diagnosis.** In *diphtheritic laryngitis* the onset is gradual; hoarseness and stenosis become progressively worse; fever and decided depression of strength are more constantly present, and the cough is not so barking. The laryngospasm of *tetany* is usually of momentary duration and may be repeated many times during the day; carpopedal spasm may be associated; and the blood calcium is low. The differentiation from acute laryngitis is described on page 416.

**Prevention.** Prophylactic treatment should be given when a child known to be subject to attacks of croup has hoarseness or a suspicious cough during the daytime. A subvomiting dose of syrup of ipecac (0.5 to 1 cc.) and a sedative dose of phenobarbital (15 to 30 mg., or  $\frac{1}{4}$  to  $\frac{1}{2}$  grain) should be given shortly before bedtime and the sleeping room kept moderately warm (70° F.) and well humidified. Similar treatment may be given for two or three evenings after an attack to prevent subsequent attacks. When there is a chronic infection of the upper respiratory tract, efforts should be made to eradicate it. Cold air should be avoided during respiratory infections; some children subject to croup cannot sleep in cold, well ventilated rooms without having an attack.

**Treatment.** Treatment consists in relief of the spasm with an emetic such as syrup of ipecac, placement of the child in an atmosphere of high humidity, and administration of a sedative after vomiting has been induced. Doses of syrup of ipecac of 2 to 4 cc. for children two to four years of age are usually adequate to induce vomiting, but may be repeated not more than once or twice at intervals of twenty to thirty minutes. After the child has vomited and there is no nausea, phenobarbital may be given if he is kept under close observation for respiratory obstruction. Intubation is rarely, if ever, necessary in spasmodic laryngitis.

## ACUTE NONDIPHTHERITIC INFECTIONS

### ACUTE LARYNGITIS, EPIGLOTTITIS AND LARYNGOTRACHEOBRONCHITIS

Most acute infections of the larynx involve to some degree the adjacent tissues above and below the glottis. In the majority of instances, however, the involvement seems to be prin-

cipally in the larynx with varying degrees of subglottic edema. Less often the involvement is predominantly in the supraglottic area and is termed epiglottitis. At times the inflammation extends into the trachea and bronchi and even into the bronchioles, when the term "laryngotracheobronchitis" is used. The clinical pattern of each of these anatomic lesions is sufficiently characteristic to justify separate designations.

*Acute laryngitis*, which is somewhat more frequent in children than in infants, may be caused by a variety of viral or bacterial agents. The majority of them appear to be viral in origin (See Myxoviruses, p. 747). The most common bacterial pathogen is type b *Hemophilus influenzae*; in some instances other organisms such as the beta hemolytic *Streptococcus*, *Pneumococcus* and *Staphylococcus aureus* may also be causative. Laryngitis may also be a manifestation of scarlet fever, influenza or measles. Noninfectious laryngitis may at times result from excessive crying or shouting or the inhalation of coal gas, dust, and the like.

*Acute epiglottitis* is also most often caused by type b *H. influenzae*. The infection may occur at any age, but most often in young children.

*Acute laryngotracheobronchitis* is a term that was reserved in the past for a characteristic syndrome involving the laryngeal and tracheobronchial passages in which there is a definite exudative reaction. In some instances the tracheobronchial tree is practically filled with a purulent exudate; in others the secretions dry rapidly, become extremely viscid and obstruct the air passages. This type of involvement has become much less common in recent years. By contrast, infections of the laryngotracheobronchial area with little or no exudative reaction are relatively frequent. For this reason it seems preferable to use the anatomic designation for all infections involving these portions of the respiratory tract, irrespective of the exudative response. These infections occur principally in the first three to four years of life. A number of viral and bacterial agents may be causative; the bacterial ones include *H. influenzae*, hemolytic streptococci, staphylococci and pneumococci.

**Clinical Manifestations.** *Acute laryngitis*. Evidence of laryngeal inflammation usually follows that of an upper respiratory tract infection by one or more days. The progression and the severity of the laryngeal symptoms vary considerably. In mild cases there are



hoarseness, a low grade fever and only mild constitutional symptoms. There is no dyspnea. In the more severe cases there is progression of the disease during the first two or three days. The patient becomes increasingly hoarse, and there may be aphonia. At this stage, dyspnea is usually present, and characteristically there are suprasternal and infrasternal retractions and stridor. The intake of air is decreased, owing to the relatively greater obstruction during the inspiratory phase of respiration. The temperature is usually elevated, often being as high as 103° to 105° F. The child may be prostrated in extreme cases. There are varying degrees of pharyngeal inflammation. Direct laryngoscopy reveals redness and swelling of the vocal cords and adjacent tissues and especially of the subglottic area.

**Acute epiglottitis.** The onset is sudden with sore throat, high fever, prostration and severe inspiratory type of dyspnea. The rapidity of the onset and of the course is characteristic and emphasizes the necessity for early recognition and, in most instances, tracheotomy. In small children who cannot complain of the soreness of the throat the only manifestations may be the extreme restlessness of air hunger, prostration and fever. The redness and swelling of the epiglottis and the immediately adjacent areas can often be seen by the usual pharyngeal examination. The aryepiglottic folds and arytenoids are usually involved, and for this reason some clinicians prefer to use the term "supraglottic laryngitis." There is usually little or no involvement of the vocal cords. The pulmonary findings are those of high (inspiratory) obstruction with suprasternal and infrasternal retractions and diminution in the intake of air.

**Acute laryngotracheobronchitis.** In most instances there is a preceding history of an acute upper respiratory tract infection for a day or more. In the more fulminating infections, most of which appear to be caused by type b *H. influenzae*, the onset may be abrupt, with high fever, prostration and extreme dyspnea. As noted earlier, there is a variety of clinical patterns. The initial respiratory difficulty is usually inspiratory, owing to the laryngeal involvement, but subsequently there is expiratory embarrassment as the inflammation extends downward into the bronchi and even into the bronchioles. Thus the clinical pattern includes features characteristic of both laryngeal (inspiratory) and bronchiolitic

(expiratory) obstructions. There are hoarseness or aphonia and infrasternal and suprasternal retractions, but when there is generalized obstructive emphysema secondary to bronchitic and bronchiolitic involvement, the retractions are not deep. The breath sounds vary considerably and often are prolonged and harsh in both phases. When the obstruction is practically complete, they may be so diminished in volume as to be barely audible. Similarly there are great variations in the adventitious sounds. Most often there are rhonchi and large rales, but there may be medium and even fine rales. If the infant or child is able to sit, he prefers this position. There is usually a persistent cough, which in the more exudative lesions is loose, rattling and croupy. The temperature is usually high, levels of 104° to 105° F. being common.

**Differential Diagnosis.** Diphtheria must be considered in the differential diagnosis of all acute laryngeal infections, and material secured for direct smear and for culture. Furthermore, though many laryngeal infections are viral in origin, bacterial culture and determination of the sensitivities of any isolated organism to various antibiotic agents are desirable; blood cultures should also be obtained.

**Retropharyngeal abscess** may cause stridor, but there is no hoarseness, and the abscess can usually be recognized by palpation of the throat or by laryngoscopic examination. A *foreign body* lodged in the laryngeal area may simulate laryngitis, and the reaction to a vegetal foreign body, such as a peanut, may simulate laryngotracheobronchitis. In such instances fluoroscopic and bronchoscopic studies are necessary.

**Prognosis.** The outcome in all three conditions depends on the severity of the infection, the age of the patient, the duration of symptoms before treatment is instituted, and the adequacy of treatment. The death rate has been high, especially in *H. influenzae* epiglottitis and exudative laryngotracheobronchitis. In cases treated early a favorable outcome can be expected.

Death occurs from respiratory obstruction and from the infection itself. An airway, when needed, can be provided by tracheotomy, and the infection can usually be controlled by appropriate antibiotic therapy.

Chronic bronchitis, bronchiectasis and pulmonary abscesses are occasional residuals of the infection. Chronic laryngeal stenosis and perichondritis are not common except as the result of improperly performed tracheotomies.

**Treatment.** In all three conditions the principles of treatment are identical, and consist in provision of sufficient air (oxygen) and control of the infection.

Humidification of the inspired air is beneficial in all laryngeal infections, irrespective of their severity, to lessen the irritation and drying of the secretions. Cold humidification is preferable to steam and is best provided in a tent or specially designed room. In the home a "croup tent" can be improvised by using a steam humidifier.

Oxygen therapy should be provided whenever the accessory muscles of respiration are used for breathing; one should not wait for the development of cyanosis.

Antibacterial therapy is indicated in all infections of moderate or marked severity. It is true that many of the infections are viral in origin, and hence will not respond to the therapy, but this cannot be predicted, and the severity of the infection justifies the therapeutic trial. Initially, material should be obtained for culture, preferably through a laryngoscope; otherwise both nasopharyngeal and pharyngeal cultures should be secured, the latter while the patient is coughing. Therapy should not be delayed, however, until the results of the culture are available. The initial therapy should be effective against the various possible bacterial pathogens (broad-spectrum). Subsequently when the report of the bacterial culture is available, any indicated changes in the prescription may be made. Inclusion of chloramphenicol in the initial therapy would seem justified in view of the frequency with which these lesions and especially epiglottitis and laryngotracheobronchitis are caused by *H. influenzae*.

Tracheotomy can be a lifesaving measure when the obstruction of the airway is severe. The determination of the need for tracheotomy and the timing of it require experience. When it is clear that the patient has an insufficient airway and that the foregoing measures would not be effective quickly enough, a tracheotomy should be performed immediately. In general, the indications for tracheotomy are the entrance of only minimal amounts of air into the lungs in spite of breathing activity, prostration with extreme pallor and/or cyanosis, and cardiac failure. However, the experienced clinician appreciates that a child can be in considerable respiratory distress and still respond adequately to oxygen, humidification and antibacterial therapy. In acute severe epiglottitis,

tracheotomy is required in 50 per cent or more of cases and should not be delayed when the indications are clear. In laryngotracheobronchitis, tracheotomy may be necessary to provide not only an airway, but also a means for aspiration of the trachea.

One of the commonest errors in the technique of tracheotomy is making the tracheal incision too high or even cutting the cricoid cartilage. This is perhaps the commonest cause of difficult decannulation and chronic stenosis. On the other hand, the tracheotomy incision can be made too low; it is sufficiently low if it is located just below the first tracheal ring. A tracheotomy can be more safely and satisfactorily performed if an intubation tube, a Mosher "life saver" or a small bronchoscope is inserted into the larynx for maintenance of quiet breathing while the operation is being performed.

For the after-care of tracheotomy a nurse, properly instructed and preferably experienced in the care of such patients, must be constantly in attendance. Not only must the inner cannula be removed and cleaned frequently, but also a small catheter should be used to aspirate the outer cannula and the tracheobronchial tree as often as necessary to keep the airway open. If dyspnea or restlessness persists after tracheotomy, the lower airway must be investigated with a small bronchoscope, which may be introduced through the tracheal fistula. In many cases the obstruction can be removed if a few drops of saline solution are dropped into the tracheal cannula with a medicine dropper before aspiration.

The child requires complete rest and must not be disturbed by unnecessary examinations or unnecessary uncomfortable therapeutic measures. Dehydration should be combated by administration of liberal quantities of fluid, preferably by mouth. Opiates and atropine should not be used, owing to their tendency to dull the protective cough reflexes and to dry secretions. If signs of cardiac failure appear, digitalization is indicated.

WALDO E. NELSON

#### REFERENCES

- Miller, A. H.: Acute Epiglottitis: Acute Obstructive Supraglottic Laryngitis in Small Children Caused by *H. Influenzae*, Type B. *Tr. Am. Acad. Ophth.*, 53:519, 1949.
- Rabe, E. F.: Infectious Group. I. Etiology. II. "Virus" Group. III. *Hemophilus Influenzae* Type B Group. *Pediatrics*, 2:255, 415, 559, 1948.



## THE THORACIC CAVITY

For neoplasms of the lung, see page 1350.

### MALFORMATIONS OF THE TRACHEA, BRONCHI AND LUNGS

*Tracheo-esophageal fistula* is the most important congenital anomaly of the trachea (p. 640). Rarely the trachea may be absent, or there may be tracheal stenosis of varying degrees. *Tracheal compression* may be produced by an anomalous aortic arch or other large vessel (p. 877). *Tracheal diverticula* are blindly ending bronchus-like projections arising from the trachea. In rare instances they may terminate in normal-appearing lung tissue (tracheal lobe). Other tracheal abnormalities are mentioned on pages 771 and 1237.

*Bronchial cysts* are usually located in the region of the bifurcation of the trachea.

*Anomalous fissures and lobes of the lungs* are frequently observed roentgenographically and at autopsy, but are usually of no clinical significance. The so-called azygos lobe is actually a part of the right upper lobe. During fetal development the azygos vein normally shifts medially into the mediastinum and onto the vertebral column. If such a migration fails to occur, the vein cuts into the growing right upper lobe, leaving a deep azygos fissure, which separates the more medially placed azygos lobe from the remainder of the right upper lobe; there is no abnormality of the bronchial tree.

*Congenital absence of both lungs* is extremely rare. Bilateral hypoplasia of the lungs may occur in anencephalic monsters or may be associated with congenital diaphragmatic hernia; in the latter instance the lung on the side of the defect in the diaphragm shows the greatest reduction in size.

*Unilateral pulmonary agenesis or hypoplasia* is compatible with life. The heart and other mediastinal structures are shifted to the affected side, and the contralateral lung is hyperexpanded and partially fills the thoracic cavity on the involved side. The stem bronchus on the affected side may be absent, rudimentary or of normal length and covered by a small rudimentary lung. Other associated extrapulmonary anomalies, especially hemivertebrae, may be present.

*A lower accessory lung* is a rare congenital

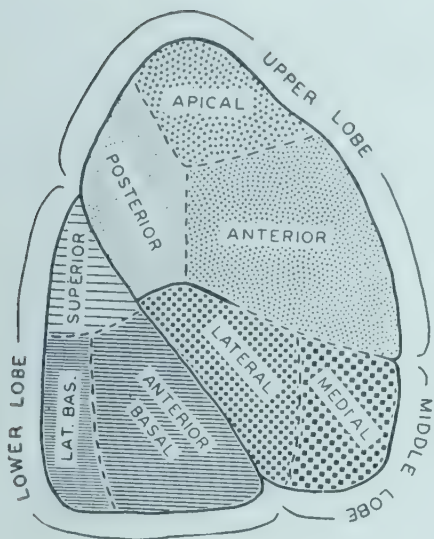
anomaly. The accessory lung does not communicate with the tracheobronchial tree, and its blood supply is usually systemic rather than pulmonary in origin. It is almost always situated at the base of the left lung, rarely below the left diaphragm. Its structure varies from normal-appearing lung to that of a cystic space containing bronchial elements, but few or no alveoli.

Instances of *anomalous (nonpulmonary) circulation* in portions of one or the other of the two lower lobes have also been observed; in these cases there is a bronchial communication, but some maldevelopment of it. The blood supply is from the systemic circulation by way of an anomalous artery from the aorta. The lung tissue is usually replaced by multiple bronchial cysts or bronchiectatic cavities. Surgical removal of the involved lung is indicated.

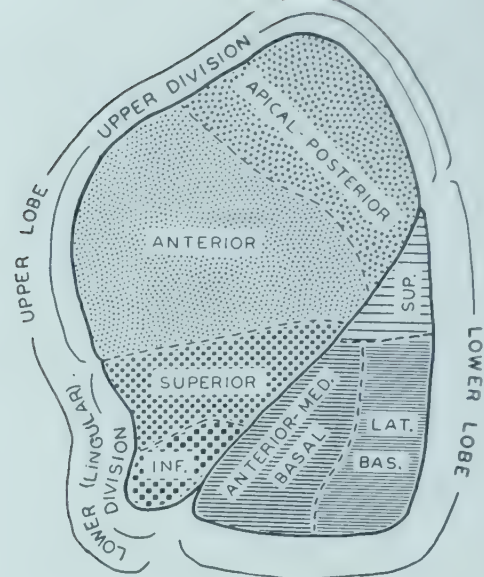
*Cysts of the lungs* are occasionally present in infants early in the newborn period and may be single or multiple, restricted to one lobe or distributed in two or more lobes. There is lack of agreement concerning the origin of many of them. It has been considered that those with an epithelial lining were congenital anomalies and that those without such a lining were the result of post-natal destructive processes. There is doubt whether this distinction is valid or whether the presence of cartilage in the wall of a cyst is in itself evidence of a congenital origin.

Cysts of congenital origin have been described in association with adenomatoid malformations of the lungs (Fig. 221). The lesion, which apparently is most often limited to one lobe, may initially appear on the roentgenogram as a solid structure. The bronchi are malformed. As the lobe is irregularly aerated during the first few days of life, air accumulates in the potential cystic structures. These progressively enlarge and may cause severe respiratory distress.

Most cystic structures in the newborn period or later are acquired and result from destruction of the pulmonary architecture. This may occur during artificial respiration (see Pneumomediastinum, p. 328) and perhaps on occasion might be responsible for an accumulation of air (cyst) within one or more lobes (see Bullous Emphysema, p. 807). Partial blockage of a bronchus with creation of a ball-valve type of mechanism will permit



Lateral View



Lateral View

RIGHT

LEFT

Medial and Basal View

Medial and Basal View

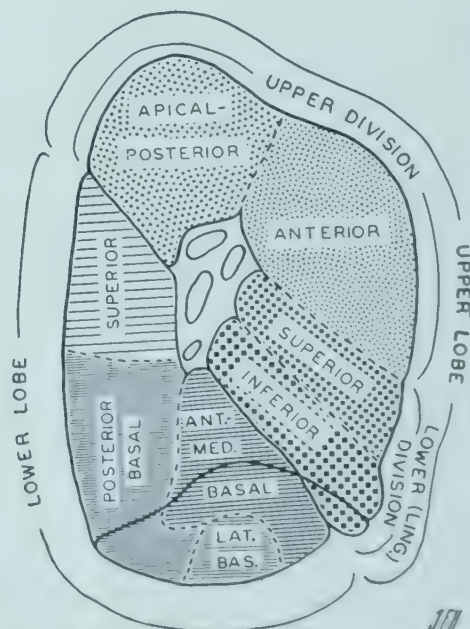
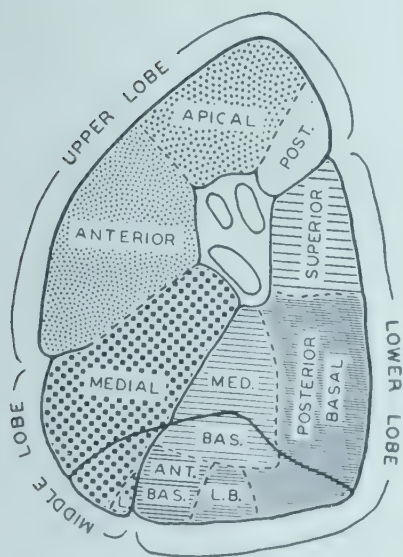


FIG. 219. The lobar and segmental bronchi and the subdivision of the lungs on the basis of bronchial distribution.

It has become significant to subdivide the lungs into parts smaller than the lobes for the sake of more accurate localization of pathologic lesions and of more economical resections in such diseases as bronchiectasis and tuberculosis. Although the lobes are classically identified by the interlobar fissures, it is obvious that a lobe is the complete branching of the bronchus which enters it. The real basis of the division of the



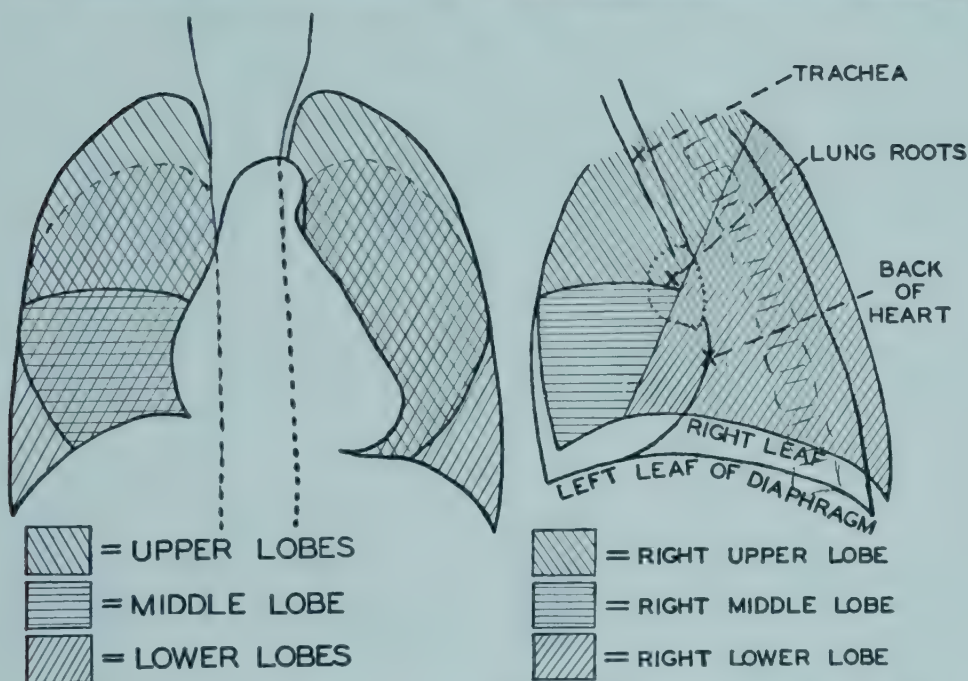
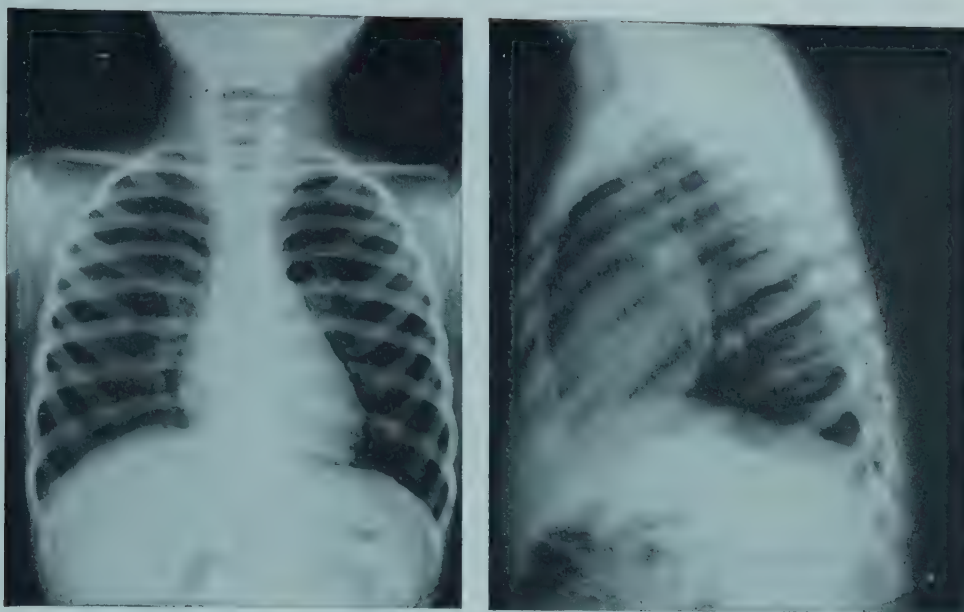


FIG. 220. Ventral and right lateral projections of the thorax in a child 20 months of age, showing normal roentgenographic appearance. The diagrams identify landmarks and indicate the correspondence between various parts of lung fields and the respective lung lobes. In lateral projections, lesions are readily localized to particular lung lobe or lobes. In ventral and dorsal projections there are large areas of the lung fields in which observed lesions might be in either of 2 lung lobes. In lateral projections, relationships to the heart shadow serve to distinguish between right and left leaves of the diaphragm. (Courtesy of Dr. W. Edward Chamberlain, Professor Emeritus of Radiology, Temple University School of Medicine.)

lungs into lobes is bronchial distribution. In a similar way, each lobe is subdivided by the branches coming from the lobar bronchus. For example, there are usually 3 branches of the right upper lobe bronchus, each of which supplies or branches out to form a definitive part of the lobe. The term "bronchopulmonary segment" is applied to that portion of a lobe supplied by a branch of the lobar bronchus. Smaller subdivisions can be made on the basis of the distribution of the branches of the segmental bronchus. These smaller subdivisions are referred to as "subsegments." Each segment is named according to its position in the lobe of which it is a portion. For example, the 3 segments of the right upper lobe are anterior, apical and posterior segments of the right upper lobe. The bronchi are correspondingly named anterior, apical and posterior segmental branches of the right upper lobe bronchus.

At an intersegmental plane the alveoli at the periphery of one segment are separated from the alveoli of the adjacent segment by a small amount of fibrous connective tissue. It is of interest to note that the tributaries of the pulmonary veins are located in the intersegmental planes and that the branches of the pulmonary arteries follow along the bronchial branchings. (Prepared by Dr. John Franklin Huber, Professor of Anatomy, Temple University School of Medicine.)

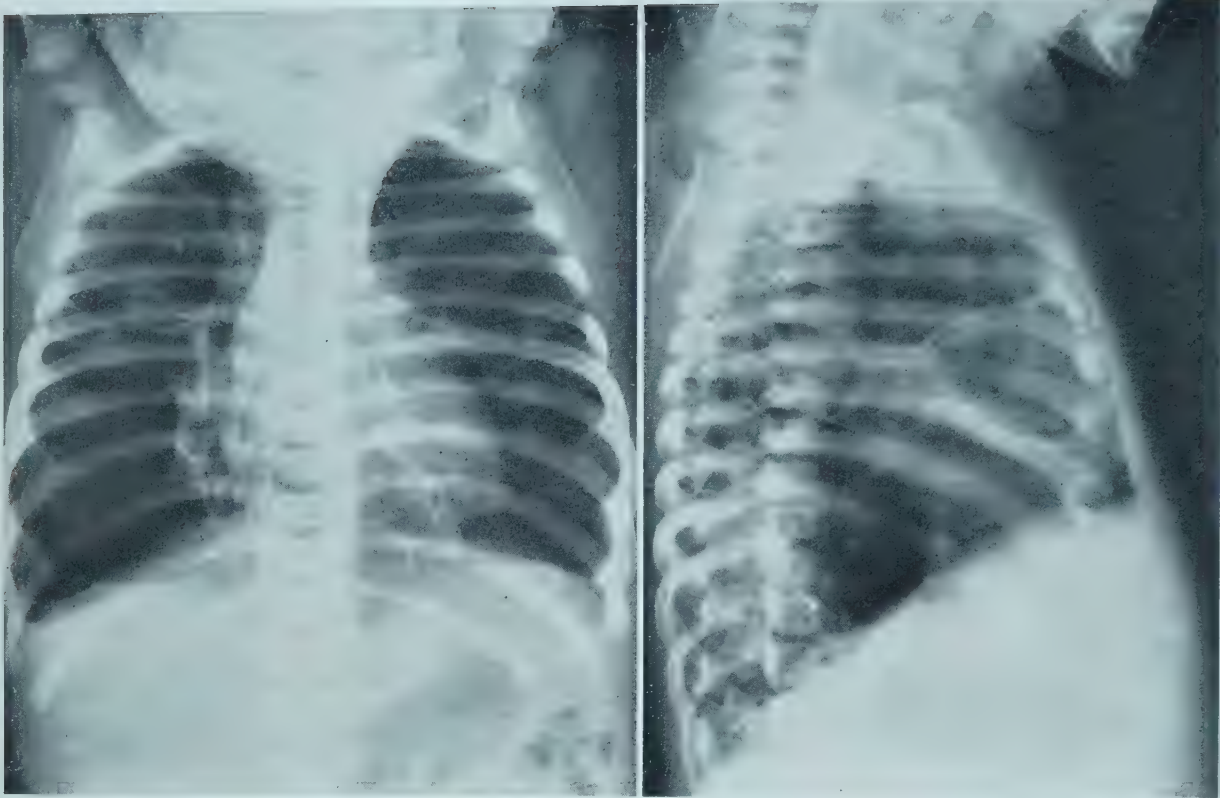


FIG. 221. Cysts of the lung. Congenital adenomatoid malformation in an infant 6 months of age. Respiratory distress was evident shortly after birth and became progressively more severe. Multiple cysts of varying sizes are demonstrated in both lung fields. At this time several sequential films indicated increasing size of several of the cysts, and the larger ones on the left side were removed surgically. There was temporary benefit. Subsequently additional cysts were removed, again with temporary relief of the dyspnea. The infant died at 12 months of age. Autopsy revealed multiple polyps in the small intestine and cysts in both kidneys in addition to the pulmonary malformations.

retention of an increasing amount of air. Under such circumstances, whether the obstruction is inflammatory or purely mechanical and whether it is intrabronchial or extra-bronchial, a so-called tension cyst is created. In other circumstances connection with the tracheobronchial tree is broken, and the accumulation of air (bullous emphysema) remains for long periods of time before it is finally absorbed and the architecture of the lungs is realigned. A wide variety of factors can be responsible for such obstructions of the bronchi, some of which may be congenital in origin, but the majority of them are probably the result of postnatal disturbances, usually inflammatory. An unusual association with cytomegalic inclusion disease has been recorded. The cysts may be filled entirely with air or fluid or with a combination of them.

Most cysts eventually disappear without interference, but when a tension cyst continues to expand and compress the other lobes, it is usually necessary to remove the lobe containing it. However, even such cysts may establish an equilibrium with the un-

involved portions of the lung, become closed and eventually disappear. For this reason decision for surgical removal must be based on the degree of respiratory embarrassment and whether it is progressive.

WALDO E. NELSON

#### REFERENCES

- Caffey, J.: On the Natural Regression of Pulmonary Cysts during Early Infancy. *Pediatrics*, 11:48, 1953.
- Craig, J. M., Kirkpatrick, J., and Neuhauser, E. B. D.: Congenital Cystic Adenomatoid Malformation of the Lung in Infants. *Am. J. Roentgenol.*, 76:516, 1956.
- Gallager, H. S.: Cytomegalic Inclusion of Infancy: Report of Case Associated with Cysts of Lung with Recovery Following Lobectomy. *Am. J. Clin. Path.*, 22:1147, 1952.
- Gruenfeld, G. E., and Gray, S. H.: Malformations of the Lung. *Arch. Path.*, 31:392, 1941.
- Huber, J. F.: Practical Correlative Anatomy of the Bronchial Tree and Lungs. *J. Nat. Med. A.*, 41:49, 1949.
- Kergin, F. G.: Congenital Cystic Disease of Lung Tissue Associated with Anomalous Arteries. I. *Thoracic Surg.*, 23:55, 1952.



- Laipply, T. C.: Cysts and Cystic Tumors of the Mediastinum. Arch. Path., 39:153, 1945.
- Potter, E. L., and Bohlender, G. P.: Intrauterine Respiration in Relation to Development of the Fetal Lung, with Report of Two Unusual Anomalies of the Respiratory System. Am. J. Obst. & Gynec., 42:14, 1941.

## BRONCHITIS

### ACUTE BRONCHITIS

Acute infection of the bronchial tree seldom if ever occurs as a primary infection or as one limited to this portion of the respiratory tract. Since the trachea is nearly always involved, it would be more exact to speak of acute tracheobronchitis. The term "capillary bronchitis" (bronchiolitis) has been used to describe an acute and serious infection which is less common in children than in infants, and in which the principal manifestations are located in the bronchioles. Though a number of pathogenic agents may be responsible for this type of infection, it appears that most of them are viruses.

Acute tracheobronchitis, or acute bronchitis, as it will be termed here, is usually secondary to an acute nasopharyngitis or to such specific infections as measles, pertussis, typhoid fever, influenza, scarlet fever and diphtheria. A variety of organisms have been isolated from acute infections of the bronchi, the more common ones being the pneumococci, hemolytic streptococci, staphylococci and *H. influenzae* bacilli. However, their presence does not, in itself, indicate that they are acting as pathogenic agents.

There are a number of predisposing causes, such as undernutrition, chronic infection of the upper respiratory tract, allergy and rickets. Age is an important factor, bronchitic infections being more frequent in the first three or four years of life than later. A high incidence within family groups is frequently noted. Certain children seem to be especially predisposed to bronchial infections.

**Clinical Manifestations.** The manifestations of bronchitis are usually preceded by an upper respiratory tract infection. The severity of the onset varies considerably. There is usually some fever, but the temperature is rarely over 102° F. Cough is the most constant symptom. Initially it is dry, at times paroxysmal, and it may be harsh and brassy. Older children may complain of a sense of dryness in the throat and of soreness and discomfort in the chest. In one or two days, when bronchial secretions become established, the cough becomes looser, and, in children

old enough to expectorate, there is sputum which rapidly becomes purulent. In infants and young children the secretions are swallowed or are aspirated into the trachea and bronchi. Vomiting is at times induced by the violence of the cough or by the gagging reflex excited by the large amounts of secretion in the throat. Constitutional symptoms are as a rule not marked.

The physical signs vary with the stage of the disease. Initially there may be none. Later, rhonchi and coarse, moist rales can be heard over the entire chest, the rales being especially prominent over the lower posterior portions. The fremitus produced by the secretions in the larger bronchi can often be felt on palpation and at times may be heard even at a distance from the chest. The percussion note is not affected. There is no relation between the extent of the rales and severity of the disease except when there are medium or fine rales as evidence of bronchiolar involvement.

The acute symptoms are usually limited to five or six days, but cough and expectoration tend to persist for another week or two. The course may be more prolonged in infants, especially in debilitated ones. Bronchitis, per se, is rarely fatal, and serious complications from it are not common. Diffuse pneumonitis is more likely to occur in infants, but is much less frequent since the availability of specific antibacterial agents. Other complications of respiratory infections, such as otitis media and laryngitis, occasionally occur. Pulmonary abscess is an infrequent complication, and chronic bronchitis is rarely a residual.

**Treatment.** The child should be confined to bed as long as there is fever. Infants should be picked up and held frequently or should have their position changed from time to time to facilitate drainage and thus lessen the danger of pneumonia. The room should be adequately ventilated, but cold air is distinctly irritating to the respiratory mucosa during these infections. The humidity of the room should be maintained at 50 per cent or higher; for this purpose cold humidification is preferable to steam. Inhalations of carbon dioxide and oxygen for five to ten minutes every half-hour or hour may be especially effective in loosening thick and viscid secretions. Other expectorants are less efficient and are of little value, especially during the acute stage. Ammonium chloride may be prescribed for older children; in the subacute phase, syrup of hydriodic acid may be given in doses of 2 cc. to infants and of 4 cc. to older chil-

dren. It is especially well taken when combined with half or equal quantities of syrup of cherry. Acetylsalicylic acid, 60 mg. (1 grain) per year of age, is useful in allaying the discomfort and quieting the child. Atropine or belladonna is contraindicated because of its effect in drying the pulmonary secretions and thus making them more tenacious and difficult to expel. Morphine and other opium derivatives should be avoided when there is extensive secretion because of suppression of the cough reflex, which is an important factor in expelling the secretions. When the infant or child is extremely restless and is not quieted by measures designed to clear the respiratory tract of secretions or by administration of acetylsalicylic acid, phenobarbital may be given. However, when there are excessive secretions, this should be avoided until the airways have been cleared. If the nose is congested, ephedrine or one of the other shrinking solutions may be used. When there is excessive bronchial secretion which cannot be adequately expelled, bronchoscopic aspiration may be helpful.

Children who have repeated attacks of bronchitis should be thoroughly studied to determine the underlying cause. Such possibilities as chronic sinusitis, infected tonsils and adenoids, bronchiectasis, tuberculosis, allergy and hypogammaglobulinemia should be carefully considered.

### CHRONIC BRONCHITIS

Chronic bronchitis is infrequent among children, and particularly so as an isolated disturbance. Perhaps it occurs most often in association with chronic infection of the nasal accessory sinuses, so-called sinobronchitis. Chronic bronchitis may also be associated with allergic conditions of the respiratory tract, especially when there is hypersensitivity to bacteria. Infrequently certain fungi may be responsible for chronic bronchitis. It may also be associated with chronic cardiac conditions when there is some degree of myocardial failure. Irritation of the bronchi from aspiration of dust, lint or gaseous fumes may be a contributing factor.

**Clinical Manifestations.** The chief symptom is cough. It is likely to be more troublesome shortly after the child has gone to bed and may be of such severity that it disturbs sleep; it is also frequently marked in the morning. During periods of exacerbation the cough tends to be loose, and there is apt to be considerable expectoration. The constitutional symptoms vary considerably; there may

be malaise and apathy. Except during acute exacerbations there is usually no fever. The physical findings are not constant. At times there are none, and at other times medium and coarse rales and rhonchi are present, and there may be fremitus on palpation. These signs often disappear after coughing and expectoration.

**Differential Diagnosis.** Roentgenograms of the sinuses and chest are essential, tuberculin and fungus skin tests should be performed, and cultures of the sputum or of bronchial aspirations for bacteria and fungi should be obtained. Bronchiectasis can be eliminated with certainty only by complete visualization of the bronchial tree by bronchography. The possibility of myocardial involvement requires consideration. The majority of cases, however, will be found to be related to infections of the sinuses, with allergy perhaps the next most common cause.

**Complications.** The principal complication is bronchiectasis. Other complications are atelectasis, emphysema, and infection of the tracheobronchial lymph nodes.

**Course and Prognosis.** The course is somewhat characteristic in that the manifestations are exaggerated during the winter and spring months, with considerable improvement during warm weather. There are frequent acute exacerbations, the clinical manifestations being those of acute bronchitis. The prognosis is dependent principally upon the cause and upon the possibility of its eradication.

**Treatment.** Treatment depends upon the cause. When there is no response to therapy, a change to a dry, warm climate may be beneficial. Expectorants, except perhaps carbon dioxide and oxygen inhalations as described under Acute Bronchitis, are of little benefit. Vaccine therapy has been disappointing, although a few patients seem to benefit by desensitization with autogenous vaccines. Antibiotic aerosol therapy has limited usefulness in conjunction with a proteolytic enzyme. Good pediatric care, physical and emotional, is essential.

### PNEUMONIA

No clinical classification of pneumonia is entirely satisfactory. It has been common practice to separate the various clinical forms of pneumonia on the basis of their anatomic distribution, the principal designations being lobar pneumonia, lobular pneumonia or bronchopneumonia, and interstitial pneumonia or bronchiolitis. If separate categories are pro-



vided for the various aspiration pneumonias and for hypostatic pneumonia, most pneumonic infections can be grouped under these anatomic headings.

More or less characteristic lesions are produced by certain etiologic agents. For example, the *Pneumococcus* produces an inflammatory lesion of the mucosa and a marked alveolar exudate, usually without destruction of the mucosal cells or extensive involvement of the interstitial tissues. The gross lesion is a consolidation of all or part of a lobe in the lobar variety, or of scattered lobules in the bronchopneumonic variety. In contrast, viral agents, *Hemophilus influenzae* and certain strains of the viridans group of streptococci invade or destroy the mucous membrane and produce principally bronchiolitis, peribronchiolitis and interstitial lesions. Secondary infections, especially in association with the primary viral infections, are often responsible for suppurative bronchiolitic, alveolar and interstitial lesions. Both the *Staphylococcus* and Friedländer's bacillus tend to destroy tissue and to produce multiple small abscesses.

Most bacteriologic infections can now be identified not only as to the causative agent, but also as to the specific type or strain of a given species. Since such identification or the failure of it has both therapeutic and prognostic significance, there are strong arguments for an etiologic classification. Since, however, it is not possible to identify the etiologic agent in all instances, it is necessary to include a grouping on a pathologic basis. Most of this latter group occur in the period of infancy, and practically all of them fall into the category of acute bronchiolitis or acute or chronic interstitial pneumonitis, and most of them probably are viral in origin.

Within limits a clinical distinction can also be made on the basis of response to antimicrobial therapy. Most of the bacterial infections are susceptible to one of these agents, whereas the viral infections usually are not. The limitations of a distinction on the basis of a therapeutic trial, however, are obvious. Some of the larger viral agents, which may cause pneumonitis, appear to be affected to some extent by the sulfonamides and the so-called broad-spectrum antibiotics. Of equal importance is the variation of antibiotic susceptibility among the different pathogenic bacteria which infect the lungs and even among the strains of a given species, viz., the *Staphylococcus aureus*.

The following classification is presented as a working basis:

#### *Bacterial Infections*

*Pneumococcus*  
*Streptococcus*  
*Staphylococcus*  
*H. influenzae*  
Friedländer's bacillus  
Tubercle bacillus  
*Treponema pallidum*

#### *Viral or Probable Viral Infections*

Bronchiolitis and interstitial pneumonitis  
Primary atypical pneumonia, etiology unknown  
Giant cell pneumonia  
Plasma cell pneumonia  
Influenza  
Q Fever

#### *Mycotic Infections*

Coccidioidomycosis  
Histoplasmosis  
Blastomycosis  
Cryptococcosis  
Mucormycosis  
Nocardiosis  
Sporotrichosis  
Thrush

#### *Aspiration of*

Amniotic contents (fetal anoxia)  
Food  
Foreign bodies  
Zinc stearate  
Dust  
Kerosene  
Lipoid substances

#### *Löffler's Syndrome*

#### *Hypostatic Pneumonia*

### BACTERIAL PNEUMONIA

#### PNEUMOCOCCAL PNEUMONIA

The *Pneumococcus* has been perhaps the principal cause of pneumonia in infants and children. In recent years, however, there has been a sharp decrease in the incidence of pneumococcal pneumonia. The rapid clinical response of most pneumococcal infections to sulfonamide or antibiotic medication and the common practice of administering these therapeutic agents to patients early in the course of an infection apparently prevent many pneumonic infections and mask the diagnosis in other instances.

The lobar type of involvement which is characteristic of pneumococcal pneumonia in adults is the usual response in children beyond the age of infancy. The lobular or disseminated type is relatively more frequent in the first year of life than it is thereafter.

**Etiology.** Some seventy-five types of pneumococci have been identified; type-specific serums have been made for thirty-two of the

first thirty-four types (except XXVI and XXX). In contrast to the frequency with which the lower types of pneumococci are isolated from adults with pneumococcal infections, the majority of those isolated from infants and young children belong in the higher numbered types (Cooper, IV to XXXIII). In patients of all ages the most frequent types in the order of their relative frequency are I, III, VIII, VII, IV, V, XIV, II, VI, XIX. In infants, however, type XIV occurs most frequently. Other common types found in the younger age group are types V, I and XIX.

**Predisposing Factors.** Though pneumococcal pneumonia is often considered a primary infection, mere contact with a case of pneumonia or even the presence of pneumococci in the nose and throat is not sufficient for the production of pneumonia. Factors which temporarily lower *resistance* to infection may make it possible for the pneumococci to get a foothold in pulmonary tissue. Age is a significant factor, the incidence rising sharply after the first month or so of life with a peak during the second year of life and declining rapidly thereafter.

**Epidemiology.** The incidence of pneumonia is at its peak during the late winter and early spring months. Though epidemics have been reported, they have been principally in institutions or military camps. Among the general population in the temperate zones, pneumonia exists as an endemic rather than an epidemic infection. The family is an important epidemiologic unit, although multiple cases of pneumonia infrequently occur in the family. Some or all of the members of the family of a patient with pneumonia usually harbor the homologous type of organism. Some of them will have no obvious infection and apparently serve only as carriers. However, infections of the upper respiratory tract due to the *Pneumococcus* are common in family contacts, and other pneumococcal infections such as otitis media, meningitis and arthritis occur less frequently. It is of interest that the patient convalescing from pneumonia soon loses his virulent strain of pneumococci, whereas members of the family who have not had pneumonia may continue to be carriers for weeks or months.

The blood of most persons contains antibodies against many types of pneumococci. Pneumococcal antibodies in the blood of newborn infants tend to parallel those in the blood of the mother. This pneumococcidal property is apparently lost by the first month of life. Pneumococcal antibodies are found

again in successively higher titers after the first year of life.

**Pathogenesis.** Pneumococci apparently gain entrance to the lungs by way of the respiratory passages and not through the blood stream. They reach the alveoli, where they incite an inflammatory response, characterized in its early stages by an outpouring of edematous fluid in which are numerous pneumococci. This fluid, laden with pneumococci, flows through the openings in the alveolar walls (pores of Kohn), through alveolar ducts and bronchioles into other lobules, and thus rapidly spreads to involve the entire lobe.

**Pathology.** The first stage, that of *engorgement*, usually lasts only a few hours. The lung is heavy, congested, dark bluish-red, but not solidified. Microscopically, the interalveolar capillaries are greatly distended, and the alveoli are filled with a serous exudate containing large numbers of pneumococci and a few red blood cells and neutrophils. In the second stage, or stage of *red hepatization*, the involved lobe is solid and airless. The red color is due principally to engorgement of the capillaries and partly to alveolar hemorrhage. The alveoli contain fibrin, neutrophils, serum, red blood cells and pneumococci. This stage passes rapidly into that of *gray hepatization*. The pleural surface is dull and lusterless, owing to the presence of a film of fibrin. Histologically, the alveoli are filled with fibrin and neutrophils; the interalveolar capillaries are no longer engorged, but are now barely visible. This stage is much more prolonged than the preceding ones, and passes into the final stage of *resolution*. The exudate now softens, and creamy pus can be expressed from the cut surface. Increasing numbers of macrophages appear in the alveolar spaces, the neutrophils undergo necrosis and fatty degeneration, and the fibrin threads are digested and disappear. The clinical crisis cannot be correlated with the stage of resolution; resolution and re-expansion in the untreated case require an additional one to three weeks after the crisis.

Pathologically, bronchopneumonia differs from lobar pneumonia principally in the patchy irregular distribution of the former.

**Clinical Manifestations.** The clinical pattern in children is more variable than in adults. Cases with an abrupt onset and sustained fever, which terminate by crisis after five to nine days, do occur at all ages, but are seen more consistently in older children than in infants and more often when the pneumonic distribution is lobar rather



than bronchial. In general, the onset of the pneumonia itself is abrupt, but is often preceded for several days by symptoms of an upper respiratory tract infection. Symptoms referable to the gastrointestinal tract and to the nervous system are more commonly observed in children than in adults. Vomiting is common in both types of pneumonia; diarrhea and convulsions are more often associated with bronchopneumonia in infants, and meningismus with the lobar variety in older children. Prostration is generally greater in the bronchopneumonic variety and the temperature more remittent in type. There are many variations, however, in the clinical patterns of both forms, and they are frequently indistinguishable on the basis of their clinical course.

Both the onset and course have been materially altered by sulfonamide and/or antibacterial therapy. When such therapy has been administered in the prodromal phase of the upper respiratory tract infection, the typical pattern may be altered or the pulmonary infection may be completely averted. When adequate therapy is instituted within the first two or three days of the pneumonia, the typical clinical manifestations are usually abolished within twenty-four hours.

**Onset.** Prodromal symptoms other than those of an upper respiratory tract infection are usually absent. The chill which is characteristic of the onset in older children and adults is frequently replaced by a convulsion in infants. Fever and respiratory distress usually appear abruptly.

**Fever.** The elevation of temperature is rapid, reaching 103° to 104° F. within a few hours. In older children with the lobar variety the daily fluctuations may not be more than a degree or so, whereas in infants, especially when they have a bronchopneumonia, the daily fluctuations are likely to be somewhat greater. The course of the untreated illness in older children is usually terminated by an abrupt drop in temperature, the so-called crisis, but usually without associated symptoms of collapse. The drop in temperature is frequently by lysis in the untreated disseminated variety.

**Respirations and pulse.** Respiratory rates of 30 to 50 per minute are common in older children, and of 40 to 80 in infants. The respiratory excursion is characteristically shallow in order to lessen pleural pain. In severe cases the accessory muscles of respiration may be brought into use with the result that there is some indrawing of the intercostal spaces.

Movement of the alae nasi is one of the more constant symptoms. An expiratory grunt is more common in older children than in infants.

The pulse rate is increased, but not to the same extent as that of the respiratory rate; instead of the characteristic ratio of 1:4, ratios of 1:2 or 1:3 may be observed. A pulse rate of 140 to 180 per minute is not infrequent in infants, but in itself is not an unfavorable sign if the tension remains good. A weak, rapid pulse and a slow pulse are both grave prognostic signs.

**Cough and expectoration.** Cough is generally present. In the early stage it is usually dry and tends to accentuate the pleuritic pain. In the stage of resolution the cough may become looser and productive, but the characteristic rusty sputum is not often seen in children.

**Pain.** Thoracic pain due to pleural involvement is often present, being accentuated by coughing and respiratory movements. Its frequency in infants is difficult to evaluate, but it is generally assumed that there is less pain in the disseminated form than in the lobar variety. The older child often lies on the affected side to lessen the pain. Not uncommonly the pain is referred to the abdomen and, when there is involvement of the right leaf of the diaphragm, may be referred to the right lower quadrant, simulating that of acute appendicitis.

**Gastrointestinal symptoms.** Vomiting at the onset is a common symptom, but is seldom continued after the first day unless feeding is forced. Initially there may also be a loose stool or two, but persistence of diarrhea is uncommon. The appetite is greatly diminished, although thirst may obscure this fact in infants, since they may continue to take the usual amount of milk.

**Nervous symptoms.** Convulsions are relatively common at the onset in infants, and headache is common in older children. Delirium may occur, especially in association with extremely high fever.

Meningismus is a comparatively common manifestation, especially in the lobar type. Though nuchal rigidity is usually the only manifestation, there may be positive Kernig and Brudzinski signs and even opisthotonos. In such instances the possibility of a coexisting meningitis can be eliminated only by examination of the cerebrospinal fluid.

**Examination of the Chest.** In the very early stage it is often difficult to make the diagnosis of pneumonia by examination of

the chest, but its presence may be suspected by the appearance of the child. Rapid, shallow respirations with associated movements of the alae nasi and sudden onset of high fever are strongly suggestive of a pneumonic infection.

The physical findings of the *bronchopneumonic* variety depend upon the number and extent of the pneumonic areas. When there are only a few small isolated areas, they may not be detected. In the early stage there may be fine or medium-sized rales over the involved areas for a short time, but these are usually missed. When the pneumonic areas become consolidated, there are likely to be neither percussion nor auscultatory changes because of the small areas involved. During the stage of resolution rales may again be present over the involved areas. Pneumonic areas which involve several contiguous lobules are usually detectable by physical examination, the sequence and nature of the physical signs being similar to those of lobar pneumonia.

In the *lobar* variety the pulmonary findings are characteristic after the first day or two of the disease. Before this time the pneumonic area may be missed on physical examination, and the disease may be suspected only from the appearance of the child, or the pneumonic lesion may be suspected on physical examination, but incorrectly localized. Initially there is little or no impairment to percussion over the pneumonic lobe, but there usually is suppression of breath sounds. The apparent exaggeration of the breath sounds in the corresponding lobe of the opposite side is often misinterpreted as tubular breathing and is assumed to be a physical sign of pneumonia. As the stage of congestion proceeds, fine rales are heard over the pneumonic area, but they are present for only a short time and disappear as soon as consolidation has occurred. At this time, usually by the second or third day, there is definite dullness to percussion, and the breath sounds are tubular in quality. The decreased excursion of the chest can be detected by observation and palpation. Pleurisy is practically always present, but a friction rub is not a common finding. At the beginning of resolution rales can again be heard for a day or two, and the signs of consolidation disappear within several days.

Consolidation can usually be demonstrated on the roentgenogram before it is detectable by physical examination. In an occasional case of bronchopneumonia individual lesions are

so small that they may be missed even on roentgenographic examination.

Roentgenographic examination also provides information about the presence of such complications as empyema, atelectasis and purulent pericarditis.

**Laboratory Data.** Except in complicated cases there is usually not more than a slight reduction in the red blood cell count and the hemoglobin. The white blood cell count is usually increased to 15,000 to 40,000 per cubic millimeter, with a preponderance of polymorphonuclear cells. White blood cell counts below 5000 per cubic millimeter, as well as excessively high counts of 50,000 to 100,000, are often associated with a grave prognosis.

The urine is usually highly colored, of high specific gravity, scanty in amount, and loaded with urates. There is usually a moderate albuminuria and a few hyaline casts. Acetonuria is common.

The *Pneumococcus* can be isolated from nasopharyngeal secretions in most instances. Typing at present has little practical value, since specific antisera are rarely used in therapy. Positive blood cultures are obtained in about 10 to 20 per cent of all cases of pneumococcal pneumonia. Bacteremia is more frequent in infections with types I, II and III than in infections with the higher-numbered types.

**Differential Diagnosis.** The principal conditions from which bronchopneumonia must be differentiated are severe acute bronchitis, acute bronchiolitis, chronic passive congestion in cardiac failure, acute exacerbations of bronchiectasis, patchy areas of atelectasis, and pulmonary tuberculosis.

Lobar pneumonia must be differentiated principally from massive atelectasis and pleural effusion, and from meningitis, gastroenteritis and appendicitis when symptoms arising from a pneumonic infection simulate one of these conditions. Tuberculosis and bronchiectasis are less likely to be confused with lobar pneumonia than with bronchopneumonia, although each of these conditions may be responsible for collapse or consolidation of an entire lobe.

**Complications.** Some degree of *plastic pleurisy* is present in nearly all cases of pneumonia; small amounts of serous effusion are common and can scarcely be considered complications. In the presulfonamide era *empyema* developed in about 5 to 10 per cent of cases. It is the most characteristic complication of pneumonia, but it is now uncommon



in cases treated early. Spontaneous pneumothorax is a rare complication. *Otitis media* was also a common complication, especially in infants and young children, but its incidence has also been reduced by antibacterial treatment. Purulent pericarditis, peritonitis and meningitis are infrequent complications. Both pneumococcal meningitis and pneumococcal peritonitis occur more frequently without a coexisting pneumonia than they do with it. Endocarditis, encephalitis, parotitis, nephritis, osteomyelitis, subcutaneous emphysema and pulmonary abscess are rare complications. Hemiplegia and other localized brain lesions have been recorded and have been attributed to thrombi and emboli. Atelectasis is an occasional complication, and it is not unlikely that a number of so-called unresolved pneumonias are actually areas of atelectasis. When atelectasis persists, there is always danger that bronchiectasis will develop. Bullous emphysematous blebs (Fig. 222; p. 807) may simulate an abscess cavity, but are usually benign and spontaneously corrected.

One of the most serious complications of pneumonia has been *abdominal distention* or *tympanites*, which, when persistent, is usually a reflection of paralytic ileus. It is now rare except in untreated infants and young children.

**Prognosis.** Both the course and the outcome of pneumococcal pneumonias have been dramatically changed by treatment with sulfonamides and antibiotics. Before effective drugs or type-specific antiserum was available the mortality in the first two or three years of life, and especially in the first, ranged from 20 to 50 per cent. In contrast, the fatality rates for the remaining years of childhood were extremely low, being only 3 to 5 per cent. When treatment is instituted early in the course of the disease, fatality rates of less than 1 per cent may be expected in both infants and children.

It is unusual when the temperature does not return to normal within twenty-four hours after the institution of adequate therapy. Simultaneously there is improvement in the clinical condition of the child, and significant complications have been virtually eliminated.

**Treatment.** The favorable response to sulfonamide and/or antibiotic therapy and the decreased need for oxygen administration when chemotherapy is instituted shortly after the onset make home care of the pneumonic patient more feasible than it was in the past. There are certain advantages in keeping a child at home, including the psychologic ef-

fect of remaining in familiar surroundings and avoidance of the trip to the hospital. Keeping the child at home depends upon the physical adequacy of the home and upon the ability of the mother or other members of the family to supply good nursing care. The development of serious complications will necessitate removal of the child to the hospital.

Nursing and medical attention are essential, and should be designed to conserve the child's energy. The child's position in bed should be changed at frequent intervals to avoid discomfort and to facilitate drainage from the tracheobronchial tree. Dietary management in the average case of pneumonia is not particularly important other than avoidance of forcing the child to eat more than he desires. Under ordinary circumstances adequate amounts of fluids to supply the increased demands of the infection will be taken, if offered. However, when there is vomiting, fluids must be supplied by parenteral means. A fluid intake of sufficient quantity to maintain an output of urine of average specific gravity is important for the excretion of toxic products and is essential to avoid renal complications during the administration of sulfonamides.

Antibacterial therapy instituted at the earliest sign of pneumonia is the most important aspect of therapy. Fortunately the *Pneumococcus* is susceptible to practically all the



FIG. 222. Bullous emphysema in left lung field. This huge emphysematous bleb developed after a pneumonic infection. Its course was marked by decrease in size in all directions until it completely disappeared.

available antibiotics and the sulfonamides, except the poorly absorbed ones. Penicillin in full dosage would appear to be the drug of choice. It can be given orally at intervals of eight hours, or the aqueous preparation can be injected parenterally at intervals of eight hours, or procaine penicillin at intervals of twelve or twenty-four hours (see p. 222 for doses of penicillin, other antibiotics and the sulfonamides). The administration of the antibacterial agent should be continued for four or five days after the temperature is normal.

Administration of oxygen may be a life-saving measure when there is severe dyspnea, with or without cyanosis. The early administration of oxygen will greatly reduce the need for sedatives and analgesics and is preferred for quieting the restless, pneumonic child. Often oxygen therapy for a day or so is all that is required and results in a much smoother convalescence. Sedatives and analgesics are rarely needed. Aspirin in doses of 60 mg. (1 grain) per year of age is perhaps the best drug for mild restlessness, and phenobarbital may be given in addition for sleeplessness.

Severe abdominal distention is a serious complication for which prophylaxis is infinitely more effective than treatment. Prophylaxis consists in early antibacterial treatment of the pneumonic infection, administration of oxygen before extreme cyanosis is present, and avoidance of constipation. When there is an extreme degree of distention, treatment is rarely effective. For this reason Prostigmin, which is the most effective therapeutic agent, should be administered for moderate distention, especially when it is not relieved by an enema. Subcutaneous doses of 0.5 to 1 cc. of a 1:4000 solution may be given to infants one to two years of age, and may be repeated in two or three hours if the distention is not relieved. Enemas, with a rectal tube left in place, should be given in addition.

**Convalescence.** Recovery from uncomplicated pneumonia is usually rapid, but a common mistake is failure to provide for an adequate convalescent period because of the child's apparent well-being following antibacterial therapy. The test of completion of the convalescent period or the return to a healthy status is based on the regaining of the pre-illness weight, a sense of well-being and absence of fatigue after average daily activity. In general, the average child requires ten to fourteen days after defervescence for completion of convalescence.

### STREPTOCOCCAL PNEUMONIA

Pneumonic infections caused by the hemolytic streptococcus are in most instances secondary and follow such infections as measles, pertussis, influenza and the common cold.

The pathologic lesion is frequently that of a bronchitis and interstitial pneumonia with an infiltrate of mononuclear cells in the walls of the bronchi and bronchioles, which extends into the interalveolar septums. In some instances the lesion produced is a hemorrhagic pneumonia. The distribution is usually lobular, with consolidation of the alveoli, although, when the distribution is extensive, especially in one particular lobe, the confluent lobules may create the appearance of a lobar pneumonia. Subpleural abscesses and empyema are frequent manifestations.

The *clinical course* of streptococcal pneumonia is usually that considered characteristic of bronchopneumonia. Immediately or shortly after the acute phase of some infection which involves the upper respiratory tract, there is an elevation of temperature, dyspnea and cough. The fever is remittent, and as a rule the infant or child is quite sick. The *physical signs* vary considerably, but often there is nothing more than scattered areas of rales with percussion dullness over the larger of these areas. The *diagnosis* is established by demonstration of pneumonic areas on the roentgenogram of the chest and by identification of the organism from cultures of nasopharyngeal secretions. Empyema is a frequent complication, except as treatment is instituted early.

The *prognosis* has been improved tremendously by antibacterial therapy. The general *treatment* is that described for pneumococcal pneumonia.

### STAPHYLOCOCCAL PNEUMONIA

Within recent years the *Staphylococcus aureus* has become the most important pulmonary bacterial pathogen encountered in pediatric practice. This changed situation is principally the result of two factors: the effective control of most other bacterial pneumonias by antimicrobial agents and the emergence of virulent, antibiotic-resistant staphylococci. The problem is largely centered in infancy, many of the pneumonic infections being acquired in hospital nurseries. The epidemiologic aspects extend beyond the nursery, however, and infections may be acquired at home, in hospital wards and in other institutions. Frequently the newborn infant acquires



skin infections in the nursery and/or becomes a carrier of virulent staphylococci in his nasopharynx. From such sources he may transmit the infection to other members of the family and may himself have a more serious staphylococcal infection, such as pneumonia, weeks or months later. The infection in the newborn period is discussed on pages 328 and 344. The Staphylococcus is also a common pulmonary pathogen in children with fibrocystic disease of the pancreas.

The onset and progression of pneumonic lesions tend to be extremely rapid. There may be a single lesion, but more often there are multiple lesions. Destruction of tissue and abscess formation are the typical pattern. Lesions near the periphery often erode into the pleura, producing tension pneumothorax and/or empyema. A roentgenogram of the chest will often give a clue to the diagnosis by the demonstration of multiple lesions which after a day or so may be suggestive of abscess formation. Nasopharyngeal cultures will usually reveal the organism, and the blood culture is frequently positive.

The case fatality rate approximated 100 per cent in infants prior to the introduction of sulfonamide and antibiotic therapy. For a few years thereafter infections were largely controlled. But, as stated above, the situation is again critical, and no completely adequate solution is at hand.

Prophylactic measures to control nursery infections are described on page 345; the principles of treatment on pages 345 and 431. It is essential that the possibility of staphylococcal pneumonia be considered initially in every instance of pneumonia in infants and young children. Nasopharyngeal and blood cultures should be obtained immediately, the patient isolated in an area where he may have constant and close nursing supervision, and antimicrobial therapy started immediately. When the possibility of staphylococcal pneumonia seems especially likely, two antibiotics, each known to be effective against a fair number of strains, should be prescribed in full dosage. No antibiotic is known to be effective against all strains; those which have the widest range of effectiveness include chloramphenicol, erythromycin, novobiocin, oleandomycin and kanamycin. The initial prescription should be altered as indicated by the result of sensitivity tests in the bacterial culture and by clinical response. The infant must be watched closely for the possible development of tension pneumothorax (p. 817) and/or empyema (p. 815). General

supportive treatment is also of great importance; this includes oxygen therapy, maintenance of fluid and electrolyte balance and scrupulous nursing care.

#### HEMOPHILUS INFLUENZAE PNEUMONIA

The epidemiology of influenzal bacillus infections is not clearly understood; whereas *H. influenzae* type b is a common cause of meningitis in infants, it is an infrequent cause of primary pneumonia. Clinically, it would seem probable that many of the pulmonary infections are mixed ones, the resultant pathologic changes being due to the synergistic action of the influenzal bacillus with some other bacterium such as the Pneumococcus or the Streptococcus or one of the viral agents, or that the influenzal infection is superimposed upon a preceding infection. Blake and Cecil, however, produced pulmonary lesions in monkeys with pure cultures of *H. influenzae* type b which are quite similar to those observed by Trask and others in man. The characteristic lesion consists in destruction of the mucosa and submucosa of the bronchi and bronchioles, resulting in a bronchiolitis and interstitial pneumonitis and a hemorrhagic edema. Practically all infections in man appear to be caused by the type b group of *H. influenzae*. It has been considered one of the etiologic agents of acute laryngotracheobronchitis and acute bronchiolitis and less often of lobar or segmental pneumonia (Nyhán). In this last instance the infection may simulate pneumococcal pneumonia, and empyema may be a complication. Type a *H. influenzae* has also been associated with acute bronchiolitis. The importance of blood cultures in the evaluation of all patients with pneumonia is especially evident in *H. influenzae* type b pneumonia, in which a positive culture is the only certain diagnostic means, except when empyema is associated and a positive culture is obtained from the pleural fluid. The child should be observed for the development of meningitis.

Treatment consists in symptomatic and supportive measures appropriate for pneumonia and in antibacterial therapy effective against the *H. influenzae*. An effective plan is the administration of sulfadiazine and chloramphenicol in combination. Streptomycin is also effective.

#### FRIEDLÄNDER'S BACILLUS PNEUMONIA

Friedländer's bacillus is an uncommon cause of pneumonia at any age, and an especially infrequent one during infancy and childhood.

The infection may be primary or secondary. The characteristic distribution of the lesions is lobar or confluent lobular, and one or more lobes may be involved. There is a tendency to abscess formation. In the acute cases the onset is abrupt, and the general symptoms are those of bronchopneumonia. Hematemesis and melena may be observed in infants and children. The most frequent complications are extensive abscess formation and empyema; other less common ones are pericarditis, meningitis and arthritis. Streptomycin or chloramphenicol in combination with a sulfonamide appears to be as effective as any available therapy.

WALDO E. NELSON

## REFERENCES

### *Pneumococcal Pneumonia*

- Bell, E. T.: A Text-Book of Pathology. 6th ed. Philadelphia, Lea & Febiger, 1947.  
 Eddy, B. E.: Nomenclature of Pneumococcic Types. Pub. Health Rep., 59:449, 1944.  
 Smillie, W. G., and Jewett, O. F.: The Relationship of Immediate Family Contact of the Transmission of Type Specific Pneumococci. Am. J. Hyg., 32: 79, 1940.

### *Staphylococcal Pneumonia*

- Cooper, M. L., and Keller, H. M.: Severe Staphylococcal Infections in Young Children. A.M.A. Am. J. Dis. Child., 95:245, 1958.  
 Pryles, C. V.: Staphylococcal Pneumonia in Infancy and Childhood. Pediatrics, 21:609, 1958.  
 Shaffer, T. E.: Staphylococcal Infections. Pediatrics, 18:336, 1956.

### *Hemophilus Influenzae Pneumonia*

- Nyhan, W. L., Rectanus, D. R., and Fonsek, M. D.: Hemophilus Influenzae Type b Pneumonia. Pediatrics, 16:31, 1955.  
 Wood, S. H., Buddingh, G. J., and Abberger, B. F.: An Inquiry into the Etiology of Acute Bronchiolitis of Infants. Pediatrics, 13:363, 1954.

### *Friedländer's Bacillus Pneumonia*

- Steiner, B., and Putnoky, G.: Klebsiella Pneumonia (Friedländer's Bacillus) Infections in Infancy. Arch. Dis. Childhood, 31:96, 1956.  
 Weiss, W., and others: Klebsiella in Respiratory Disease. Ann. Int. Med., 45:1010, 1956.

## VIRAL OR PROBABLY VIRAL INFECTIONS

### ACUTE BRONCHIOLITIS AND INTERSTITIAL PNEUMONITIS

(VIRUS PNEUMONIA, VIRAL PNEUMONITIS OF INFANTS, CAPILLARY BRONCHITIS)

The terms "acute bronchiolitis" and "acute interstitial pneumonitis" are used more or less interchangeably, especially in pulmonary in-

fections in infants and very young children. Perhaps bronchiolitis might be considered a more appropriate clinical diagnostic term, but it is difficult to conceive of the existence of a pure bronchiolitis without involvement of the interstitial tissues.

The clinical pattern of acute bronchiolitis is seen with frequency only in the first two years of life, and the majority of infections occur in the first six months. It may be that infections of this type actually occur more frequently in this age group than in older children and adults, but there is some reason to doubt whether this is the sole explanation. There may be anatomic differences in the pulmonary trees of infants and older children that are responsible for variations in clinical patterns or the responses to the same etiologic agents (see Primary Atypical Pneumonia).

**Etiology.** No single etiologic agent is responsible for this disease. Failure to isolate any of the usual pathogenic organisms of the respiratory tract in a significant number of instances and the failure of the disease to be affected by sulfonamide or antibiotic therapy have been responsible for the belief that a virus is the usual etiologic agent. Certain viruses and rickettsiae (the viruses of influenza, psittacosis, ornithosis, lymphogranuloma venereum, lymphocytic choriomeningitis and the rickettsia of Q fever), some of which respond to sulfonamides and/or antibiotics, may be responsible for bronchiolitis and interstitial pneumonitis, but in the main the viral agents are not known. It may be that some of them are responsible for acute upper respiratory tract infections in the majority of instances, especially in older children and adults. Adams reported several epidemics of primary viral pneumonitis among full term and premature newborn infants when the onset of the pneumonia was within the first twenty-four hours of life and the mother had an acute upper respiratory tract infection. There is some evidence to indicate that so-called Streptococcus MG and *H. influenzae* (both types a and b) may be occasional causative agents. Adams presented data suggestive of a possible relation between the etiologic agent of primary viral pneumonitis in infants and that of distemper in dogs.

**Epidemiology.** The incidence of acute bronchiolitis is highest in the winter and early spring months. Most infections occur sporadically, but an increased number of cases in infants often coincides with epidemics of upper respiratory tract infections among older children and adults. There are



no known sex or race differences, and nutritional status does not appear to be a factor.

**Pathology.** The lungs are emphysematous with scattered areas of atelectasis. Histologically, the most striking changes are in the walls of the bronchi and bronchioles, which are thickened by an infiltrate of small lymphocytes, plasma cells and scattered neutrophils; these lumina contain mucus and varying amounts of neutrophilic exudate. The inter-alveolar septums about the bronchioles are thickened as a result of an inflammatory infiltrate similar to that present in the bronchiolar walls. Intra-alveolar exudate is usually minimal unless secondary infection has occurred.

**Clinical Manifestations.** The description which follows applies to the infection in infants and young children. The description of similar infections in older children is given under Primary Atypical Pneumonia.

The onset of bronchiolitis usually follows that of an upper respiratory tract infection by two or three days and is characterized principally by a dry, persistent cough and increasing dyspnea. The clinical pattern varies in severity and to a less extent in the manifestations themselves. In atypical cases the cough may so closely simulate that of pertussis that differentiation can be made with certainty only by bacteriologic cultures, although the nature of the disease may be suggested by the white blood cell count. Initially, the respiratory symptoms are more marked than those of toxicity, and the clinical pattern is suggestive of bronchial asthma. The temperature is extremely variable, but most often there is only a slight elevation to 100° or 101° F. Most important is the fact that there is no correlation of the clinical severity with the temperature elevation. Vomiting may occur, but it is usually not a serious problem, nor is severe diarrhea. Feeding, however, may present difficulties, because sucking is interrupted by the dyspnea, and the distention of the thoracic cavity compresses the abdomen.

On physical examination the infant is found to be alert, apprehensive and exceedingly irritable. The respirations are rapid and shallow and often accompanied by an expiratory grunt. The accessory muscles of respiration are used actively so that there is suprasternal and subcostal indrawing with inspiration, but the depth is not as great as in laryngeal obstruction, owing to distention of the lungs. The physical findings in the severe case are those of generalized obstructive emphysema (see pp. 775 and 806).

Cyanosis may be marked, and often there is extreme pallor. The percussion note is hyperresonant; there may be no rales, or there may be widely scattered fine or medium ones. Wheezing may be prominent and accompanied by sibilant and musical sounds. When bronchiolitic obstruction is nearly complete in the most severe cases, the breath sounds may barely be audible.

Dehydration may be relatively severe, owing to the excessive loss of water through hyperventilation. Death may be due to exhaustion from respiratory effort or to cardiac failure.

**Diagnosis.** The roentgenographic and fluoroscopic examinations reveal generalized obstructive emphysema of varying degree (see p. 806) with or without evidence of scattered parenchymal infiltration.

The white blood cell count is usually not significantly altered. Nasopharyngeal cultures as a rule do not reveal significant deviations from the usual flora. There may be respiratory acidosis.

The differential diagnosis in the main includes those diseases which also cause generalized obstructive emphysema, and particularly those which have an acute onset. Thus asthma is simulated most closely; it does occur in infants, but is relatively uncommon at this age. Cystic fibrosis of the pancreas, the onset of miliary tuberculosis, pertussis (cough), aspiration of zinc stearate or other irritant substances, silicate poisoning (hyperpnea) and endocardial fibroelastosis must also be considered.

**Prognosis.** Though there is no specific therapy, a favorable outcome can be expected in most instances, even in the more severe cases, if adequate supportive therapy is provided. There are no adequate case fatality data, but the rate is probably less than 5 per cent. In newborn infants, and especially in premature ones, it may be higher. Adams observed case fatality rates of 28 and 14 per cent, respectively, in two of three epidemics.

Complications include bacterial bronchopneumonia, otitis media, pulmonary atelectasis and abscess and cardiac failure. Permanent sequels are extremely rare.

**Treatment.** The treatment is symptomatic. All infants with bronchiolitis should be placed in an atmosphere of high humidity, preferably with cold vapor rather than steam. Those with even moderately severe dyspnea should also receive oxygen therapy; one should not wait for the development of cyanosis. The infant is usually more comfortable if the head

and chest are slightly elevated. The dehydrating effects of the dyspnea should be combated by ample oral intake of fluids or, when this is not adequate, by parenteral administration of water and glucose. No concern need be felt if the caloric intake is not adequate during the few days of the acute phase, and the infant should be permitted to eat as he desires. Generous amounts of the water-soluble vitamins should be provided.

Although antibiotic therapy has not been effective in many instances of bronchiolitic infections, broad-spectrum coverage (p. 208) is indicated for severely ill infants since an occasional case has seemed to have been benefited. The experience with corticosteroids does not indicate any significant effect. When they are used, it is obligatory that broad-spectrum antibiotic therapy also be provided.

When there is considerable accumulation of exudate in the tracheobronchial tree and/or when there is atelectasis, bronchoscopic aspiration may be beneficial.

#### PRIMARY ATYPICAL PNEUMONIA, ETIOLOGY UNKNOWN

This diagnostic term is used for a respiratory infection characterized by a more or less acute onset with fever, malaise, persistent and distressing cough, and as a rule little dyspnea, at least in older children and adults. The roentgenographic evidence of pneumonic involvement is characteristic in its distribution and out of proportion to the physical signs, which may even be absent.

**Etiology.** Present evidence suggests that a variety of viral agents may be responsible for the syndrome (see p. 794). There are also some data indicating that *Streptococcus MG* may have an etiologic role.

**Epidemiology.** All ages are apparently susceptible, though no accurate data are available. The disease is apparently not limited in its geographic distribution. Epidemics may occur, but the disease is endemic, and cases are observed throughout the year.

**Pathology.** The following description is from Golden:

The weight of the lungs is average or only moderately increased. The pleural surfaces are smooth or glistening with occasional patches of frank fibrinous exudate. In a few instances there were small pleural effusions of an amber colored fluid. The parenchymal distribution varied from a portion of one lobe to a diffuse bilateral involvement. The focal lesion grossly resembled a miliary granuloma. However, these whitish nodules were found to be thickened bronchiolar walls from which frank pus exuded. The immediately surrounding pulmonary tissue was

either spongy and grossly normal or at times edematous, hemorrhagic, and congested. The mucous membrane of the large branches of the tracheobronchial tree either appeared normal or slightly edematous and congested; rarely was it acutely inflamed or ulcerated. The principal lesions appeared to be in the bronchioles where, in focally distributed lesions, there was desquamation of the mucosal surfaces. The lumens contained frank pus, mucoid fluid, and desquamated epithelial cells. Bacteria were not commonly present and there was no consistency in the types of those found. The bronchioles were markedly dilated and their walls were infiltrated with cells which were chiefly mononuclears. This cellular infiltration radiated into the regional interstitial tissues, the alveolar walls, and the pulmonary septums. The alveoli either contained air or were collapsed, but were free of exudate. Evidences of pneumonia were present when there was secondary bacterial invasion.

**Clinical Manifestations.** The incubation period has been estimated to be from ten to twenty-one days; by experimental inoculation (throat spray) it is seven to fourteen days (Dingle). The onset is usually gradual; initially for a few days there is malaise and a slight cough, then an elevation in temperature which may range from 101° to 105° F., but usually is not more than 103° F. The cough becomes more severe and is usually the most troublesome symptom; it is often paroxysmal, and in children may simulate that of pertussis so closely that this disease may be suspected. The cough is dry, and there is no sputum during the initial stage, but it is often present in the later stage of the illness and may become blood-streaked.

The *older child* does not as a rule appear to be as ill as his fever would indicate. The respiratory and pulse rates are usually only slightly increased. Severe degrees of dyspnea are uncommon, and cyanosis is rare. The throat may be mildly injected, and there may be slight enlargement of the cervical lymph nodes. The paucity of abnormal findings is striking; often there is none at all. Rales are occasionally heard in isolated areas, and infrequently there are isolated areas of dullness, usually with diminished breath sounds. Evidences of extensive consolidation, of friction rubs and of pleural fluid are rare. Meningismus has been noted in a few instances.

There is little information about the clinical pattern of primary atypical pneumonia in infants, but there is presumptive evidence that some of the cases of bronchiolitis may belong in this category (p. 794).

The roentgenogram usually shows changes out of proportion to the physical findings. Characteristically, there are evidences of in-



filtration which extend from the hilar regions and branch out as they approach the periphery (Fig. 223), or there may be diffuse nodular areas. The lesions may be confined to one lobe, more commonly a lower one, or may be present in several or all lobes. There may be widespread, generalized obstructive emphysema, especially in infants.

**Laboratory Data.** The white blood cell count is rarely significantly altered; it may be slightly increased or decreased. Total counts below 4000 or above 15,000 per cubic millimeter are unusual. The erythrocyte sedimentation rate is usually increased, and the increased rate often persists for several weeks into the convalescent phase. The urine shows no consistent abnormalities.

In many cases of primary atypical pneumonia of unknown etiology cold agglutinins against group O human erythrocytes develop in high titer. They usually appear during the second week after the onset of fever and persist for several weeks. Significant titers of cold agglutinins are rarely encountered in bacterial pneumonias and in other acute respiratory infections. Agglutinins to *Streptococcus MG* are also observed after primary atypical pneumonia with a frequency about equal to that of cold agglutinins. Temporary, falsely positive serologic tests for syphilis are also occasionally noted.

**Differential Diagnosis.** *Pneumonias* resulting from infection with the common as well as the unusual bacterial agents must be excluded by bacteriologic means. The principal confusion is likely to be with *influenzal virus infections*; cold agglutinins are rarely found in association with this infection. During the acute stage the possibility of tuberculosis must also be considered, but is readily eliminated by the natural course of the infection. At present the diagnosis of primary atypical pneumonia is made by exclusion of other diseases, by the more or less characteristic roentgenographic pattern, by the subsequent appearance of cold agglutinins or of agglutinins to *Streptococcus MG*, and by failure of the patient to respond to antibacterial therapy.

**Complications.** In contrast to the bacterial pneumonias, complications are uncommon. Occasional instances of recurrence have been recorded. Otitis media occurs at times; empyema, pneumothorax and bronchiectasis are rare complications.

**Course and Prognosis.** The course of the acute phase averages about eight to ten days, but shorter or longer periods are common.

Roentgenographic evidence of the pulmonary lesion may persist for several weeks. The child should be permitted a convalescent period at least equal to that of the acute phase, and a longer period if the usual strength and vigor have not been regained.

The prognosis for complete recovery is good in children beyond the age of infancy, the case fatality rate being less than 1 per cent. (For infants, see p. 795.)

**Treatment.** Treatment is symptomatic. The child is usually more comfortable in an atmosphere of high humidity; for this purpose cold vapor is preferable to the steam inhalator. Phenobarbital may be required to secure adequate rest for the child because of the coughing. No antibacterial therapy is indicated in older children; for infants, see treatment of bronchiolitis. Secondary bacterial infections should be treated with appropriate antibacterial agents.

### GIANT CELL PNEUMONIA

Giant cell pneumonia (Hecht) is a subacute or chronic interstitial pneumonitis occurring in infants and young children. Clinically, it is indistinguishable from other subacute or chronic pneumonitides. Pathologically, it is characterized by the presence of multinucleated giant cells containing intranuclear and



FIG. 223. Primary atypical pneumonia. Extensive changes throughout most of the right lung and base of left lung. There is more abnormality in the left lower lobe than appears on the roentgenogram, because much of it is hidden behind the heart.

intracytoplasmic inclusion bodies; it seems probable that demonstrations of such giant cells in the sputum might be of value in the antemortem diagnosis of the disease. The etiology has not been established, but the similarity of the lesions to those of distemper in animals and the frequent association with measles strongly suggest a viral origin.

#### PLASMA CELL PNEUMONIA

This pneumonic involvement, which is now considered by some observers to be a primary disturbance, appears to be limited to infants of one to four or six months of age and occurs principally in premature and debilitated full term ones. The geographic distribution is of equal interest; it has been observed with any degree of frequency only in the central and northern European countries, and a few cases have been described in the United States within the past few years.

The etiology is not definitely known, but the protozoan, *Pneumocytis carinii*, initially observed in the alveolar exudate by Vaněk and co-workers, has now been identified in tissue sections by a number of other investigators.

On examination the lungs are typically pale gray to gray-blue in appearance and do not collapse. Only the anterior portions of the lung have any significant amount of air-bearing alveoli, where there may be some obstructive emphysema. Histologically, the septums are widened, and the alveoli are mostly collapsed or filled with exudate. The cellular infiltrate is composed almost entirely of mononuclear cells, which resemble plasma cells, histiocytes and intermediary forms.

Clinically, the onset is slow and insidious, in some instances being preceded by an upper respiratory tract infection or diarrhea by several days or weeks. The incubation period has been estimated to be twenty to sixty days. Initially, there is nothing to direct attention to the pulmonary involvement. The infant becomes apathetic, loses his appetite and either fails to gain or loses weight. Then within a week or two his respirations begin to increase in rapidity. This tachypnea is considered the most characteristic sign; the rate may be 80 to 120 per minute. Cough and fever are not prominent, but as the disease progresses the infant becomes cyanotic, often exhibiting a grayish cast of the skin.

The physical examination is not characteristic. There may be scattered areas of impaired resonance and suppressed breath sounds, and often widely scattered fine rales.

Emphysema is a common complication; presumably starting interstitially, it may be responsible for pneumomediastinum, pneumothorax and subcutaneous emphysema. The white blood cell count may be increased up to 20,000 per cubic millimeter. Roentgenographically, there are scattered small infiltrative areas and at times larger ones.

The course is prolonged in the nonfatal cases, from four to six weeks. The case fatality rate is not known, but has been estimated to be from 20 to 50 per cent.

There is no known specific treatment.

WALDO E. NELSON

#### REFERENCES

##### *Bronchiolitis and Interstitial Pneumonitis*

- Adams, J. M.: Primary Pneumonitis in Infancy. J.A.M.A., 138:1142, 1948.  
 Goodpasture, E. W., Auerbach, S. H., Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections. Am. J. Dis. Child., 57:997, 1939.  
 Wood, S. H., Buddingh, G. J., and Abberger, B. F.: An Inquiry into the Etiology of Acute Bronchiolitis of Infants. Pediatrics, 13:363, 1954.

##### *Primary Atypical Pneumonia*

- Commission on Acute Respiratory Diseases, Fort Bragg, N. C.: Transmission of Primary Atypical Pneumonia to Human Volunteers. J.A.M.A., 127:146, 1945.  
 Golden, A.: Pathologic Anatomy of "Atypical Pneumonia Etiology Undetermined." Arch. Path., 38:187, 1944.

##### *Giant Cell Pneumonia*

- Pinkerton, H., Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions; Lesions Common to Hecht's Disease, Distemper, and Measles. Am. J. Path., 21:1, 1945.

##### *Plasma Cell Pneumonia*

- Ahvenainen, E. K.: Interstitial Plasma Cell Pneumonia. Pediat. Clin. North America, 4:203, 1957.  
 Vaněk, J., Jérovec, O., and Lukés, J.: Interstitial Plasma Cell Pneumonia in Infants. Ann. paediat., 180:1, 1953. Abstr., Yearbook of Pediatrics, 1953-1954.

#### MYCOTIC PULMONARY INFECTIONS

See also Coccidioidomycosis, Histoplasmosis, Blastomycosis, Cryptococcosis, Mucormycosis and Sporotrichosis in their respective sections.

#### THRUSH PNEUMONIA

Oral infections with *Candida albicans* are discussed on page 633, and the occasional complication of an esophagogastritis is mentioned. Adams reported seven cases of pneumonia in infants with oral thrush. The presence of



pneumonia was confirmed by roentgenographic examination. Death occurred in one infant, and the autopsy revealed a widespread staphylococcal pneumonia with multiple small abscesses. A synergistic action between *C. albicans* and a strain of *Staphylococcus* was postulated.

WALDO E. NELSON

#### REFERENCE

Adams, J. M.: A Revaluation of the Pneumonias of Infancy. *J. Pediat.*, 25:369, 1944.

#### ASPIRATION PNEUMONIAS

For Fetal Anoxia with Aspiration of Excessive Amniotic Debris, see page 321.

#### ASPIRATION OF FOOD

Infants with obstructive lesions, such as tracheo-esophageal fistula and duodenal obstruction, and weak and debilitated infants who have no obstructive lesions may aspirate, or regurgitate and then aspirate, a sufficient amount of food to cause significant mechanical damage. At times it is an immediate cause of death by asphyxiation. In other instances the irritated mucous membrane becomes a site for bacterial invasion. Prophylaxis is of the greatest importance. Care should be taken to avoid amounts of feedings that will overdistend the stomach; this is especially true for infants whose feeding is gavage. After the infant has been fed he should be placed on his abdomen or on his right side. When in the supine position, care should be taken to see that his head is not lower than the rest of his body. Drainage from the lungs may, however, be materially aided by lowering the head of the bed while the infant is lying on his abdomen.

#### ASPIRATION OF ZINC STEARATE

Aspiration pneumonia resulting from inhalation of zinc stearate powder, once relatively common, has now become comparatively rare because of efforts directed against the use of this powder for infants. The containers have also been equipped with an automatic closing device, but this is not infallible. Severe respiratory distress follows inhalation almost immediately. There is a generalized obstructive emphysema with an expiratory type of dyspnea. In the severe cases dyspnea and cyanosis persist in spite of oxygen therapy. The embarrassment to respiration appears to be the result of two factors, a mechanical obstruction and an inflammatory reaction caused by the irritation of the zinc stearate.

Owing to the extreme lightness of the powder it is almost immediately drawn into the finer bronchioles, and for this reason bronchoscopic aspiration is of little avail except to remove the secretions which subsequently accumulate. If the child survives the acute episode, he is especially liable to bronchopneumonic infections.

Immediate *treatment* consists in oxygen therapy in an atmosphere of high humidity. Bronchoscopic aspiration is indicated when there is an excessive accumulation of secretions in the larger air passages. If the infant survives the mechanical phase, an antibacterial agent should be prescribed for prophylactic purposes.

#### ASPIRATION OF DUST

A type of bronchitis has been described which is associated with prolonged exposure to high concentrations of dust. In a reported instance the source of the dust was a large clay playground. The complaints are an uncomfortable tickling sensation in the throat and an explosive, intractable, nonproductive cough. The only abnormal physical signs are rhonchi and some wheezing sounds. The cough persists for ten to fourteen days. Roentgenograms of the chest show a soft patchy mottling with increased bronchovascular markings, usually in the lower lobes.

*Treatment* is symptomatic and should include humidification during the stage of irritation. The prevention of dust dispersion is accomplished by frequent wetting of the soil, by utilization of some binder such as calcium chloride, or by asphaltting the surface.

#### KEROSENE PNEUMONIA

Pulmonary disturbances are frequently associated with the accidental ingestion of kerosene. (See Hydrocarbons, page 1388, for other manifestations of kerosene poisoning.)

There are conflicting interpretations of the *pathogenesis* of the pulmonary lesions. Some investigators contend that most of the kerosene reaches the lungs after absorption from the gastrointestinal tract, whereas others believe that aspiration during swallowing, vomiting or gastric lavage provides the principal means for pulmonary contamination. Consequently there are divergent views concerning the advisability of gastric lavage after the ingestion of kerosene or other hydrocarbons. The pulmonary changes observed in animals are edema, inflammation and hemorrhage.

Coughing and vomiting follow ingestion almost immediately. There is an elevation of

temperature (100° to 104° F.), and the child may be drowsy or comatose. The pulmonary findings are diminished resonance on percussion, suppressed or tubular breath sounds, and rales. The presence of pneumonic involvement is disclosed more frequently by roentgenographic examination than by physical findings. Pleural effusion, which may become purulent, pneumothorax, and subcutaneous emphysema of the chest wall have occurred as *complications*. In spite of the stormy clinical course, which averages two to five days, recovery occurs in most instances.

*Treatment* is symptomatic. An antibiotic should be administered prophylactically, or therapeutically if a secondary infection has occurred. When only small amounts of kerosene have been ingested, and especially if several hours have elapsed, gastric lavage probably should be omitted. When large quantities of kerosene or other hydrocarbons have been ingested, lavage should be performed with great care to avoid aspiration. In either instance a saline cathartic should be administered. If there is dyspnea or cyanosis, the child should be placed in an oxygen tent.

#### LIPOID PNEUMONIA

Lipoid pneumonia is a chronic, interstitial, proliferative inflammation resulting from aspiration of lipid material; it occurs principally in debilitated infants.

The factors which may be responsible for aspiration of oil include (1) intranasal instillation of medicated oils, (2) any condition which interferes with the swallowing act, such as cleft palate, debilitation, and an enforced horizontal position during feeding, and (3) forced feeding and especially the administration of cod liver oil, castor oil or mineral oil to crying children.

The severity of the pulmonary reaction depends upon the type of oil inhaled. Vegetable oils as a group are the least irritating; such oils as olive, cottonseed and sesame produce no inflammation; chaulmoogra, a vegetable oil, on the other hand, is responsible for extensive damage. Animal oils, owing to their high fatty acid content, are the most damaging. Cod liver oil belongs in this category. Liquid petrolatum is chemically inert and is not so irritative as some of the other oils, but does act as a foreign body.

Initially, the reaction within the lung is essentially an interstitial proliferative inflammation with which there may be an exudative pneumonia. In the second stage there



FIG. 224. Roentgenogram showing increased density radiating from the hilum of each lung in an infant 13 months of age after intranasal application of liquid petrolatum 3 times a day for 5 months.

is diffuse, chronic, proliferative fibrosis. Acute bronchopneumonia is not infrequently superimposed in this stage. In the third stage there are multiple localized nodules, the so-called tumor-like paraffinomas. Microscopically there are numerous macrophages in the involved areas with giant cell formation of the foreign body type. The lipid substance is both intracellular and extracellular. The oil-laden cells may be carried through the lymphatic channels to the hilar lymph nodes.

**Clinical Manifestations.** There are no characteristic signs or symptoms. The most common symptom is cough, and in severe cases there may be dyspnea. Unless there is a superimposed infection, there are usually no fever and no physical signs. With extensive involvement there may be some impairment to percussion and increased or decreased voice and breath sounds. Secondary bronchopneumonic infections are common.

The only characteristic finding is the roentgenographic appearance. When there is only a mild involvement, there is an increase both in the degree of density and the extent of the hilar shadows. With increasing involvement there is greater density of the perihilar shadows with widening in all directions (Fig. 224). In a few instances the pulmonary changes have been limited to the right lung, and, in the infant who is recumbent most of the time, the changes may be largely in the right upper lobe.

**Prognosis.** The prognosis is guarded. It depends upon the extent of pulmonary damage, the discontinuance of oil inhalation, the general condition of the infant, and the avoidance of intercurrent infections.

**Prevention.** Intranasal medication in an



oily vehicle should never be used. Concentrated preparations of vitamins A and D in water-miscible vehicles should be substituted for cod liver oil. Administration of mineral oil and castor oil should be avoided. Infants who regurgitate or vomit frequently should be placed on their abdomens to lessen the likelihood of aspiration.

**Treatment.** There is no specific treatment. The administration of oil should obviously be discontinued. The infant's position should be changed frequently to lessen the chances of hypostatic pneumonia. Efforts should be made to avoid contact with infectious diseases.

WALDO E. NELSON

## REFERENCES

### Zinc Stearate

Heiman, H., and Aschner, P. W.: Aspirations of Stearate of Zinc in Infancy. *Am. J. Dis. Child.*, 23:503, 1922.

### Dust

Toomey, J. A., and Petersilge, C. L.: Dust Bronchitis. *J. Pediat.*, 25:25, 1944.

### Lipoid

Bromer, R. S., and Wolman, I. J.: Lipoid Pneumonia in Infants and Children. *Radiology*, 32:1, 1939.  
Nathanson, L., Frenkel, D., and Jacobi, M.: Diagnosis of Lipoid Pneumonia by Aspiration Biopsy. *Arch. Int. Med.*, 72:627, 1943.

## LÖFFLER'S SYNDROME

### (EOSINOPHILIC PNEUMONIA)

This condition is a clinical syndrome characterized by widespread, small, transitory pulmonary infiltrations which roentgenographically bear a resemblance to those of miliary tuberculosis, and by a blood eosinophilia which often is as high as 40 to 70 per cent. The *clinical course* is, as a rule, not particularly severe and varies from a few days to several months. Features more or less common to the reported cases are paroxysmal attacks of coughing, dyspnea, pleurisy and little or no fever. Zuelzer and others have called attention to the association of hepatomegaly in this syndrome, especially in infants and young children. Biopsy sections of the livers revealed multiple focal areas of necrosis, granuloma formation and eosinophilic infiltration. These children also had hyperglobulinemia, presumably as the result of hepatic dysfunction. Reported autopsy studies have revealed evidences of eosinophilic infiltrations in the lungs and in other organs. Instances have also been recorded of localized pneu-

monic consolidations with an eosinophilia as high as 22 per cent. There is some doubt whether Löffler's syndrome is a clinical entity, and the possibility has been suggested that it is merely an unusual allergic manifestation. Cat and dog ascarids have been shown to be a cause of this syndrome (p. 578); whether they are the sole cause is yet to be established.

WALDO E. NELSON

## REFERENCES

Beaver, P. C., and others: Chronic Eosinophilia Due to Visceral Larva Migrans. *Pediatrics*, 9:7, 1952.  
Nemir, R. L., Heyman, A., Gorvoy, J. D., and Ervin, E. N.: Pulmonary Infiltration and Blood Eosinophilia in Children (Löffler's Syndrome): Review with Report of Eight Cases. *J. Pediat.*, 37:819, 1950.  
Zuelzer, W. W., and Apt, L.: Disseminated Visceral Lesions Associated with Extreme Eosinophilia: Pathologic and Clinical Observations on a Syndrome of Young Children. *Am. J. Dis. Child.*, 78:153, 1949.

## HYPOSTATIC PNEUMONIA

Hypostatic pneumonia occurs after prolonged passive pulmonary congestion and may occur in any marantic state. Lying for a long time in one position favors its development. The pathologic lesion consists in dependent congestion, edema and pneumonia.

**Clinical Manifestations.** The symptoms are not characteristic. There is neither dyspnea nor fever, unless these symptoms are dependent upon the primary disorder. The physical signs are principally slight dullness on percussion, feeble respiratory sounds, and the presence of moist rales. Hypostatic congestion is usually a terminal event.

**Treatment.** Treatment is that of the primary affection. Prophylaxis is of the greatest importance; the position of the patient should be frequently changed when there is a possibility of development of passive pulmonary congestion.

## IDIOPATHIC PULMONARY

### HEMOSIDEROSIS

#### (ESSENTIAL BROWN INDURATION OF THE LUNGS)

Idiopathic pulmonary hemosiderosis is a rare condition in which the onset appears to be in childhood and the disease is largely limited to this age period. There does not appear to be a hereditary or familial factor. This condition is not part of a generalized hemosiderosis, nor is there any disturbance of iron metabolism as in hemochromatosis. Wyllie suggests

that the primary defect may be in the pulmonary interstitial tissue where capillary stasis results in hemorrhage by diapedesis and deposition of hemosiderin. Steiner has postulated an antigen-antibody reaction and reports improvement in a boy after splenectomy. *Pathologic changes* are limited to, or maximal in, the lesser circulation. Myocardial changes are insufficient to account for the pulmonary lesions. Anemia, when present, appears to be secondary; in some instances there is a compensatory rise in the red blood cell count in association with cyanosis in the final stages of the disease. Secondary inflammatory changes in the lungs are not common.

Characteristically there are recurrent attacks, often sudden in onset, of fatigue, cyanosis, pallor, dyspnea and accelerated pulse rate. Cough is troublesome, often followed by vomiting, and there may be small or large quantities of blood in the sputum or vomitus. Occult blood can also be demonstrated in the feces. Abdominal pain may be a feature, and the temperature may be elevated slightly or to as much as 103° F. at the height of the attack. The acute phase, which may be extremely severe, lasts two or three days and may be followed by a subacute phase. The clinical pattern of the acute phase is one of congestive cardiac failure. Pallor, jaundice, and enlargement of the liver and spleen may be features of the subacute phase, and clubbing of the fingers may develop. The *prognosis* is grave.

The *roentgenographic findings* are mottled shadows most noticeable in the hilar areas with a diffuse speckling throughout the lung fields, resembling somewhat the appearance of miliary tuberculosis.

*Hemosiderin* may be seen in macrophages in the sputum or in material obtained bronchoscopically or by gastric lavage.

WALDO E. NELSON

#### REFERENCES

- Steiner, B.: Essential Pulmonary Haemosiderosis as an Immuno-haematological Problem. *Arch. Dis. Childhood*, 29:391, 1954.  
Wyllie, W. G., Sheldon, W., Bodian, M., and Barlow, A.: Idiopathic Pulmonary Haemosiderosis (Essential Brown Induration of the Lungs). *Quart. J. Med.*, 17:25, 1948.

#### ATELECTASIS

Congenital atelectasis is discussed on page 324.

#### ACQUIRED ATELECTASIS

**Etiology.** Atelectasis, imperfect expansion or collapse of the air-bearing tissue of the lung, is relatively common in infants and children. Collapse may be produced by any factor which completely obstructs the intake of air into the alveolar sacs and persists for a sufficient time to permit absorption of the existing alveolar air into the blood stream. In general, the causes may be divided into two groups: (1) external pressure directly upon the pulmonary parenchyma or a bronchus or bronchiole, and (2) intrabronchial or intrabronchiolar obstruction. Any factor responsible for a continuously decreased amplitude of respiratory excursion or for respiratory paralysis may be contributory. Reflex stimuli have also been considered initiating factors. De Takats demonstrated that at least three distinct stimuli, namely, pulmonary embolism, intra-abdominal manipulation and trauma to the chest wall, are capable of initiating bronchoconstriction and increased bronch secretion. Allergy may be responsible for atelectasis by spasm of the bronchial or bronchiolar musculature and/or by production of an exudate which occludes the lumen.

**Atelectasis from external pressure.** External factors may be operative in one of four ways: (1) interference with the movements of the thoracic cage (neuromuscular abnormalities as in cerebral palsy, poliomyelitis, amyotonia congenita, myasthenia gravis; osseous deformities as in rickets, scoliosis, kyphosis; scleroderma; splinting of the chest by casts and surgical dressings); (2) defective movement of the diaphragm (paralysis of phrenic nerve, increased abdominal pressure); (3) direct interference with expansion of lungs (pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia); and (4) external compression of a bronchus completely obstructing ingress of air (enlarged lymph node, tumors, cardiac enlargement).

**Atelectasis from intrabronchial or intrabronchiolar obstruction.** (See also p. 774.) Complete intraluminal obstruction of a bronchus may be produced by a foreign body, by a neoplasm, by granulomatous tissue as in tuberculosis or by secretions as with bronchiectasis, pulmonary abscess or a tumor or allergy, chronic bronchitis or acute laryngotracheobronchitis.

Obstruction of one or more bronchioles in a given area may be produced by any of the conditions mentioned, but widespread bronchiolar obstruction is most often produced by



bronchiolitis or interstitial pneumonitis and by asthma. Generalized obstructive emphysema is the initial result of such bronchiolar obstructions; but as the pathologic changes progress, some of the bronchioles may become completely obstructed, and there are then interspersed small areas of atelectasis and emphysema. Patchy atelectasis is not frequent in acute bronchiolitis or in asthma, and is probably always present in advanced chronic diffuse infections such as the pulmonary infection associated with cystic fibrosis of the pancreas.

**Pathology.** The atelectatic areas are airless, congested, deep red, of a firm consistency, and depressed below the neighboring healthy or emphysematous lung. When there is extensive atelectasis of one or more lobes, there is usually compensatory emphysema of the air-bearing lung.

**Clinical Manifestations.** The symptoms vary with the cause and with the extent of the atelectasis. When only a small area is atelectatic, there are likely to be no symptoms referable to it. When a large area of the lung becomes atelectatic, and especially when it does so suddenly there is dyspnea with rapid shallow respirations, tachycardia, and often cyanosis. If the obstruction is removed, the symptoms disappear rapidly. Even atelectasis of an entire lobe may not be responsible for changes in the percussion note, owing to the compensatory emphysema of the adjacent

lung tissue. Breath and voice sounds are decreased or absent over extensive atelectatic areas.

**Diagnosis.** The diagnosis can usually be established by roentgenographic examination (Fig. 225). Small areas may be indistinguishable from pneumonic consolidations, but those that involve as much as several lobules of a lobe can usually be identified by the contraction of the area. When one or more lobes are atelectatic, the roentgenographic findings are those of massive collapse. Bronchoscopic examination will reveal a collapsed main bronchus when the obstruction is at the tracheobronchial junction and may also disclose the nature of the obstruction.

**Prognosis.** This depends upon the underlying cause. If the obstruction disappears spontaneously or is removed, the atelectasis usually disappears unless there is secondary infection. In the persistent cases bronchiectasis is a frequent complication and pulmonary abscess an occasional one.

**Treatment.** Bronchoscopic examination is indicated when an isolated area of atelectasis persists for several days, and immediately if it is the result of a foreign body or there is reason to believe that it is due to a bronchial obstruction which may be relieved. Frequent changes in the child's position and deep breathing may be beneficial. Oxygen therapy is indicated when there is dyspnea, and in all instances the child should be kept in an

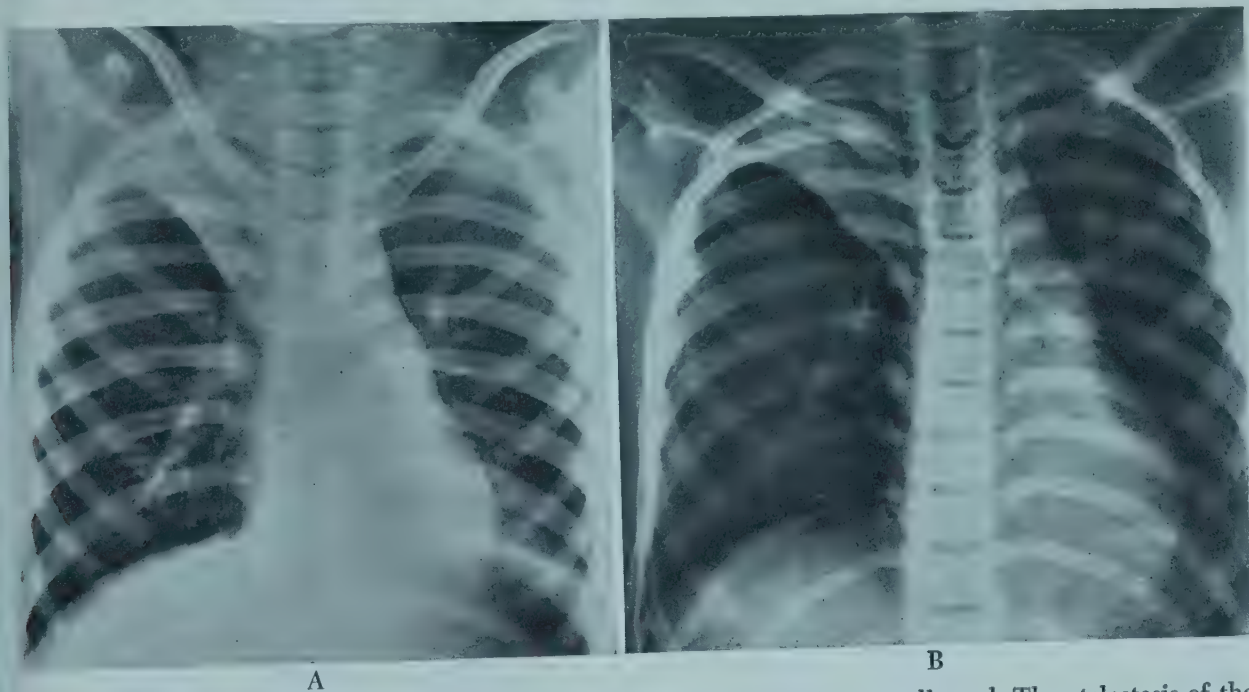


FIG. 225. Atelectasis. The right upper lobe and the left lower lobe are collapsed. The atelectasis of the left lower lobe is demonstrated on the overpenetrated film (B). The atelectases occurred postoperatively and disappeared spontaneously.

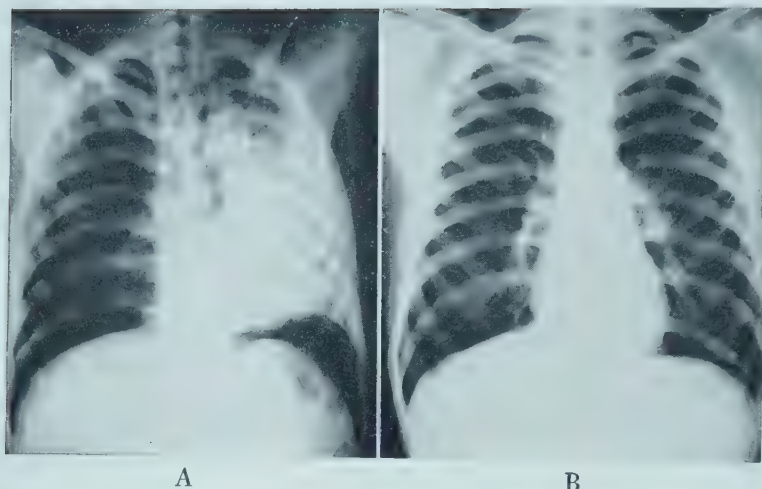


FIG. 226. A, Massive atelectasis of the left lung, postoperative, with (B) comparison study after re-aeration of left lung. Onset of symptoms and signs occurred a few hours after appendectomy. Note the pneumoperitoneum, resulting from residual air when abdomen was closed. The heart and all other mediastinal structures have been drawn far to the left as a result of the atelectasis.

environment of high humidity (cold). Morphine and atropine are contraindicated.

#### MASSIVE PULMONARY ATELECTASIS

Massive collapse of one or both lungs is most often a postoperative complication, but occasionally results from other causes such as trauma, asthma, pneumonia, tension pneumothorax, the aspiration of foreign material (either a solid object large enough to obstruct the trachea or liquids such as water or blood) and paralysis such as that in diphtheria or poliomyelitis. Massive atelectasis is usually produced by a combination of factors: immobilization or decreased use of the diaphragm and the respiratory muscles, obstruction of the bronchial tree and abolition of the cough reflex. The Jacksons demonstrated that bronchial obstruction by thick secretions is present in a large percentage of postoperative cases and that prompt removal of it by bronchoscopic aspiration is successful in relieving the atelectasis.

**Clinical Manifestations.** The onset in postoperative cases is usually within twenty-four hours after operation, but may not appear for several days. There is dyspnea, cyanosis and tachycardia. The child is extremely anxious, there is likely to be prostration, and, if he is old enough, he usually complains of pain in the chest. The temperature may be as high as  $103^{\circ}$  or  $104^{\circ}$  F.

The physical signs are characteristic. The chest on the affected side appears flat, and there is decrease of respiratory excursion on that side. The intercostal spaces are narrowed, and there is dullness or flatness to percussion.

Breath and voice sounds are usually feeble or absent. The lower lobes are more frequently involved than the upper ones. The heart and mediastinum are displaced toward the affected side except in bilateral cases. Roentgenograms show the collapsed lung, elevation of the diaphragm, narrowing of the intercostal spaces and displacement of the mediastinal structures and heart toward the affected side.

**Prognosis.** Bilateral massive collapse is usually rapidly fatal, although prompt bronchoscopic aspiration and artificial respiration may be lifesaving. In the unilateral cases the prognosis is usually good.

**Prevention.** Prophylaxis is of the greatest importance. The incidence of postoperative atelectasis can be reduced by adequate ventilation during anesthesia. After operation the child's position in bed should be changed frequently, collections of secretions in the oropharynx should be aspirated, and, when consciousness returns, the child should be encouraged to breathe deeply. Tight thoracic or abdominal binders should be avoided.

**Treatment.** When there is bilateral atelectasis, bronchoscopic aspiration should be performed immediately.

When there is only unilateral atelectasis, the child should be placed on the unaffected side. Forced coughing or crying while the child is lying on the unaffected side may also be helpful. When these measures are not successful, bronchoscopic aspiration should be performed.

Relapses are not infrequent, and the child should be kept under constant observation.



## EMPHYSEMA

Pulmonary emphysema is a distention or rupture of the alveoli. It may be localized and involve part or all of one lung, or it may be generalized. From an etiologic standpoint it may be compensatory or obstructive.

### COMPENSATORY EMPHYSEMA

This may be either acute or chronic. It occurs in normally functioning pulmonary tissue when for any reason a sizable portion of the lung is partially or completely airless as in association with pneumonia, atelectasis, empyema and pneumothorax.

### OBSTRUCTIVE EMPHYSEMA

Obstructive emphysema results from partial obstruction of a bronchus or bronchiole when the difficulty of getting air out of the alveoli is greater than getting it in, so that there is a gradually increasing accumulation of air distal to the obstruction. This is the so-called bypass or check-valve type of obstruction. Such obstructions may be intrabronchial or extrabronchial (see p. 802).

### LOCALIZED OBSTRUCTIVE EMPHYSEMA

When the main stem bronchus is occluded in this manner, the entire lobe is emphysematous; only individual lobules are affected when the obstruction is that of a secondary bronchus. Localized obstructions which may be responsible for emphysema include foreign bodies and the inflammatory reaction to them, intrabronchial tuberculosis or tuberculosis of the tracheobronchial lymph nodes and intrabronchial and lymph node tumors. When most or all of a lobe is involved, the percussion note will be hyperresonant over the area and the breath sounds decreased in intensity. The distended lung may extend across the mediastinum into the opposite hemithorax. Fluoroscopically, it can be observed that during expiration the emphysematous area does not decrease in size, and the heart and mediastinum shift to the opposite side.

*Congenital obstructive lobar emphysema* may account for severe respiratory distress in early infancy. A part or usually all of a lobe may be involved; the left upper lobe seems to be the one most often affected. In some instances there is no demonstrable obstruction,

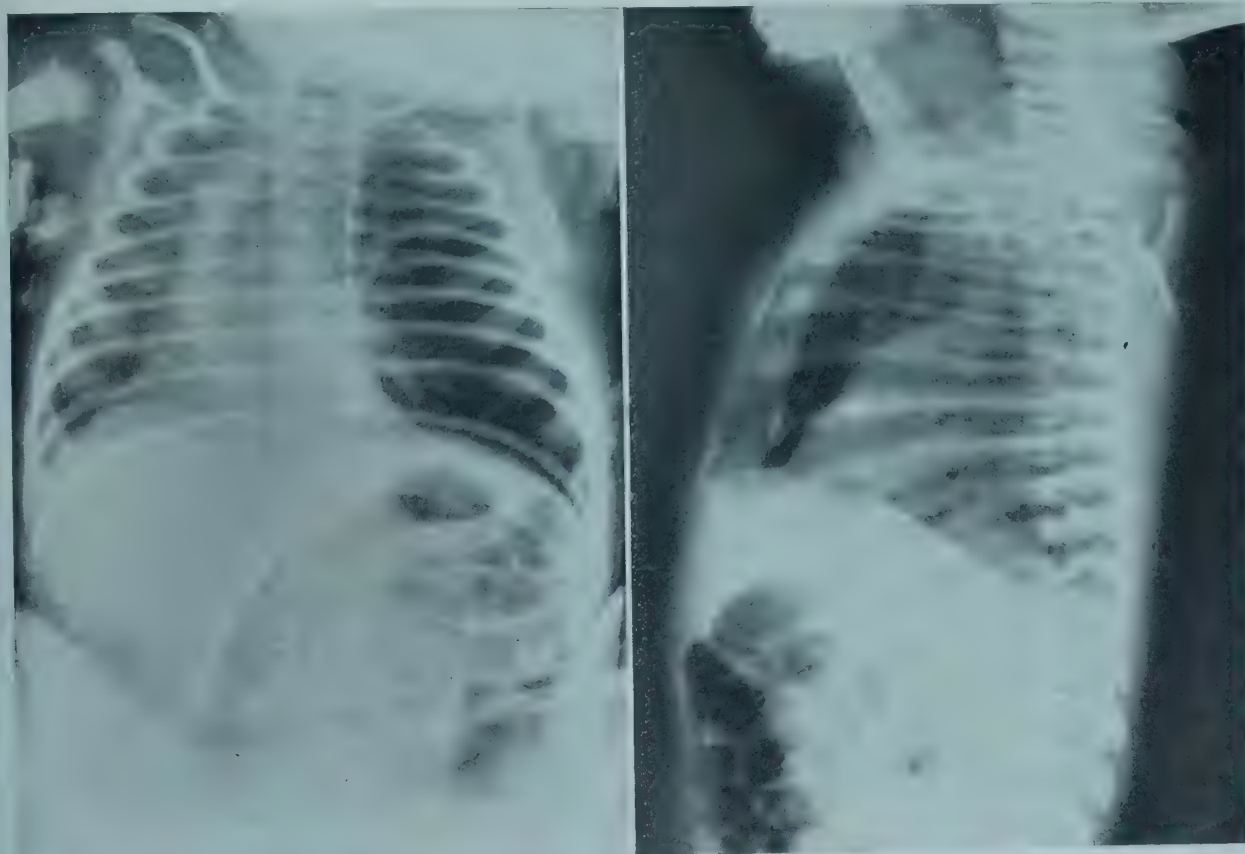
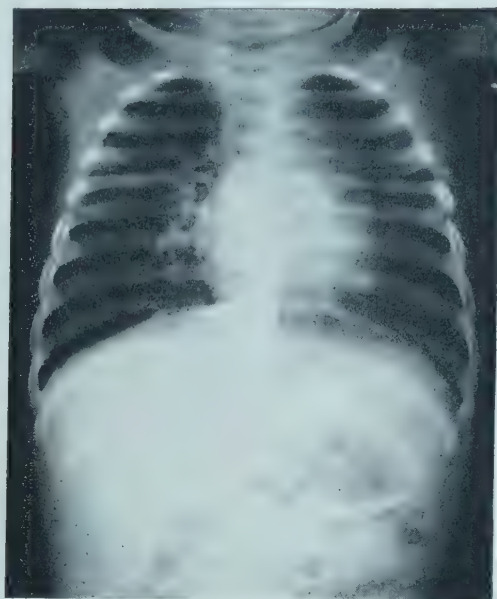
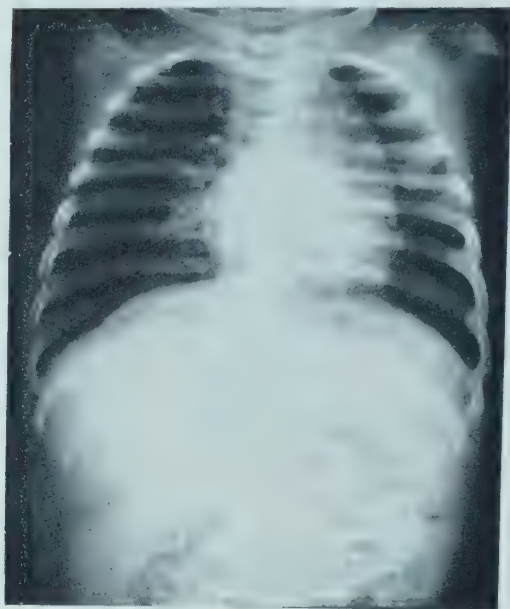


FIG. 227. Congenital lobar emphysema in an infant 4 weeks of age. Severe dyspnea and wheezing of 4 days' duration. The left upper lobe is emphysematous and protrudes across the midline anteriorly (note lateral projection). The mediastinal structures are displaced to the right. Relief of symptoms followed removal of the left upper lobe.



INSPIRATION



EXPIRATION

FIG. 228. Generalized obstructive emphysema: dorsal projections of thorax in inspiratory (left) and expiratory (right) phases of respiration. Notice the relative failure of the lungs to empty in the expiratory phase. The left lung is less obstructed than the right (empties to a greater degree in the expiratory phase). This difference between the lungs is not apparent from a study of the diaphragm, which moves very little during respiration; it is evident, however, in the upper portions of the left lung space. (From Nelson and Smith: *J. Pediat.*, Vol. 26.)

but it is assumed to be produced by a check-valve type of mechanism. Such obstructions have been attributed to defective cartilage in the bronchi, mucosal folds which create a valvelike obstruction, bronchial stenosis and external compression by aberrant vessels, tumors and the like. When the distention is marked, the emphysematous lung compresses the unaffected lung below or above it and the contralateral lung by extending across the mediastinum (Fig. 227). In most instances lobectomy is indicated.

Emphysema of all three lobes of the right lung has been produced by anomalous location of the left pulmonary artery, which partially constricts the right main bronchus.

#### GENERALIZED OBSTRUCTIVE EMPHYSEMA

This depends upon widespread involvement of the bronchioles. It occurs more commonly in infants than in older children and may be secondary to a number of different clinical conditions, including respiratory infections associated with cystic fibrosis of the pancreas, acute bronchiolitis or interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis. Asthma is a relatively frequent cause

in older children, but an uncommon one in infants.

The emphysematous portion of the lung is paler than usual, usually a light pink, and is distended and does not readily collapse. In chronic emphysema there is permanent loss of elasticity; many of the alveoli are ruptured and communicate with one another, producing distended saccules. As a result of the rupture of the alveoli, air may enter the interstitial tissue (*interstitial emphysema*) and result in pneumomediastinum and pneumothorax.

**Clinical Manifestations.** Generalized obstructive emphysema is characterized by an expiratory type of dyspnea. Owing to the relatively greater difficulty in expiration than in inspiration, air is trapped in the alveoli, the lungs become increasingly overdistended, and the chest remains expanded during expiration. Just the reverse happens in laryngeal obstruction, in which interference with exchange of air is relatively greater during inspiration and the lungs cannot be fully inflated. There is an increased respiratory rate and decreased respiratory excursions associated with the utilization of the accessory muscles of respiration. The overactivity of these muscles results in some inspiratory in-drawing at the suprasternal notch, the supra-



clavicular spaces, the lower margin of the thorax and the intercostal spaces, but this indrawing is not nearly so great as in laryngeal or tracheal obstruction. There is scarcely any reduction in size of the overdistended emphysematous chest during expiration, in contrast to the flattened chest during both inspiration and expiration when there is laryngeal obstruction. There is no hoarseness or stridor as there is in laryngeal obstruction; there is usually audible wheezing in asthma. Cyanosis is common in the severe cases. The percussion note is hyperresonant, and, on auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium rales may or may not be present.

The roentgenographic and the fluoroscopic examinations of the chest are of the greatest help in establishing the diagnosis. Both leaves of the diaphragm are low and flattened, the ribs are farther apart than usual, and the lung fields are less dense. There is a marked restriction in the movement of the diaphragm (Fig. 228); this is demonstrated best by fluoroscopic examination. The normal "doming" of the diaphragm during expiration is decreased, and the excursion of the low, flattened diaphragm in the severe cases is barely discernible. Another evidence of retention of air in the lungs during expiration is a paradoxical increase in the horizontal diameters of the chest during this phase, suggesting that the emphysematous lungs are merely being forced into a different position by the diaphragmatic activity (the abdominal respiratory effort is relatively stronger than that of the intercostals) rather than emptied of any significant amount of trapped air.

#### **BULLOUS EMPHYSEMA**

Bullous emphysematous blebs or cysts (pneumatocele) result from overdistention and rupture of alveoli during birth or shortly thereafter (p. 781), or they may be sequels of pneumonia and possibly of other conditions. These emphysematous areas presumably result from the rupture of emphysematous alveoli so that a single or multiloculated cavity is formed. At times the cysts may assume large proportions (Fig. 222). They may contain some fluid, and an air-fluid level may be demonstrated on the roentgenogram. The differential diagnosis must be made from pulmonary abscess. In most instances the cysts disappear spontaneously within a few months, although they may persist for a year or so. There is almost never any indication

for treatment; aspiration or surgery should be avoided unless there is severe respiratory and cardiac embarrassment.

#### **SUBCUTANEOUS EMPHYSEMA**

Subcutaneous emphysema occurs whenever free air finds its way into the subcutaneous tissue. It may be a complication of a fracture of the orbit permitting air to escape from the nasal sinuses. In the neck and over the thorax, emphysema may follow tracheotomy, deep ulcerations in the pharyngeal region, esophageal wounds or any perforating lesion of the larynx or trachea. It is an occasional complication of thoracentesis. Air may also be formed in the subcutaneous tissues by gas-producing bacteria.

WALDO E. NELSON

#### **REFERENCES**

- Caffey, J.: *Pediatric X-ray Diagnosis*. 3rd ed. Chicago, Year Book Publishers, Inc., 1956.
- Currarino, G., and Silverman, F. N.: Roentgen Diagnosis of Pulmonary Disease of the Newborn Infant. *Pediat. Clin. North America*, 4:27, 1957.
- Landing, B. H.: Anomalies of the Respiratory Tract. *Pediat. Clin. North America*, 4:73, 1957.
- Nelson, W. E., and Smith, L. W.: Generalized Obstructive Emphysema in Infants. *J. Pediat.*, 26: 36, 1945.

#### **PULMONARY EDEMA**

**Etiology.** Pulmonary edema results from escape of serous fluid from the pulmonary capillaries into the alveoli and bronchioles. It is usually a manifestation of circulatory or neurocirculatory collapse and is often a terminal condition. It may vary in severity, but even in its milder stages should be considered a serious omen. It is a common manifestation of myocardial failure in acute or chronic rheumatic carditis. It may be a manifestation of acute or chronic nephritis and of pneumonic and other infections which have a high degree of toxicity. Poisoning by a number of substances, such as the barbiturates, morphine, epinephrine and alcohol, may be responsible for the development of pulmonary edema, as may the asphyxiating gases and a number of the irritating gases used in warfare.

**Clinical Manifestations.** The onset is variable. The child often complains of a sense of oppression or pain in the chest. Cough is usually present and is often productive of a frothy sputum which may be blood-tinged. The cardiac action is weak and the pulse rapid and feeble. There is usually pallor and

cyanosis, and the child has an anxious expression. There may be some dullness to percussion over the lower portion of the chest, and there are numerous moist, bubbling rales, which are more marked in this area.

**Treatment.** Treatment depends upon the cause. The management of myocardial failure, nephritis and the various poisonings is discussed elsewhere. The fluid intake should be reduced, and the child should be placed in an oxygen tent with concentrations of oxygen maintained at 50 per cent or higher. Favorable experience with the use of an antifoaming agent in combination with pressure oxygen therapy has been reported in adults; the oxygen is bubbled through 50 per cent ethyl alcohol. The administration of morphine is helpful in quieting the child and often seems to have a favorable effect upon the edema. Atropine has been recommended, but is of doubtful benefit and should not be used if there is a coincidental infection responsible for a viscid bronchial secretion. If the child is in a state of shock, blood or plasma may be given intravenously, provided cardiac failure is not present and administration is by drip method to avoid strain on the heart.

WALDO E. NELSON

#### REFERENCE

Gootnick, A., Lipson, H. I., and Turbin, J.: Inhalation of Ethyl Alcohol for Pulmonary Edema. *New England J. Med.*, 245:842, 1951.

### PULMONARY EMBOLISM AND INFARCTION

Pulmonary embolism as a recognized cause of disturbance in infants and children is rare. Emboli most often arise from thrombi in the femoral and pelvic veins and are usually post-operative complications. Fat emboli are most likely to be derived from fractured bones. Multiple pulmonary infarcts as evidence of small pulmonary emboli are occasionally found at autopsy. They are commonly associated with bacterial endocarditis and with longstanding nutritional deficiencies.

Embolism of the pulmonary artery or its larger branches is attended by a characteristic clinical picture. There is sudden pulmonary pain which is usually substernal, but may be pleural and radiate to the shoulder. There are dyspnea, tachycardia and signs of collapse. Though there are often no physical signs, if the infarct is sufficiently large (the base is at the periphery and the apex toward the mid-

line at the point of infarction), there may be impaired resonance and a pleural friction rub. Breath sounds may be distant or absent, and there may be moist rales. Expectoration, which may be profuse, often contains blood. The case fatality rate is high, but recovery may occur even when the area of infarction is relatively large. Secondary infection may result in abscess formation.

**Prevention.** The prevention of pulmonary infarction depends essentially upon two factors: (1) prevention of vascular stasis and (2) maintenance of a good nutritional status. The latter is especially important in bedridden children. Substances which decrease the coagulability of the blood such as heparin and Dicumarol have a limited usefulness in pediatric practice.

**Treatment.** The treatment of embolism of the larger branches of the pulmonary artery is a medical emergency. The child should be given morphine sufficiently often to induce quietness and allay fears, and should be placed in an oxygen tent for the relief of dyspnea and cyanosis.

WALDO E. NELSON

#### REFERENCES

- Moore, R. A.: *A Textbook of Pathology*. 2d ed. Philadelphia, W. B. Saunders Company, 1951.  
Reimann, H. A.: *Pulmonary Infarction—Pulmonary Embolism and Thrombosis*; in Cecil, R. L., and Loeb, R. E.: *Textbook of Medicine*. 8th ed. Philadelphia, W. B. Saunders Company, 1951.

### PULMONARY SUPPURATION

Pulmonary suppuration is due mainly to the combination of infection and blockade of bronchi. The principal lesions are bronchiectasis and pulmonary abscess; less frequent ones are pulmonary gangrene and chronic purulent bronchitis. Pulmonary abscess differs from gangrene of the lung in the extent and rapidity of the process. Both are necroses. The term "gangrene" is reserved for rapid involvement of large areas such as that of one or more lobes. Abscesses frequently develop in bronchiectatic lesions, and many primary abscesses leave as a residual some degree of bronchiectasis.

#### BRONCHIECTASIS

Bronchiectasis is a chronic, progressive, inflammatory disease of bronchi and their supporting tissues, resulting in denudation and dilatation of the bronchi, which serve as reservoirs for purulent material.

The condition is frequently overlooked for



years, being misdiagnosed as chronic bronchitis, asthma or recurrent pneumonitis. Often the symptoms date from an attack of pneumonia, measles or pertussis, any of which may be causative or the "trigger mechanism" for a pre-existing bronchiectasis. Congenital anomalies of bronchi may be responsible for bronchiectasis; Kartagener's syndrome, the triad of chronic sinusitis, bronchiectasis and situs inversus, is included in this group.

Chronic sinusitis, allergy, pulmonary abscess, foreign body, pancreatic fibrosis or bronchial occlusion from any cause such as neoplasm or tuberculous lymphadenopathy, may be the contributory factor.

**Pathology.** The fundamental change is dilatation of the bronchus, which is fusiform in the milder, and saccular in the more advanced form. There is thickening of the bronchial wall with loss of elasticity and decreased mobility. Mucosal changes are progressive with loss of cilia, a change from columnar to cuboidal and then to squamous epithelium and even complete denudation, leaving ulcerated, fibrosed and often bleeding surfaces. Stenosis may develop within the lumen; stagnation and accumulation of secretions favor the growth of anaerobic bacteria and the persistence of infection. There are variable degrees of peribronchial inflammation. One or more lobes may be affected, and the lower portions of a lobe are more likely to be involved than the upper portions.

**Clinical Manifestations.** Cough is the outstanding symptom. Usually it is productive of mucopurulent sputum, which young children ordinarily swallow, but may vomit during a paroxysm of coughing. Cough is often initiated by change of position such as lying down, rolling over, getting up or bending over which moves accumulated secretions to new locations. There is usually increased susceptibility to respiratory infections, which tend to be protracted. Repeated episodes of pneumonitis may be interpreted as influenza, pneumonia, pertussis, and the like. Bouts of fever are not uncommon and may be the only symptom. Remissions and exacerbations are the rule, with local progression and spread to new areas.

In severe cases retarded development, poor physique, dyspnea, clubbing of the digits and hypochromic anemia may occur.

Physical signs are variable and may be surprisingly minor or even absent. Moist rales are usually present, and in severe disease there may be a variety of manifestations pro-

duced by atelectasis, fibrosis, "drowned segments" and diffuse pneumonitis.

Roentgen examination may reveal heavy linear shadows radiating into the involved lobe, and atelectasis is relatively common, but the findings may be minimal and in any instance are not diagnostic. The diagnosis is established by bronchograms with opaque media (such as Dionosil or Lipiodol); it is essential to map the entire bronchial tree. More than 50 per cent of the unsatisfactory results of resection have been due to residual disease, which was not detected because of incomplete bronchographic delineation.

Bronchoscopy is essential to determine the presence of bronchial stenosis, tumor, compression or foreign body, and to obtain secretions for culture and tests of the susceptibility of the organisms to antibiotic agents. An adequate evaluation of the patient must also include examination for infected foci such as sinusitis, infected tonsils and oral sepsis, as well as for allergic disturbances.

**Treatment.** Removal of the diseased portions of lung is the only method of cure for saccular bronchiectasis and for the fusiform



FIG. 229. Bronchiectasis of the type ordinarily associated with long-standing upper respiratory tract infection. Bilateral fusiform bronchiectasis in the caudal portions of both lungs is usually secondary to severe chronic sinusitis. White male 18 years of age. History of chronic cough and expectoration from "bronchitis" since the age of 4 years. Pneumonia and bilateral empyema had occurred in the past year. Excision of left lower lobe and lingula of left upper lobe, followed in 5 months by resection of right lower lobe. All remaining lobes had been "mapped" and found normal. After recovery he attended college and was known to have been free of symptoms, except for slight decrease in respiratory capacity, for 9 years.

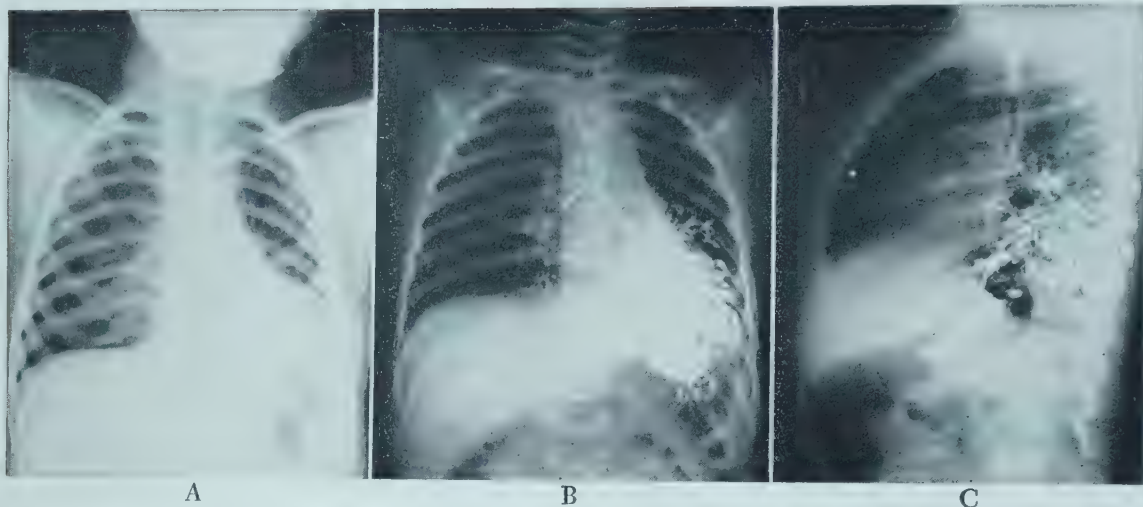


FIG. 230. Bronchiectasis in left lower lobe. A, The loss of volume of the diseased left lung has resulted in displacement of mediastinal structures. Much of the consolidation is hidden behind the heart in the ventral projection. B and C, Lipiodol bronchography reveals both types of bronchiectasis, fusiform and saccular. The patient was a white female 3 years of age who had pneumonia followed by empyema and rib resection 18 months before admission. Thereafter she had chronic cough and expectoration, a foul breath and occasional bouts of fever. After thorough study the entire left lung was removed in one stage. The patient was observed for 3 years, during which she had the ability to play normally and had no apparent respiratory deficiency.

type when there are persistent or recurring symptoms. Extremely mild degrees of fusiform bronchiectasis with little or no symptoms should be treated conservatively along the following lines: (1) elimination of such foci of infection as sinusitis, oral sepsis and infected tonsils; (2) avoidance of irritant dusts and of contact with respiratory infection; (3) desensitization to and avoidance of any allergens to which susceptibility has been demonstrated; (4) postural drainage, the child assuming the position which produces the greatest expectoration; (5) bronchoscopic aspiration once or twice weekly to assist in evacuation, to aid in aeration and so inhibit anaerobic infection, and the instillation of shrinking solutions in order to improve drainage and ventilation; (6) aerosol inhalations of antibiotic agents in conjunction with a proteolytic enzyme. The appropriate antibiotic agents should be determined by susceptibility tests on the bacteria obtained from cultures of bronchial secretions. Inhalations should be carried out two or three times each day for seven to ten days. Such courses can be repeated from time to time, but there is danger that the bacteria will develop resistance to the antibiotic agents. Systemically administered antibacterial agents have little direct effect on bronchial secretions, but are efficacious in the control of associated pneumonitis or parenchymal infection and in preparation for excision of the lung. (7)

Change of residence to a mild climate in which respiratory infections are infrequent may aid in decreasing the frequency of acute exacerbations.

**Postoperative Results.** Although lobectomy leaves the patient with less pulmonary area, his dyspnea is usually lessened, owing to decreased toxemia and to eradication of associated generalized bronchitis. Children who have had one or even two lobes removed seem to be capable of all the usual activities of childhood without evidence of respiratory difficulty. In adults external spirometry and bronchospirrometry bear out these clinical observations and often reveal better utilization of oxygen than preoperatively.

If all the diseased lung is removed and if the contributory factors such as infected sinuses and respiratory allergy are corrected, further bronchiectasis rarely develops.

#### PULMONARY ABSCESS

Multiple small pulmonary abscesses are seen in association with general sepsis, in pneumonia caused by the *Staphylococcus*, by Friedländer's bacillus and occasionally by other bacteria, and in the terminal phase of diffuse bronchiolitis, especially that associated with cystic fibrosis of the pancreas.

Single, nontuberculous abscesses may be due to aspiration of infected material or to infected emboli. The first is the more common and may be associated with tonsillec-



tomy, extraction of teeth and even dental hygiene procedures. Local anesthesia for tonsillectomy decreases but does not abolish the incidence, since, as demonstrated by bronchoscopy after operation, the regional anesthesia permits the otherwise unrecognized aspiration of the contents of the throat. A good many abscesses are insidious in onset and may have their origin from aspiration during sleep or from suppurative pneumonitis.

**Pathology.** An abscess is a localized area of suppurative necrosis and liquefaction which may be partially or completely evacuated into adjacent bronchi or occasionally into the pleural space. When the abscess erodes into a large bronchus, and drainage is adequate, healing may be fairly rapid and complete. Since, however, the abscess is usually near the periphery and the communicating bronchi are small, mucosal swelling and granulations in them contribute to inadequate drainage and thus to persistence and often spread of the abscess. Under these circumstances anaerobic bacteria thrive and a chronic infection, abscess or bronchiectasis, is established.

Perforation into the pleural space produces an empyema, usually of the "putrid" variety, which is extremely serious unless treated promptly. Infected emboli may be responsible for brain abscesses.

**Clinical Manifestations.** The onset is usually within one to four days after infection. There may be a persistent cough with little or no sputum at this time; the temperature is elevated as a rule ( $101^{\circ}$  to  $103^{\circ}$  F.), and there are such other evidences of sepsis as leukocytosis and malaise.

An area of consolidation in the lung may be detected clinically, but frequently it is not, owing to the locations of the abscess along the mediastinal border or at the extreme base. A roentgenogram of the chest at this time will reveal an area of induration which is often wedge-shaped and usually evenly consolidated (Fig. 231). Unless some other pulmonary lesion is responsible for the abscess, expectoration is not a prominent feature until rupture occurs into a bronchus, when there is a definite increase in the amount of purulent sputum, which often has an offensive, putrid odor. Rarely the quantity of pus discharged at the time of rupture of the abscess is sufficient to drown the child. Hemoptysis is often present during this phase, but may also be present at any time in the course of the disease. When drainage from the abscess is adequate, there is rapid subsidence of symptoms within two to four weeks, with rapid disappearance of the physical and roentgenographic evidences of infection. The cavity is usually demonstrable on the roentgenogram after the abscess has ruptured and until healing has occurred. At times the cavity may again become completely filled with fluid and appear as a solid mass, but it usually is partially empty, and a fluid level can be seen. Clubbing of the fingers may develop within a few weeks, especially when there is some dyspnea and cyanosis.

**Treatment.** Early recognition of a suppurative pneumonitis and adequate systemic antibiotic therapy are often responsible for prevention of a pulmonary abscess or eradication of an abscess during the early stages of de-

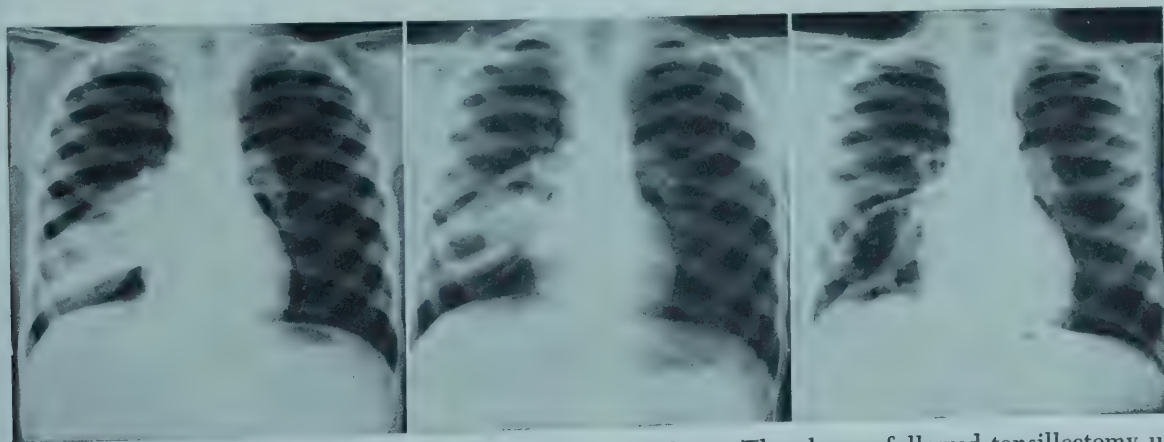


FIG. 231. Pulmonary abscess in a white boy 8 years of age. The abscess followed tonsillectomy under general anesthesia 18 months previously. Conservative treatment before admission. Progressive excavation without clinical improvement occurred for 4 additional weeks during which bronchoscopic aspiration was done. The abscess was then drained externally. Recovery was rapid and satisfactory. Subsequently there were no symptoms for  $7\frac{1}{2}$  years in spite of Lipiodol evidence of a small persisting bronchiectatic cavity. Then after 6 months of cough and hemoptysis the right lower lobe was removed. The subsequent course was uneventful.

velopment. Supportive therapy consists in (1) liquefaction of secretions by a proteolytic enzyme and appropriate antibiotic agents; (2) removal of secretions by postural drainage and bronchoscopic aspiration; and (3) aspiration of the abscess under biplane or multiplane fluoroscopic guidance with simultaneous instillation of concentrated solutions of antibiotics. This last method has been dramatically effective and, combined with systemic administration of antibiotics, is the preferred method of treatment. Surgical drainage should be instituted when improvement is not manifest after the first week of treatment. Lobectomy is required for chronic lung abscesses and for residual bronchiectasis.

### PULMONARY GANGRENE

Gangrene of the lung is a rare condition at any age and especially in infants and children. The factors responsible for the rapidly destructive process of pulmonary gangrene are not understood.

**Pathology.** The characteristic lesion of gangrene consists of an irregular brownish or greenish-black necrotic area containing a single or many ragged ulcerated cavities. The process is usually confined to a single lobe, most frequently a lower one. Involvement of the pleura with the production of putrid empyema is not uncommon.

**Clinical Manifestations.** The principal symptoms are the extremely foul odor of the breath and the expectoration of putrid sputum, which may contain blood or have a prune juice appearance. At times there may be extensive hemorrhage. There is a high remittent fever, rapid pulse and profound prostration. The physical and roentgenographic findings are suggestive of either pneumonia or pulmonary abscess, unless the pleura is involved, when the findings are those of a pleural effusion.

**Prognosis and Treatment.** Subacute and

chronic forms of gangrene are rare, and in most instances death occurs in one to three weeks. The only hope lies in early surgical removal of the diseased portion of the lung in conjunction with appropriate antibacterial therapy, selected on the basis of cultures and sensitivity tests.

### REHABILITATION

After any infection or operation of the pleura, lungs or mediastinum, intelligently directed pulmonary and thoracic exercises can reclaim much, if not all, of the function which has been temporarily lost. This phase of treatment was developed to a remarkable degree in the Military Chest Centers during World War II. In small children such exercises can be supplanted by blowing horns or balloons or colored water from one bottle to another, changing colors to maintain interest. Early physical activity is advantageous to most convalescent patients and definitely shortens the period of disability.

W. EMORY BURNETT

### REFERENCES

- Burnett, W. E., Rosemond, G. P., and Bucher, R. M.: *Diagnosis and Treatment of Bronchiectasis*. M. Clin. North America, 37:1023, 1953.
- Burnett, W. E., Rosemond, G. P., Caswell, H. T., Hall, J. H., and Bucher, R. M.: *The Topical Treatment of Lung Abscess*. Pennsylvania M. J., 52: 719, 1949.
- Cooley, J. C., Ginsberg, R. L., Olsen, A. M., Kirklin, J. W., and Clagett, O. T.: *Surgical Treatment of Bronchiectasis in Children*. J.A.M.A., 158:1007, 1955.
- Field, C. E.: *Bronchiectasis in Childhood*. Pediatrics, 4:231, 1949.
- Linker, C. R., Reiser, H. G., Roettig, L. C., and Curtis, G. M.: *Enzymatic Lysis of Respiratory Secretions for Aerosol Trypsin*. J.A.M.A., 149: 816, 1952.
- Parsons, C.: *The Child with Chronic Lung Disease*. Practitioner, London, 174:407, 1955.
- Strang, C.: *The Fate of Children with Bronchiectasis*. Ann. Int. Med., 44:630, 1956.

## DISEASES OF THE PLEURA

### PLEURISY

Inflammatory reactions of the pleura may be divided into three general groups: (1) the dry or plastic form; (2) the serous or serofibrinous form; and (3) empyema, or the purulent form. A plastic pleurisy may eventually produce a serous exudate, and a serofibrinous pleurisy may become purulent. Pleuritic involvement is less frequent than

formerly because of the decreased incidence of tuberculosis and because of the early treatment of bacterial pneumonic infections with specific agents.

### DRY OR PLASTIC PLEURISY

Acute inflammatory changes of the pleura are often associated with pneumonia, especially pneumococcal pneumonia. Occasionally they occur in association with infections of



the upper respiratory tract; in some of these instances the pleuritic involvement so overshadows the initial infection that it appears to be primary. Occasionally it is a manifestation of rheumatic fever or of tuberculosis in children. Probably in all instances there is a serofibrinous effusion initially, which is not marked and is relatively quickly absorbed.

In mild cases the involvement is limited to the visceral pleura over the affected lung, but in more extensive cases the parietal layer is also involved. The pleura is rough, dry and lusterless and, in advanced cases, is covered with fibrin which may be in shreds or may form a thick, yellowish-green layer. After the acute phase, adhesions usually remain between the pleural surfaces. In tuberculous pleurisy tubercles are present, and thickening of the pleura is likely to be extensive.

**Clinical Manifestations.** The symptoms may be indefinite; in pneumonia they may be obscured by the primary disease. There may be pain over the affected region, or it may be referred to the abdomen, the shoulder or neck. It is exaggerated by deep breathing or coughing and disappears when the breath is held. Pain from apical pleurisy tends to be referred to the shoulder; that of diaphragmatic pleurisy to the abdomen, supraclavicular area or the neck. There may be some local tenderness on pressure. There is often a sharp, frequently occurring and painful cough. The child often lies on the affected side, since pain from respiratory movements is thus decreased. The percussion note is usually not impaired. A to-and-fro leathery friction rub heard through both phases of respiration may at times be detected over the involved area. It may be obscured by the presence of pneumonia or difficult to detect when there are fine, crepitant rales.

**Differential Diagnosis.** The possibility of *epidemic pleurodynia* should be considered, though, in the absence of an epidemic, differentiation may be impossible. When the pain is referred to the abdomen, *acute abdominal conditions* such as appendicitis and mesenteric adenitis must be considered. The prodromal pain of *herpes zoster* may be responsible for pain over the chest area, but in this infection the pain is not related to respiratory movement. A diagnosis of dry pleurisy is not complete without the establishment of its etiology. When there is an acute pneumonic process, it may be assumed that the pleurisy is related to it. In other instances, or when the pleurisy persists after the patient

has recovered from the pneumonia, *tuberculosis* must be eliminated as an etiologic factor.

**Treatment.** Treatment is directed toward the primary disturbance. Considerable relief from pain may be secured by immobilizing the chest, strapping it with adhesive plaster. This procedure, however, should not be utilized in the presence of pneumonia. An ice bag over the affected area may afford some relief, as may salicylates. When the pain is severe, codeine may be given.

#### SEROFIBRINOUS PLEURISY

Serous effusions in the pleural cavity are often tuberculous in origin (p. 459) and should be regarded as such until proved otherwise. Such effusions, however, may be a manifestation of rheumatic fever, of neoplasms which involve the pleura or are contiguous with it, and of nonpurulent pleural involvement during the course of pneumonia.

The effusion may be loculated or fill the pleural cavity. It is nearly always unilateral. Depending upon the amount of fibrin and leukocytes, the fluid is clear to slightly turbid. The exudate is absorbed with varying degrees of rapidity, but thickening of the pleura persists to some degree; in long-standing cases the thickening may be sufficient to be responsible for permanent changes in the percussion note.

**Clinical Manifestations.** Except perhaps for a greater degree of fever, the initial symptoms are likely to be similar to those of plastic pleurisy. Within a few days—rarely longer—fluid appears in the pleural cavity. If it is present in considerable quantity, the pain and cough are decreased, but dyspnea becomes obvious, and even orthopnea, and cyanosis may develop. In other instances the onset is insidious, the child makes no complaint, and the pleural fluid is discovered only on physical examination.

In patients with considerable effusion the interspaces on the affected side appear to be full and may even bulge. There is diminished expansion and broadening of the costosternal angle. Palpation reveals diminished or absent tactile fremitus and a distinct sense of fullness and of resistance in the intercostal spaces. The heart is displaced to the side opposite the effusion; the displacement is likely to be greater in effusions of the left pleural cavity. The percussion note is flat over most or all of the involved side of the chest in large effusions, but in smaller effusions the percussion note may be tympanitic above a lower

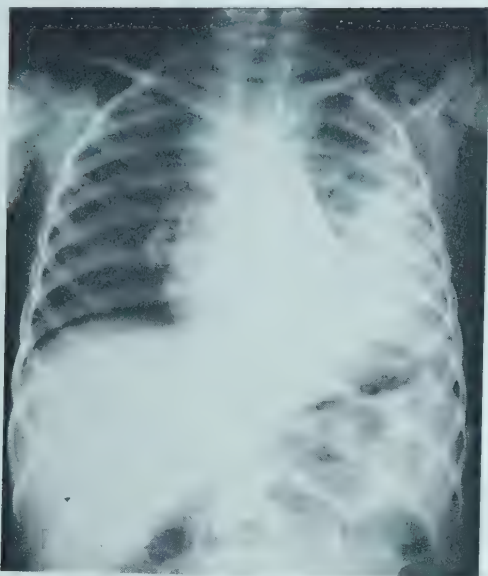


FIG. 232. Pleural effusion with characteristic outlines of encapsulation. In addition to the obvious collection of fluid between lung and axillary portions of ribs, there is evidence of some fluid at the mediastinal aspect of the left lung.

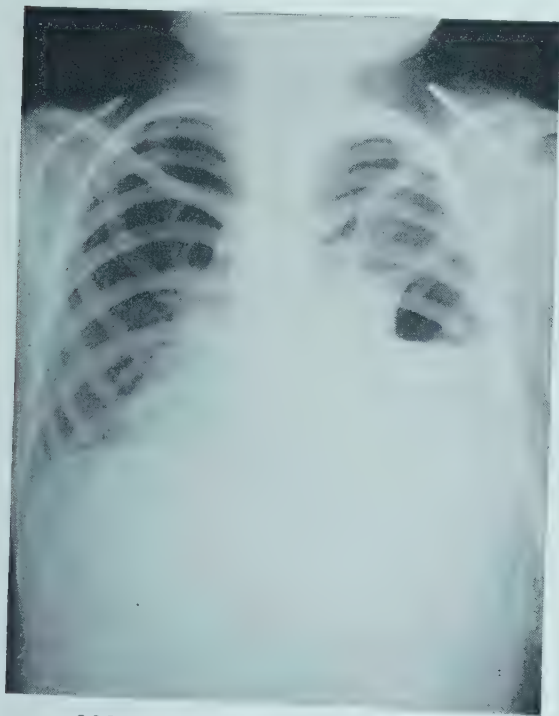


FIG. 233. Fluid and air encapsulated in the pleural space. There is obvious compression of part of the lung with some mediastinal displacement. Note straight line of fluid level due to presence of air.

area of dullness. Grocco's triangle or sign is present on the opposite side of the chest in extensive effusions. This consists in a triangular area of dullness, at the vertebral-diaphragmatic angle, the hypotenuse extending from the diaphragm to the sternal border.

If the effusion is on the right side, the lower border of hepatic dullness is likely to be depressed. Auscultatory signs are less consistent than in adults, especially in infants and small children. Breath sounds may be feeble or absent, though in many instances there is not much change, and in some instances there is actually an increased pitch suggestive of bronchial breathing, and the presence of pneumonia may be suspected. Not uncommonly, rales may be transmitted through a layer of fluid sufficiently thick to produce dullness on percussion. Friction sounds are at times heard above the level of the effusion. When the fluid is free and the patient is in the sitting position, the greatest amount will be found at the base. The fluid is readily demonstrated roentgenographically, there being a uniform shadow in the region of the fluid with a curved upper line (Fig. 232), unless air is also present, when the upper line of the fluid will be straight (Fig. 233). When the effusion is extensive, the diaphragm will be depressed and the cardiac shadow displaced to the opposite side. Roentgenograms taken in the lateral and oblique positions are of value both in differentiating the shadow from one caused by pulmonary consolidation and as a means for establishing more accurately the position of a localized effusion.

**Differential Diagnosis.** The principal problem is the differentiation between *serous* and *purulent effusions*. This can be done only by thoracentesis and examination of the fluid. An effusion which is initially serous may become purulent, especially when associated with a pneumonic infection. At times there may be difficulty in distinguishing between a small free or loculated collection of fluid and a pneumonic consolidation. Lateral and oblique roentgenograms are often helpful in this respect, but an exact diagnosis is often impossible without a thoracentesis. *Hydrothorax* may be suspected if there is myocardial or renal disease, if there is a generalized edema, and especially if there is a bilateral pleural effusion. The diagnosis is confirmed by examination of the fluid, which in hydrothorax has a low specific gravity (below 1.015), and the few cells present are mesothelial rather than leukocytic. *Massive collapse* of the lung gives rise to dullness on percussion and to feeble respirations. However, the diaphragm on the affected side is high, and the heart is displaced toward and not away from the affected side. A *pericardial effusion*, if large in amount, may simulate pleural effusion of the left side, but a distinc-



tion can usually be made by fluoroscopic and roentgenographic examination. Nonpurulent fluid should always be examined for the presence of tubercle bacilli.

**Course and Prognosis.** Both the course and prognosis depend upon the underlying disease. When the effusion is associated with an acute pneumonic process, there is a strong possibility that it may become purulent, but in many instances the fluid is quickly absorbed when the pulmonary infection is controlled. In tuberculosis and rheumatic fever, effusions may persist longer, but even with these infections there may be a rapid disappearance of the fluid. In most instances there are residual adhesions and some pleural thickening, but as a rule there is little if any residual respiratory embarrassment.

**Treatment.** Rarely is treatment required for the serous effusion, the treatment being that of the underlying disease. Occasionally, symptoms of compression are of such an order that removal of fluid is indicated.

#### PURULENT PLEURISY

##### (EMPHYEMA)

Purulent pleurisy is an accumulation of purulent fluid in the pleural space which may be localized (encapsulated) or may involve the entire pleural cavity. The incidence has been greatly reduced by the effective treatment of bacterial pneumonias. Pneumococcal and streptococcal empyemas are now uncommon except in untreated or inadequately treated cases of pneumonia. The incidence is highest in infancy, the majority of infections being caused by the *Staphylococcus* and less frequently by various gram-negative bacilli.

**Pathology.** Both massive and loculated empyema produce notable thickening of the overlying parietal pleura and some thickening of the visceral pleura and, if not previously present, pneumonitis of the adjacent lung tissue. When the empyema is not drained surgically, there is a tendency to burrow into lung tissue with partial excavation of the pus through bronchi, producing bronchopleural fistulas. Rarely the chest wall is penetrated, and the pus appears under the skin as an *empyema necessitatis*. Even less frequently the pus may break through the diaphragm. There is a continued thickening of the serous surfaces so that chronic, thick-walled cavities may be produced in the pleura which are difficult to eradicate, even by adequate drainage. Massive empyemas which are

not properly treated in their early stage lead to fibrosis of the lung in a collapsed position, necessitating decortication or extensive thoracoplastic surgery. When recovery takes place under proper treatment, adhesions will result, but they usually cause no obvious respiratory embarrassment, although bronchspirometry will usually show lessened function on the affected side.

**Clinical Manifestations.** When empyema follows a pneumonic infection, there may or may not be a symptomless interval. In older children who have had sufficient antibacterial treatment to suppress their pneumonic lesion without eradicating the organism, there may be an interval of several weeks. The onset in such instances as in those with no preceding pneumonia is marked by irregular fever, increased rapidity of the pulse and respiration, dyspnea, cough and prostration.

In infants staphylococcal empyema is usually a continuation of a pneumonic infection, either an acute pneumonitis or a chronic one as with cystic fibrosis of the pancreas, less frequently of a staphylococcal infection elsewhere. Unless one is aware of the relative frequency with which infections may occur in infants with little or no febrile response and of the lesser frequency of symptoms related to the lesion itself, not only the location but also the presence of the infection may be missed until the infant is practically moribund. Any of the symptoms characteristic of pneumonia and empyema may be present in mild or severe form, or there may be only pallor, prostration and anorexia.

The physical signs of empyema usually do not differ from those characteristic of serous effusion. Breath and voice sounds, are not decreased to the same extent with pleural effusions in infants and small children as they are in adults. Effusions of sufficient extent to be responsible for flatness to percussion often permit the transmission of breath sounds with relatively little reduction in their intensity or apparent volume. Failure to recognize this fact may be responsible for serious delay in diagnosis and hence in treatment. When the pus is localized, it is usually at the base, but it may be near the apex, between two of the lobes of the lung or between the lung and the mediastinum. Pulsating empyema is rare in children.

**Diagnosis.** The differential diagnosis of pleural effusions is discussed on page 814. A roentgenogram will usually confirm the presence of fluid in the pleural space, but the

type of fluid can be demonstrated only by thoracentesis. The fluid should be examined for the presence of bacteria by direct smear and culture, and antibiotic susceptibility tests should be obtained immediately.

**Complications.** Local complications include purulent pericarditis, pulmonary abscess, bronchial fistula, pyopneumothorax and—after operation—osteomyelitis of the ribs. Blood stream infection may account for such foci as meningitis, arthritis and peritonitis; the last may also occur by rupture through the diaphragm. In long-continued cases clubbing of the fingers may develop.

**Course and Prognosis.** Mortality rates are directly related to the promptness of starting therapy and its adequacy. The recovery from empyema treated early is usually complete, the lung expanding fully and little if any deformity of the chest remaining. If operation is unduly delayed, there is danger that unyielding adhesions will persist, with failure of the lung to expand and resultant contraction of the chest wall.

**Treatment.** The accumulation of small pleural effusions which contain few or no bacteria is not an unusual manifestation of pneumococcal pneumonia. These collections of fluid often disappear without the production of empyema.

Treatment of the underlying cause is essential. Although it is feasible to obtain cure in adults by multiple aspirations and instillation of antibiotics and fibrolytic agents (such as streptokinase and streptodornase, trypsin or pancreatic dornase), the process is too uncomfortable, abhorrent and prolonged for children. Closed or controlled drainage of the pleura by intercostal tube inserted under local or general anesthesia is preferable. This can be instituted without delay unless the patient is too ill to withstand anesthesia, when preliminary preparation and support may be necessary. A polyethylene tube, inserted through a large needle, may suffice; such drainage allows control of the intrapleural pressure. The lung tends to re-expand rapidly as fluid is removed, and the infection is usually controlled by instillation of appropriate antibiotics and fibrolytic agents.

Antibiotics should also be administered systemically. Pulmonary exercises with the aid of blow bottles, balloons or horns will hasten obliteration of the empyema cavity.

The presence of a bronchopleural fistula may require mechanical suction; irrigation should be avoided. Such lesions usually do not significantly delay recovery.

## PUTRID EMPYEMA

This malodorous infection of the pleura is produced by anaerobic hemolytic streptococci in combination with various other organisms such as nonhemolytic streptococci, staphylococci and Vincent's fusospirochetal organisms. This type of infection is significant for the following reasons: (1) It is practically always secondary to pulmonary suppuration. (2) It is the only form of empyema which will produce phlegmonous infection along the tract of aspiration with any degree of regularity. (3) It causes severe toxemia, and there may be sudden peripheral vascular collapse. The fatality rate is high if much time elapses between the occurrence of the disease and surgical drainage. Often the underlying pulmonary suppuration can be drained at the same operation. Even though it has perforated into the pleura, the abscess may be inadequately drained, and more thorough drainage is indicated if the focus can be located.

W. EMORY BURNETT

## REFERENCES

- Bloomer, W. E., Giammona, S., Lindskog, G. E., and Cooke, R. E.: Staphylococcal Pneumonia and Empyema in Infancy. *J. Thorac. Surg.*, 30:265, 1955.  
Lindskog, G. E.: Present-Day Management of Pleural Empyema in Infants and Adults. *New England J. Med.*, 255:320, 1956.

## PNEUMOTHORAX

Pneumothorax in the newborn period may be related to factors incident to birth and be associated with interstitial emphysema and pneumomediastinum (p. 328). In staphylococcal pneumonia in infancy the incidence of pneumothorax is relatively high (p. 792). Aside from the accidental introduction of air into the pleural cavity during thoracentesis, pneumothorax is uncommon during childhood. Pneumothorax may occur in pneumonia, usually in connection with empyema; it may also be secondary to pulmonary abscess, gangrene, infarct, rupture of a cyst or an emphysematous bleb, foreign bodies in the lung and external thoracic trauma or surgical procedures. In association with mediastinal emphysema it is an occasional complication of tracheotomy.

Pneumothorax may be associated with a serous effusion (*hydropneumothorax*) or a purulent effusion (*pyopneumothorax*). In pneumothorax the lung collapses toward the



hilum, unless prevented by adhesions. Rarely is there a bilateral pneumothorax.

**Clinical Manifestations.** The onset is usually abrupt. When the pneumothorax is extensive, there is likely to be pain, dyspnea and cyanosis. In infancy both the symptoms and physical signs may be difficult to recognize. If the pneumothorax is only moderate in extent, there may be little or no displacement of intrathoracic organs and few or no symptoms.

The percussion note over the involved area is tympanic; on auscultation respiratory sounds are feeble or absent. The larynx, trachea and heart may be shifted toward the unaffected side. The breath sounds may have an amphoric quality if there is an open fistula from air-bearing tissues into the pleural cavity. When fluid is present, there is usually a sharply delimited area of tympany above a level of flatness to percussion. In evaluation of a case it is important to determine whether the pneumothorax is an open (*tension pneumothorax*) or a closed one. The presence of amphoric breathing or of gurgling sounds synchronous with respirations when fluid is present in the pleural cavity is suggestive of an open fistula. Confirmatory evidence is provided when the pneumothorax fills rapidly after aspiration of it. Another means for determining whether there is an open fistula is examination of the aspirated air for its oxygen content. If a fistula is present, the oxygen content of the air in pneumothorax remains constant. If there is no connection with the bronchial tree, the oxygen content is low, since it is rapidly absorbed. The diagnosis can usually be established by roentgenographic examination (Fig. 234).

**Differential Diagnosis.** Pneumothorax must be differentiated from localized or generalized emphysema, from an extensive emphysematous bleb, from large pulmonary cavities or other cystic formations, from diaphragmatic hernia and from gaseous distention of the stomach. In most instances a simple roentgenogram will be all that is necessary for the differentiation. In the case of diaphragmatic hernia, however, a small amount of barium may be necessary to demonstrate that a portion of the gastrointestinal tract is in the thoracic cavity.

**Prognosis and Treatment.** The prognosis depends upon the cause. When there is no fistula connecting the air-bearing tissue and the pneumothorax, the air is usually absorbed within a week or so, and no treatment is nec-



FIG. 234. Pneumothorax. Note the atelectasis of a large part of the right upper lobe with continued partial aeration of middle and lower lobes. Adhesions between the chest wall and lung are apparent at several points.

essary unless there are symptoms of excessive pressure, when the air should be aspirated.

Tension pneumothorax with a communicating fistula is usually best managed with a closed thoracotomy and drainage of the trapped air through a catheter whose external opening is kept in a dependent position under water. If the bronchopleural fistula is large, negative pressure in the drainage tube may be necessary. If the tension pneumothorax is not relieved by this means, surgical closure of the fistula should be considered. Treatment of a coexisting empyema is of course essential (p. 816).

## HYDROTHORAX

In hydrothorax, the fluid is noninflammatory in origin and has a lower specific gravity (less than 1.015) than that of a serofibrinous exudate. It contains less protein and fewer cells, which are mesothelial rather than leukocytic, and is usually associated with an accumulation of fluid in other parts of the body such as the peritoneal cavity and the subcutaneous tissues. Hydrothorax is most often associated with cardiac or renal disease, although on occasion it may be a manifestation of severe nutritional edema, and rarely it results from venous obstruction by neoplasms, enlarged lymph nodes or adhesions. Hydrothorax is usually bilateral in renal disease and in nutritional edema and may be in myocardial disease, although in this instance

it may be limited to the right side, or the accumulation of fluid may be greater on the right than on the left side. The physical signs are those described under Serofibrinous Pleurisy (p. 813), but there is more rapid shifting of the level of dullness with changes of position. The *treatment* is that of the primary disorder, although aspiration may be necessary when pressure symptoms are marked.

## HEMOTHORAX

Extensive bleeding into the pleural cavity may result from erosion of a blood vessel in association with such inflammatory processes as tuberculosis and empyema, but is not common. It is also an occasional manifestation of intrathoracic neoplasms, various blood dyscrasias, and may be the result of thoracic trauma. Rupture of an aneurysm is not likely during childhood. When a pleural hemorrhage occurs in association with a pneumothorax, it is termed *hemopneumothorax*. The *diagnosis* of a hemothorax can be made only by thoracentesis. In every instance an effort must be made to determine the cause, the *treatment* obviously depending upon it. Surgical intervention may be required to control active bleeding, and transfusion is necessary when loss of blood is excessive.

## CHYLOTHORAX

Chylothorax is a rare condition at any age, but especially in childhood, although it has been observed in infants even during the neonatal period. It depends upon the escape of chyle from the thoracic duct into the thoracic cavity. In the majority of instances thoracic trauma is responsible for rupture of the duct, but the escape of chyle apparently can occur without rupture of the duct as a result of pressure by enlarged lymph nodes or neoplasms. Thrombosis of the duct or the

subclavian vein and congenital anomalies of the duct system have also been reported as causes. Chylothorax is rarely bilateral, usually being on the left side.

The *symptoms* and physical signs are those related to the presence of fluid in the thoracic cavity. The *diagnosis* is established by thoracentesis and the demonstration of a chylous effusion, a milky fluid containing fat, protein and other constituents of chyle. A pseudo-chylous milky fluid has been reported in cases of serous effusion in which the fatty material was assumed to be due to the degenerative changes within the fluid and not to the presence of lymph. It has been suggested that this type of fluid can be distinguished from one containing chyle by shaking with alkalis or ether, when the fluid containing chyle tends to become clear. Spontaneous recovery has occurred in over half of the reported cases in infants under one year of age. Repeated aspiration may be required to relieve the symptoms of pressure. The aspirated chyle has been reinjected intravenously without untoward reactions, although there is some doubt whether it has any particular benefit. The diet should be low in fat content and high in protein. The lowered intake of fat is thought to be associated with a decreased production of chyle. The high protein intake is required because of loss of protein in the chyle. The total caloric intake must be above the average requirement, and several times the daily requirements of the various vitamins, especially the fat-soluble vitamins A and D, should be added.

WALDO E. NELSON

## REFERENCES

- Riker, W. L.: Lung Cysts and Pneumothorax in Infants and Children. *S. Clin. North America*, 36: 1613, 1956.
- Watson, E. H., and Foster, L. F.: Spontaneous Chylothorax in Infancy: Prognosis and Management. *Am. J. Dis. Child.*, 72:89, 1946.



# The Cardiovascular System

## THE HEART AND CIRCULATION IN HEALTH AND DISEASE

**Inspection and Palpation.** In early life the heart is situated somewhat higher in the chest in a more nearly horizontal position than in later years. The apex beat in the newborn infant may be palpated in the fourth left interspace in or just lateral to the left mid-clavicular line. After the age of two years the apical impulse is usually in the fifth intercostal space in or just medial to the mid-clavicular line. The flexibility of the mediastinum permits the heart to shift towards the side on which the patient lies. Although the relation of the apical thrust to the position of the mid-clavicular line is not an accurate index of cardiac size, it is helpful in making an estimate.

A hyperdynamic thrust, often extending over one or more interspaces, may accompany hypertrophy and dilatation of the ventricles. When the left ventricle is enlarged, the apex is likely to be one or two interspaces lower and farther to the left than normally. Enlargement of either ventricle, but especially of the right, tends to push the left side of the chest wall forward if the cardiac disease develops in early life, when the ribs are soft and pliable. Displacement of the apex beat to the right or left without cardiac enlargement may be caused by pulmonary conditions such as empyema, atelectasis or the collapse of one lung, and sometimes by scoliosis of the spine or defects of the diaphragm.

A clinical evaluation of ventricular hypertrophy can be made by palpation of the apical impulse. In the presence of right ventricular hypertrophy the sensation of a *tap* is transmitted to the hand, whereas in left ventricular hypertrophy the apical impulse is *heaving*. Right ventricular hypertrophy is usually associated with clockwise rotation of the heart, so that the right ventricle accounts for nearly all the anterior surface of the heart. This can be appreciated by palpation of a sternal and

a parasternal lift. Epigastric pulsations are commonly seen and felt in the presence of right ventricular hypertrophy, owing to the proximity of that chamber to the diaphragm. Biventricular hypertrophy can be suspected by a combination of the foregoing signs, namely, a sternal and parasternal lift associated with a left ventricular apical thrust.

*Thrills* may be detected during palpation; they should be timed in relation to the cardiac impulse or carotid pulse. If the child is able to cooperate with the examiner, thrills should be felt during full expiratory apnea. Apical thrills are felt more easily in the left lateral position, and basal thrills are more readily palpable with the patient sitting and leaning forward. Abnormal pulsations may also be detected, such as those produced by aneurysms or collateral vessels. Thrills are detected more readily with the palm of the hand than with the finger tips.

**Percussion.** Percussion of the cardiac borders in infants is difficult, owing to the thick layers of subcutaneous fat on the chest wall and the barrel shape of the thorax. Light percussion by direct tapping with the finger is generally preferable to the heavier double-finger method used in the examination of adults. Although the right border of the normal heart extends slightly to the right of the sternum, it can rarely be detected by percussion. Any dullness to the right of the sternum may suggest enlargement of the right ventricle or right atrium, or possibly the presence of pericardial effusion.

In the apical area any extension to the left beyond the usual limits may be due to enlargement of either ventricle or to pericardial effusion. The enlarged right ventricle tends to push the left border laterally, and the enlarged left ventricle extends downward as well as laterally. The value of percussion in the diagnosis of heart disease is frequently

overstressed. This method can be helpful in the evaluation of pericardial effusion, dextrocardia and movement of the mediastinum secondary to pulmonary or pleural space disease. Accurate assessments of cardiac size, shape and position can usually be made only by radiography.

**Auscultation.** In newborn and young infants the two heart sounds are about equal in intensity. Later in infancy the first sound becomes the louder of the two at the apex, and the second sound the more prominent at the base. Throughout childhood the second sound at the base is loudest in the second interspace to the left of the sternum and is often split into two distinct components.

The first heart sound is produced by closure of the atrioventricular valves; its intensity is governed mainly by the position of these valves at the beginning of ventricular systole. If the duration of atrial systole is comparatively long, the valve cusps have already partially returned toward the position of closure. Since the remaining distance through which they will move during ventricular systole will be short, the first heart sound will be of poor intensity. On the other hand, if atrial systole is short, the mitral and tricuspid valves are widely patent, and their closure produces a sound of greater intensity. Other factors which may modify the intensity of the heart sounds include the thickness of the chest wall, the amount of lung and mediastinal tissue covering the heart and perhaps the strength of ventricular contraction.

The second heart sound is produced by closure of the aortic and pulmonary valves, the aortic valve closing just before the pulmonary valve. This produces the normal splitting of the second heart sound, which is frequent in children and is often best heard at the end of inspiration. Recognition of variations of the normal splitting of the second heart sound is of considerable diagnostic importance. Wide splitting of this sound is often associated with conditions causing left-to-right shunting of blood such as may occur in atrial septal defect. In the presence of severe pulmonary stenosis the intensity of the systolic murmur frequently obscures the aortic element of the second heart sound. This produces a single second sound which arises from late closure of the pulmonary valve. In tetralogy of Fallot the pulmonary element of the second sound is not audible, resulting in a single second sound due to aortic valve closure.

Leatham has pointed out the clinical value of dividing systolic murmurs according to their recorded shape and relation to the heart sounds. According to their characteristics, systolic murmurs may be divided into two types: (a) ejection, (b) regurgitant.

**Ejection systolic murmurs** are produced by turbulence of blood flow through the aortic or pulmonary valves in the presence of stenosis, valvular damage without stenosis, poststenotic dilatation or increased flow through the valve. These murmurs are mid-systolic and usually basal. The interval between the first sound and the onset of the murmur depends on the time taken by the ventricle to raise its pressure sufficiently to open the aortic or pulmonary valve. The murmur rises in intensity in mid-systole and diminishes as the ventricle relaxes. The murmur ceases before the second sound.

**Regurgitant systolic murmurs** are pansystolic and caused by flow of blood from a chamber or vessel that is at a higher pressure throughout systole than the receiving vessel or chamber. In mitral or tricuspid incompetence the ventricular pressure rapidly exceeds that in the atrium. This backward flow results in a systolic murmur which begins soon after the first sound, continues throughout systole and tends to obscure the second sound.

Many attempts have been made to correlate the intensity of the second heart sound, especially the pulmonary element, with the degree of pulmonary hypertension. Although it is true that in many instances the second heart sound at the base is loud in the presence of moderate or severe pulmonary hypertension, this rule does not always apply. Thus the second heart sound may be loud in the presence of congenital heart disease and left-to-right shunt with normal or slightly elevated pressures in the pulmonary artery.

The sounds and murmurs produced by valves are not always heard at the positions on the chest wall to which these sounds might be expected to be transmitted. For example, the diastolic murmur of rheumatic aortic insufficiency is usually best heard over the pulmonary area and radiates down the left sternal border. Therefore care should be taken to auscultate the whole precordium and not to localize the examination to certain predetermined points on the left chest. Murmurs of congenital heart disease in children may be widely transmitted, so that it is necessary also to auscultate both sides of the neck and the back. On the other hand, the friction



of a pericardial rub may be localized fairly accurately over the area in the pericardium from which it emanates.

In older, cooperative children, sounds and murmurs may be more easily heard by varying the child's position, listening in various phases of respiration and by noting the effects of exercise. Thus mitral systolic and diastolic murmurs are more easily heard with the child in the left lateral position, especially after exercise, and basal murmurs are more obvious in the forward sitting position with the patient in full expiratory apnea.

**Innocent murmurs.** Little is known of the etiology of functional or accidental\* murmurs which are frequently heard throughout childhood. Leatham has recorded basal ejection vibrations in many normal subjects and suggests that some slight increase in their intensity is probably responsible for most innocent murmurs. In the newborn infant it is not unusual for soft systolic murmurs to be heard, usually to the left of the sternum in the third and fourth interspaces, but they generally disappear after a few days or weeks. In older children soft, blowing systolic murmurs may be heard in the area to the left of the sternum or at the base of the heart. They may become less audible or disappear completely when the patient changes from a supine to an upright position, after mild exercise or during various phases of respiration. Occasionally they remain constant under all conditions and persist until adolescence. Soft murmurs often develop during an acute illness or severe anemia and disappear during convalescence. The intensity of innocent systolic murmurs is usually increased during an intercurrent acute infection. Although the quality, location and variability of such murmurs usually indicate their innocuousness, frequent observation of the patient over a period of years may be required to make sure that no organic lesion is present.

A *venous hum* is produced by turbulence of blood in the jugular venous system. The hum has no pathologic significance and may be heard in the neck or anterior part of the upper chest. It produces a soft humming sound which may be heard in both systole and diastole. The murmurs can be exaggerated or made to disappear by varying the

\* The terms "functional" and "accidental" have been used synonymously to designate murmurs which appear to be unrelated to any cardiac disturbance or anatomic abnormality. Though common usage has been responsible for their continuation, the term "innocent" is recommended by the American Heart Association.

position of the head or by light compression over the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease.

**Arterial Pulse.** The *cardiac rate* of newborn infants is rapid and subject to wide fluctuations. The average rate, ranging from 120 to 140 beats per minute, may increase to 170 or more during periods of crying and activity and drop to between 70 and 90 during sleep. As the child grows older the average pulse rate becomes slower. At the age of two it is about 110, at six years about 100, at ten years about 90, and the adult range of 70 to 80 is attained by the end of the adolescent period. After the age of about twelve years the pulse rate of boys is somewhat slower than that of girls. Table 95 lists rates compiled from several sources.

Throughout childhood the pulse rate is labile and increases rapidly in response to muscular activity or emotional stimuli. The average rate is generally higher in the afternoon than in the morning and more rapid after than before eating.

*Tachycardia* persisting for weeks or months has been observed in adolescent children, especially girls, without any discernible cause. Persistent tachycardia (over 200 in newborns, 150 in infants or 120 in older children) must be investigated to exclude pathologic arrhythmias. The apprehension induced by a visit to the doctor will often cause a fast rate at the time of examination. In order to determine the cardiac rate when it is not influenced by external stimuli, the parents may record the pulse rate several times throughout the day or night when the child

Table 95. Average Pulse Rates at Different Ages

Age	Lower Limits of Normal		Average		Upper Limits of Normal	
	Girls	Boys	Girls	Boys	Girls	Boys
Newborn.....	70		120		170	
1-11 months.....	80		120		160	
2 years.....	80		110		130	
4 years.....	80		100		120	
6 years.....	75		100		115	
8 years.....	70		90		110	
10 years.....	70		90		110	
	Girls	Boys	Girls	Boys	Girls	Boys
12 years.....	70	65	90	85	110	105
14 years.....	65	60	85	80	105	100
16 years.....	60	55	80	75	100	95
18 years.....	55	50	75	70	95	90

Table 96. Average Blood Pressures of Children

Age	Systolic	Diastolic
4.....	85	60
5.....	87	60
6.....	90	60
7.....	92	62
8.....	95	62
9.....	98	64
10.....	100	65
11.....	105	65
12.....	108	67
13.....	110	67
14.....	112	70
15.....	115	72
16.....	118	75

is quiet or asleep. In infants the pulsations of the carotid or temporal arteries may be easier to count than those of the radial artery.

*Slow pulse rates* are rare in children until the end of the adolescent period, when rates as low as 60 per minute may be encountered. If the pulse is persistently slower than this, some organic disturbance of the cardiac conductive mechanism must be suspected.

*The rhythm of the cardiac beat* in the newborn infant is often irregular and seems to be closely related to respiration. When the infant is asleep, there may be periods of apnea and a slow cardiac rate, but when respiratory movements are resumed, the pulse rate speeds up again. This arrhythmia is exaggerated in premature infants and in those who have suffered considerably from shock or possibly from intracranial hemorrhage. After the neonatal period and throughout the first few years of life the cardiac rhythm is generally regular, but by the age of about three years many children have a respiratory or *sinus arrhythmia* characterized by acceleration of the cardiac rate with inspiration and slowing with expiration. In some children this arrhythmia is marked, and careful examination may be necessary to determine that it is sinus in origin. Respiratory arrhythmia is most frequently associated with slow pulse rates and rarely occurs in children whose pulse rates have been accelerated by infection or cardiac disease. The presence of the arrhythmia is therefore generally considered to be evidence of normal cardiac action.

Diagnostic information may also be obtained by analysis of the *quality* and *amplitude* of the peripheral pulse. A water-hammer pulse in the forearm or a Corrigan pulsation in the carotid arteries signifies a large pulse pressure commonly found in patent ductus

arteriosus, aortic insufficiency or general vasodilatation. Capillary pulsation often accompanies such a finding. An anacrotic or plateau pulse of small volume signifies aortic stenosis, and pulsus bisferiens suggests combined aortic insufficiency and stenosis. Examination of the peripheral pulse should not be localized to the radial artery, but should include inspection and palpation of all major accessible arteries. Comparison of the amplitude of pulsation of the arteries on both sides of the body may help to localize a point of proximal compression. Routine examination of all infants and children should include palpation of the femoral vessels. Characteristically the femoral pulsation is diminished or delayed in nearly all cases of coarctation of the aorta.

**Arterial Blood Pressure.** It is often difficult to determine arterial blood pressure with accuracy in infants and young children. The patient must be quiet, and the arm cuff should be narrow enough so that it covers only about two thirds of the upper arm. With narrower cuffs erroneously high blood pressure readings are obtained, and the converse with wider cuffs. When the thigh is used as the site for measuring blood pressure, the cuff should likewise cover two thirds of the surface area of the thigh, especially when the pressure in this location is to be compared with that in the arm.

The blood pressure varies with the age of the child and is closely related to his height and weight. Significant increases occur during the adolescent period, and many temporary variations occur at this time before the more stable levels of adult life are attained. Exercise, excitement, coughing and straining may raise the systolic pressure of children as much as 40 to 50 mm. above their usual levels. Variability of blood pressure among children of approximately the same age and body build must be expected.

Table 96 was prepared by averaging data of the blood pressures of normal children from several studies. Standard deviations are in the range of 5 to 8.

In infancy and early childhood the blood pressure readings are approximately the same as those of the four-year-old child listed in the table. Any systolic pressure consistently above 120 mm. during childhood suggests some disease of the kidneys, heart, adrenals or blood vessels. In aortic insufficiency and patency of the ductus arteriosus there may be an elevation of the systolic pressure and a lowering of the diastolic pressure. In coarctation of the aorta there is frequently an in-



crease in the systolic and diastolic pressures of the arms and a decrease of pressures in the legs. Ordinarily the pressure in the legs is about 20 mm. of mercury higher than that in the arms. Lower than average pressures may be caused by shock, myocardial failure, pericardial effusion, aortic stenosis, Addison's disease or hypothyroidism.

**Venous Pulse.** Inspection of the cervical veins may yield considerable diagnostic information. The patient should be propped in bed at an angle of about 45 degrees with his neck muscles relaxed. Distention of the external jugular veins, owing to constriction of their passage through the deep cervical fascia, occurs in many normal children. Distention and pulsation of veins situated above the sternal angle are abnormal. In many instances an increased venous pressure is transmitted to the internal jugular vein in the form of venous pulsations. In these cases visible distention does not occur even though the venous pressure is raised. Of greater significance than distention are the presence and the quality of venous pulsations. Such pulsation does not occur in normal children reclining at an angle of 45 degrees. The height of venous pressure can be measured by observing the vertical height to which the distended and pulsating portion of the vein rises above the sternal angle. This clinical

observation is of great help, since the difficulties of measuring the resting venous pressure by venipuncture in small patients often preclude the determination of exact pressure.

Venous pulsations may be distinguished from those of arteries in the following ways (Wood): (1) Venous pulsations undulate, yield readily to pressure, vary with the position of the patient, and usually consist of multiple components, whereas those of the carotid artery are single, abrupt, only compressible with moderate pressure and do not vary with the patient's position. (2) Abdominal pressure, especially over the right hypochondrium, increases the height of the venous pulse, but has no effect on the arterial pulsation. (3) Mild compression of the external jugular vein in the supraclavicular fossa will abolish venous pulsations and distend the vein, but will not affect the carotid pulsation. (4) The height of venous pulsation will increase with expiration and decrease with inspiration. Arterial pulsations are not affected by respiration.

The normal jugular phlebogram or direct tracings from the superior vena cava show three positive components corresponding to each cardiac cycle. They are termed "a," "c" and "v" respectively (Fig. 235). The "a" wave is synchronous with atrial systole, the "c" wave with early ventricular systole and

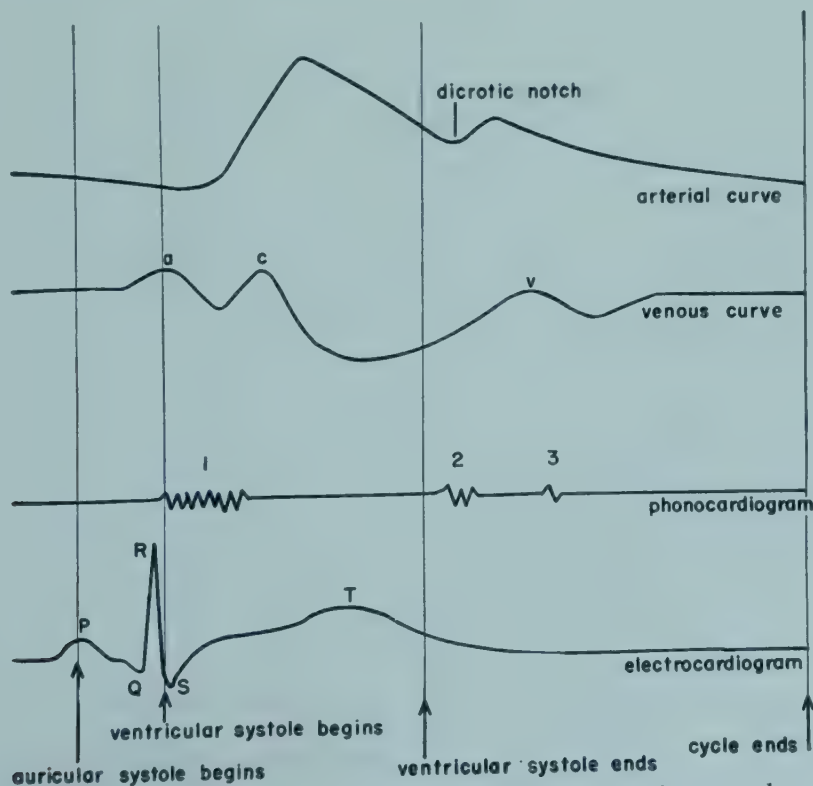
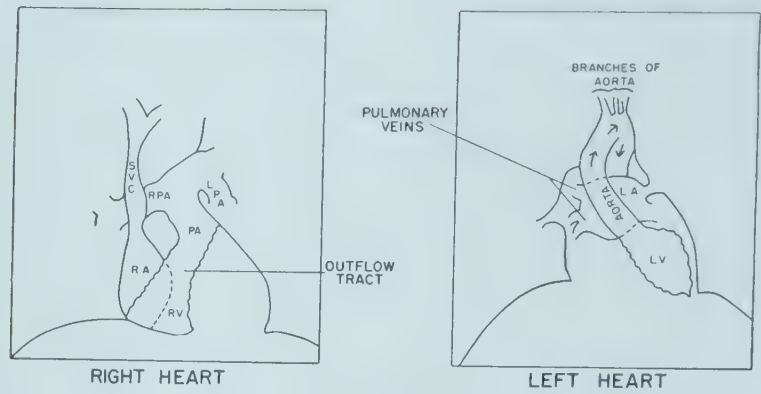
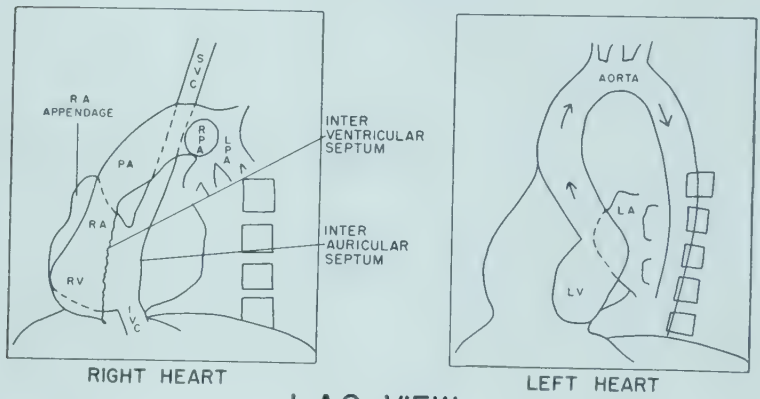


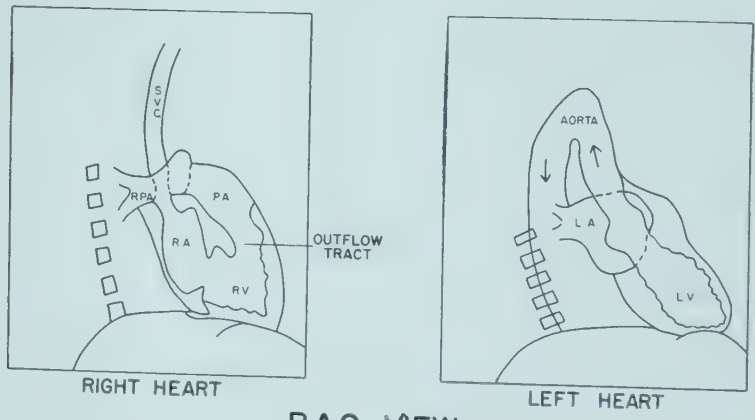
FIG. 235. Diagram showing the relationship of various events of the normal cardiac cycle.



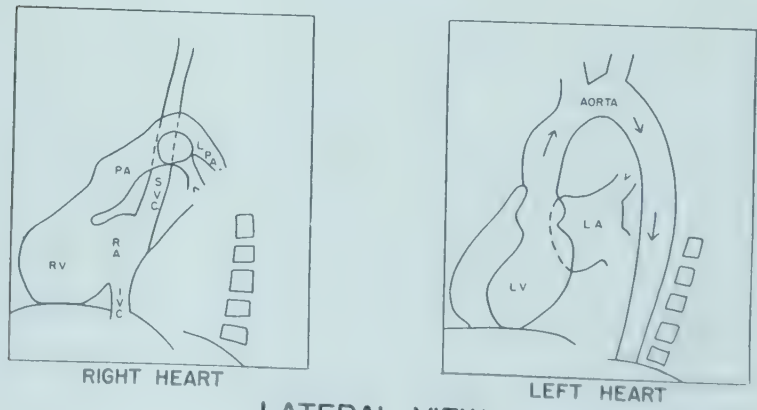
P.A. VIEW



L.A.O. VIEW  
A



R.A.O. VIEW



LATERAL VIEW  
B



the "v" wave with atrial diastole. Since the great veins are in direct communication with the right atrium, changes of pressure and volume of this chamber are transmitted to the veins. For example, (1) in congestive cardiac failure the increased right atrial pressure is transmitted to the cervical veins. The main pulsation at the upper part of distribution of these veins appears to be in late diastole. (2) Cardiac compression due to pericardial effusion or constriction increases the jugular pressure, but the amplitude of venous pulsation is small. (3) In relatively severe pulmonary stenosis the right ventricular diastolic pressure may be elevated. Emptying of the right atrium is dependent upon a systolic pressure in excess of the right ventricular diastolic pressure. A conspicuous presystolic "a" wave is present under these conditions. (4) A presystolic "a" wave is also frequently present in tricuspid stenosis or atresia, and the transmission of this wave to the inferior vena cava and hepatic veins produces presystolic hepatic pulsations. (5) In tricuspid insufficiency some of the right ventricular systolic pressure is transmitted to the right atrium, resulting in large conspicuous venous pulsations, which correspond to ventricular systole and produce a fusion of the "c" and "v" waves. (6) In complete heart block the occurrence of cervical venous pulsations will depend on the position of the tricuspid valve at the time of atrial systole. If the right atrium contracts when the tricuspid valve is closed, a large venous pulsation will occur. (7) In superior vena caval obstruction the jugular venous pressure is increased, but the veins do not pulsate.

Direct determinations may be made by inserting a needle in a peripheral vein. The venous pressure may be read on a water manometer, using the sternal angle as the reference point. By this method the average venous pressure of children over the age of three years is about 50 mm. of water (Lambert).

**Congestive Heart Failure.** In older children the signs and symptoms of congestive heart failure are similar to those in adults. In addition to breathlessness at rest, the systemic venous pressure is elevated as gauged by

clinical assessment of the jugular venous pressure, the liver is enlarged and tender and edema is present. Orthopnea and basal rales are commonly present, and edema usually occurs in dependent portions of the body. However, older children may occasionally prefer to lie in the flat position, which causes generalized anasarca.

During infancy the presence of congestive heart failure may be more difficult to determine. A clinical assessment of the jugular venous pressure in infants may be difficult, owing to the short structure of the neck and the difficulty of securing a relaxed state, although it should always be attempted. Edema in infants with cardiac failure is commonly generalized, involving the eyelids as well as the sacrum, legs and feet. Because right ventricular failure is more common than left ventricular failure in young patients, the classic signs of edema of the lungs are not commonly encountered. In infants breathlessness and hepatomegaly are constant signs of congestive heart failure, and a sudden increase in weight which decreases after diuretic therapy is common.

**Roentgenographic Examinations.** Roentgenographic examinations furnish the most accurate information of the cardiac size and shape. Many variations occur in normal persons, owing to differences in body build, abnormalities of the thoracic cage, the phase of respiration or cardiac cycle, subdiaphragmatic pressure or pulmonary disease which may displace the heart to one side or the other.

**Fluoroscopy.** Fluoroscopic examination provides important information, but since determination of size and configuration of the heart often requires detailed and prolonged observation, special precautions must be taken to adjust accommodation of the eyes and to protect the child and the physician from radiation. Not only the heart, but also the great vessels, lungs, thoracic cage and diaphragm must be observed.

In infants the thymic shadow may overlap the shadow cast by the base of the heart. In the anteroposterior view the left border of the cardiac shadow consists of three convex shadows from above downwards produced by the aortic knob, the pulmonary arc and the

FIG. 236. Idealized diagrams showing the normal position of the cardiac chambers and great blood vessels. Abbreviations are as follows: P.A., posteroanterior; L.A.O., left anterior oblique; R.A.O., right anterior oblique; S.V.C., superior vena cava; R.A., right atrium; R.V., right ventricle; P.A., pulmonary artery; R.P.A., right pulmonary artery; L.P.A., left pulmonary artery; L.A., left atrium; L.V., left ventricle; I.V.C., inferior vena cava. (Adapted and redrawn from Dotter and Steinberg: *Angiocardiographic Interpretation*. Radiology, Vol. 53.)

left ventricle, respectively (Fig. 236). In cases of moderate to gross left atrial enlargement the atrium may project between the opposing movements of the pulmonary artery and of the left ventricle. Angiocardiographic and cardiac catheterization studies have conclusively proved that the outflow tract of the right ventricle or the pulmonary conus does not contribute to the shadows formed by the left border of the heart (Fig. 236). In infants and children the aortic knob is not as easily visualized as in adults. Three structures also contribute to the right border of the cardiac silhouette. From above downward they are the superior vena cava, the ascending aorta and the right atrium. It is of fundamental importance also to assess the degree of pulmonary vascularity as represented by the intrapulmonary shadows. Angiocardiographic studies have shown that the hilar shadows are mainly vascular. Pulmonary overcirculation is usually associated with left-to-right shunts, and undercirculation with stenosis of the outflow tract of the right ventricle or pulmonary valve.

Fluoroscopic examination is not complete until the cardiac shadows have been studied in both oblique and lateral views (Fig. 236). The right anterior oblique view is optimal for the study of the left atrium and main pulmonary artery, whereas the left anterior oblique view is used for evaluation of the left and right ventricles, the aorta and the left atrium.

The esophagus is closely related to some of the cardiac chambers and great blood vessels, and its visualization with a barium emulsion helps to further delineate these structures, especially in the right anterior oblique view. The esophagus is indented in turn by the aorta, pulmonary artery and left atrium from above down. Permanent records of fluoroscopic findings may be made by accurate paper tracings (orthodiagraphy).

Interpretation of atrial or ventricular enlargement in infants and children by radiographic means is difficult. A hypertrophied ventricle may displace a normal chamber, giving a false impression of ventricular enlargement. Thus posterior displacement of a normal left ventricle by a hypertrophied right ventricle may cause the radiographic picture to resemble that of biventricular enlargement. The roentgenograms of patients with tetralogy of Fallot may not indicate the presence of right ventricular hypertrophy; conversely, the cardiac silhouette of patients with tricuspid atresia and an underdeveloped right ventricle may give the false impression of right ven-

tricular hypertrophy. It is therefore apparent that the radiographic findings should be complemented by an electrocardiogram, which is a more sensitive and accurate index of ventricular enlargement.

**Teleroentgenograms.** Taken with the roentgen tube approximately 6 feet from the patient, teleroentgenograms represent fairly accurately the size of the heart and chest. For a complete assessment of cardiac configuration, posteroanterior, oblique and lateral views are essential. The positions of the various cardiac chambers and great vessels are shown in Figure 236.

The most frequently used measurement of cardiac size is the maximum width of the cardiac shadow in posteroanterior teleroentgenograms. When the cardiac width is more than half of the maximal chest width, the heart is usually enlarged. In infancy the cardiothoracic ratio is a less accurate index of cardiac enlargement than it is in subsequent years, because the horizontal position of the heart may increase the ratio to more than half in the absence of true enlargement. In children with vertical hearts the cardiothoracic ratio will tend to give an erroneously low impression of the true heart size.

The width of the heart also bears a fairly definite relationship to other body measurements. The transverse diameter is approximately 7 or 8 per cent of the body height and is more closely related to this factor than to age or weight.

Cardiac area may prove helpful in borderline cases. To make this measurement, a curved line must be constructed at the base to connect the two angles produced by the junction of the great vessels and the heart. The inferior cardiac border, which lies beneath the shadow of the diaphragm, must be completed in an arbitrary fashion. The enclosed area may be measured by means of a planimeter. Tables comparing cardiac area and body size have been compiled (Hodges, Adams and Gordon).

**The Electrocardiogram.** The electrocardiogram in pediatric practice is not only of diagnostic aid in congenital and rheumatic heart diseases, but also is frequently helpful in the detection and management of disturbances of electrolyte metabolism, endocrine and metabolic diseases and acute infections. Electrocardiographic examination is not complete unless the standard leads are supplemented by the unipolar limb leads and multiple chest leads. It is beyond the scope of this text to discuss the physiologic concepts



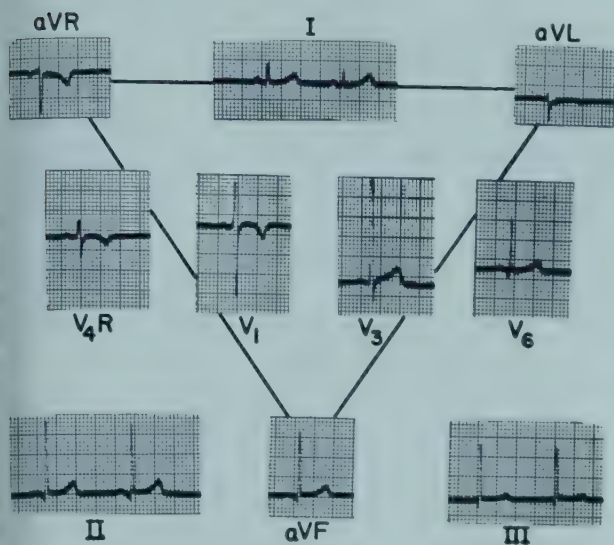


FIG. 237. Electrocardiogram of a normal child. The position of the heart is vertical. Note the relatively tall R waves and inversion of the T waves in  $V_4R$  and  $V_1$ .

of unipolar electrocardiography. A study of standard leads is valuable in the diagnosis of arrhythmias and for the measurements of the duration of various parts of the cardiac cycle. Axis deviation usually denotes the electrical position of the heart. Thus right axis deviation is usually associated with a vertical heart with clockwise rotation\* and left axis deviation with a horizontal heart. Although the anatomic and electrical positions of the heart may coincide, this is not always the case.

A wide electrocardiographic exploration of the chest is advised in children and especially in infants. In addition to the conventional leads of  $V_1$  through  $V_6$ , leads over the right chest ( $V_4R$  or  $V_3R$ ) are essential for adequate assessment of right ventricular activity.

**The normal electrocardiogram.**† In the majority of children the electrical position of the heart is vertical with varying degrees of clockwise rotation (Fig. 237). In a minority of cases the heart may assume a horizontal position. The unipolar chest leads have a different pattern from that observed in the normal adult. In infants the right ventricular surface leads show an  $R_s$  pattern which usually persists for the first two years of life and may be found up to the age of four years (Fig. 238). The T waves are inverted in leads  $V_4R$ ,  $V_3R$ ,  $V_1$ ,  $V_2$  and  $V_3$  in almost all infants and may remain inverted in  $V_4R$ ,

$V_3R$  and  $V_1$  up to the middle of the second decade of life. However, in the first twenty-four to forty-eight hours of life the T wave is usually upright in  $V_4R$ ,  $V_3R$  and  $V_1$ , and may be inverted in  $TV_5$  and  $V_6$ . Because of these normal patterns of the QRS-T in infants and children, the changes produced by right ventricular hypertrophy are different from those in adults. The diagnosis of ventricular hypertrophy is sometimes based on the increased voltage of the R and S waves in the unipolar chest leads. However, since the height of these waves is mainly governed by the proximity of the exploring electrode to the surface of the heart and since the chest wall of infants and children is relatively thin, the diagnosis of ventricular hypertrophy should not be based on voltage changes alone. The normal electrocardiographic pattern of infants and children has been described by Ziegler and others.

**Electrocardiographic abnormalities.** See Abnormalities of Cardiac Rhythm (p. 883).

**The P wave.** Tall, narrow and spiked P waves are seen in congenital pulmonary stenosis (Fig. 239) and tricuspid atresia and sometimes in cor pulmonale. These abnormal waves are probably due to right atrial hypertrophy, are usually taller than 2.5 mm. and are most obvious in standard lead II,  $V_4R$ ,  $V_3R$  and  $V_1$ . Similar waves are sometimes seen in thyrotoxicosis. Flat and widened P waves, commonly bifid, are seen in chronic mitral stenosis and are probably due to left atrial hypertrophy. Flat P waves may be found in hyperkalemia. Inversion of the P wave occurs in all leads in nodal rhythm, in

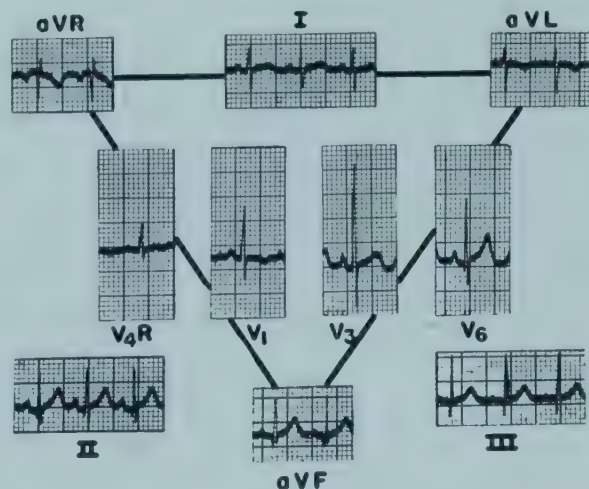


FIG. 238. Normal infant's electrocardiogram. Note the tall R and small s waves in  $V_4R$  and  $V_1$  and the inverted T wave in these leads. The heart is vertical with clockwise rotation.

\* In clockwise rotations the right ventricle moves to occupy more of the anterior surface of the heart.

† In this text capitalized letters refer to waves of high voltage (tall or deep waves), and small letters are used to designate waves of low voltage.

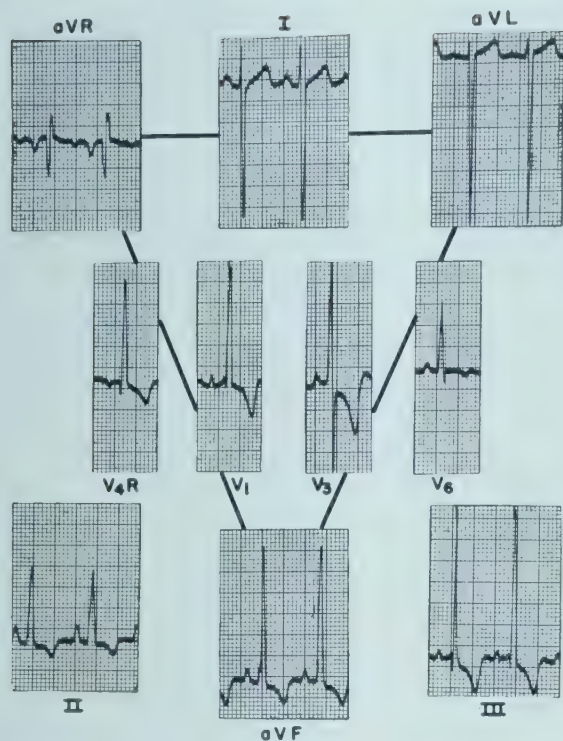


FIG. 239. Electrocardiogram showing right ventricular hypertrophy in a 7-year-old boy with pulmonary stenosis. Note the tall, spiked P wave in lead II, qR in  $V_4R$  rsR' in  $V_1$  and inversion of the T wave in leads II, III, aVR, aVF and all the chest leads. The heart is vertical with clockwise rotation.

standard lead I in dextrocardia and occasionally in standard leads II and III without obvious cause.

**Prolongation of the P-R interval.** This abnormality is a form of heart block. Permanent prolongation of the P-R interval may be congenital or due to scarring from rheumatic carditis. Any active carditis, including acute rheumatic fever, may produce transient prolongation of the P-R interval. Other causes of temporary prolongation of the P-R interval include digitalis therapy and carotid sinus pressure. No treatment is required specifically for this abnormality.

**Right ventricular hypertrophy.** Right ventricular surface leads of infants and children differ from those of adults, and tracings of the right chest ( $V_4R$  or  $V_3R$ ) are essential in young children. Review of electrocardiographic tracings in infants with known right ventricular hypertrophy has shown that the following changes may occur singly or in combination (Fig. 240): (1) a qR pattern in the right ventricular surface leads; (2) a positive T wave in leads  $V_4R$  through  $V_3$  after the first twenty-four to forty-eight hours of life; (3) a monophasic R wave in  $V_4R$ ,  $V_3R$  or  $V_1$ ; (4) prolongation of the intrinsicoid

deflection in right ventricular surface leads to greater than 0.03 second; (5) the R wave in the right chest leads is usually taller than 7 mm., but this sign alone is not sufficient for the diagnosis; (6) aVR usually shows a QR pattern. It is uncertain whether this is due to right ventricular hypertrophy or to the clockwise rotation with which it is commonly associated. (7) In the presence of incomplete right bundle branch block, right ventricular hypertrophy is indicated by a tall secondary R wave.

Older children and adolescents who have right ventricular hypertrophy show the same changes, but in addition may have the following abnormalities of the R and S waves of the unipolar leads: (1) the sum of  $RV_1$  or  $RV_3R$  and  $SV_5$  or  $SV_6$  totals 11 mm. or more. (2) The depth of the S wave in  $V_1$ ,  $V_3R$  or  $V_4R$  is less than 2 mm. It cannot be overstressed that the evaluation of ventricular hypertrophy should not be based on voltage changes alone.

Cabrera and Sodi-Pallares have correlated abnormal hemodynamics with electrocardiographic patterns. They have shown that obstruction to right ventricular and pulmonary flow (e.g., with pulmonary stenosis and primary pulmonary hypertension) is associated with a *systolic overload pattern*. This is characterized by an increasingly tall and late R wave in the right precordial leads. In these leads the T wave is initially upright and later becomes inverted (Figs. 239, 240). In contradistinction *diastolic overload* of the right ventricle (e.g., with atrial septal defect) is characterized by the pattern of incomplete

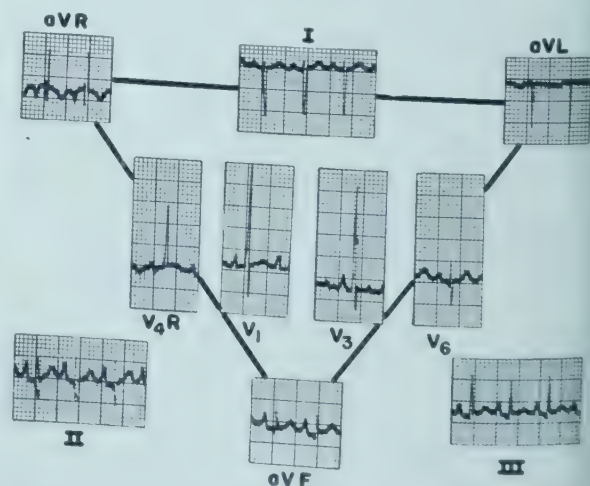


FIG. 240. Electrocardiogram showing right ventricular hypertrophy in an infant with tetralogy of Fallot. Note the spiked P waves in lead II, monophasic R wave in  $V_4R$ , delay in the intrinsicoid deflection in  $V_4R$  and  $V_1$  and the positive T waves in  $V_4R$  and  $V_1$ .



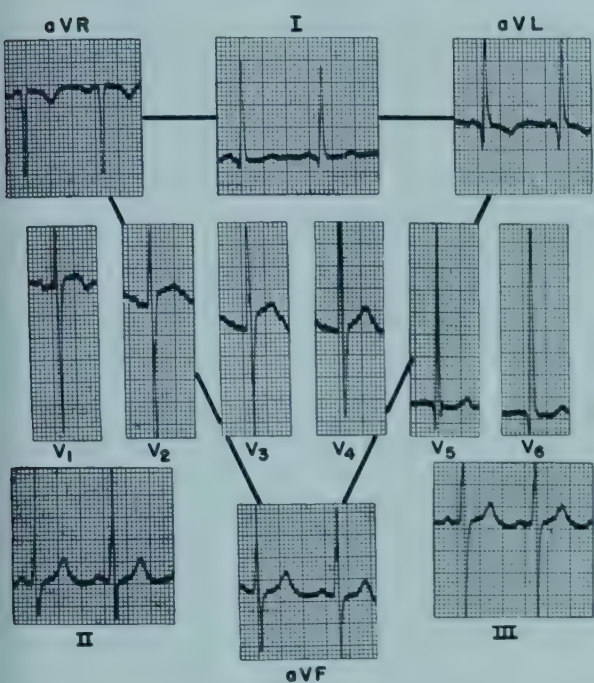


FIG. 241. Electrocardiogram showing left ventricular hypertrophy in a 12-year-old boy with chronic rheumatic heart disease. Note the tall R in  $V_6$ , deep S in  $V_1$ , deep, wide Q and inverted T in aVL.

or occasionally complete right bundle branch block (Fig. 242). Although this concept appears to be true in extreme examples, there are many instances in which the dynamics of systolic overload may be associated with incomplete right bundle branch block.

**Left ventricular hypertrophy.** The following features, alone or in combination, suggest dominance of the left ventricle (Fig. 241): (1) depression of the S-T segment and inversion of the T waves in left ventricular surface leads (i.e.,  $V_5$ ,  $V_6$  or  $V_7$ ; aVF if the heart is vertical and aVL if the heart is horizontal); (2) delayed onset of the intrinsicoid deflection in  $V_5$  or  $V_6$  (greater than 0.04 second); (3) increased voltage of the QRS complex. In older children or adolescents the sum of the left ventricular potentials (i.e.,  $RV_6$  and  $SV_1$ ) is greater than 35 mm. Also  $RV_5$  or  $RV_6$  exceeds 26 mm. If the heart is vertical,  $RaVF$  exceeds 20 mm., and in a horizontal heart  $RaVL$  exceeds 11 mm. It is again stressed that the evaluation of ventricular dominance should not be based on voltage changes alone.

Cabrera and Sodi-Pallares have applied their concept of overload of the ventricles to the left heart. They suggest that *systolic overload of the left ventricle* is characterized by depression of the S-T segment and inverted T waves in the left precordial leads. *Diastolic overload of the left ventricle* is suggested by

tall R waves with a late activation time and tall upright and symmetrically peaked T waves in the left precordial leads. The foregoing electrocardiographic diagnoses, especially diastolic overload of the left ventricle, are frequently difficult to establish (Nadas).

**Bundle branch block.** Complete right or left bundle branch block is not frequently encountered in pediatric practice, and the electrocardiographic pattern does not differ from that in adults. However, *incomplete right bundle branch block* with or without right ventricular hypertrophy is not uncommon. Incomplete right bundle branch block is suggested by an early R wave and a late R' in the right precordial leads and a relatively broad  $SV_6$  (Fig. 242). If there is associated right ventricular hypertrophy, the secondary R wave in the right precordial leads is tall and usually exceeds 10 mm. It is often difficult to differentiate incomplete right bundle branch block from right ventricular hypertrophy.

**Duration of electrical systole (Q-T interval).** The duration of the Q-T interval (electrical systole) varies with the cardiac rate, and many formulas have been devised in an attempt to adjust this differential. Taran and Szilagyi's modification of Bazett's formula states that the corrected Q-T interval (Q-TC) equals the measured Q-T interval divided by the square root of the cycle length (R-R

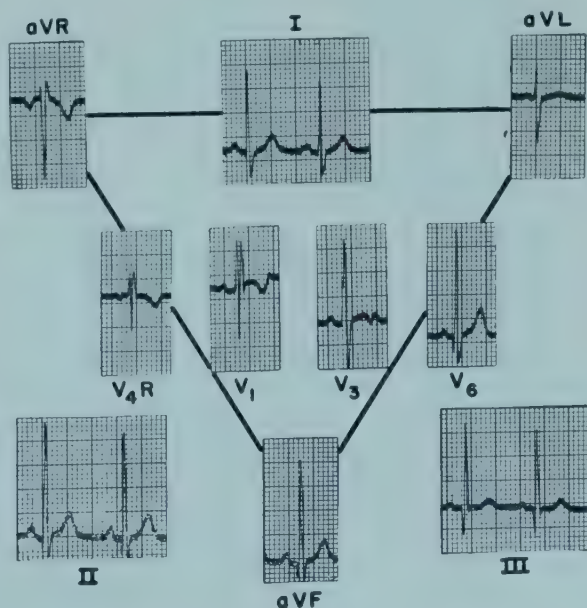


FIG. 242. Electrocardiogram showing incomplete right bundle branch block in a patient with septal defect, in which there was a direct communication between the left ventricle and right atrium. Note the RSR' in  $V_4R$ , RSR's in  $V_1$  and stumpy S wave in  $V_6$ .

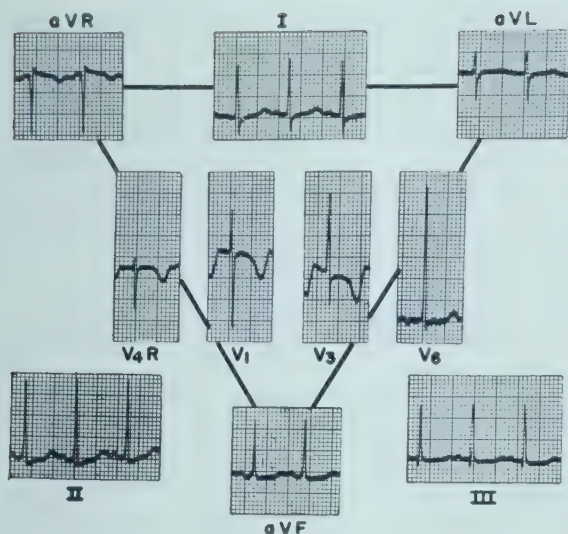


FIG. 243. Electrocardiogram in hypocalcemia and hypokalemia (serum calcium, 1.8 mEq./L.; serum potassium, 2.2 mEq./L. at time of tracing). Note prolongation of electrical systole due to long S-TU segment. This graph also shows left ventricular hypertrophy.

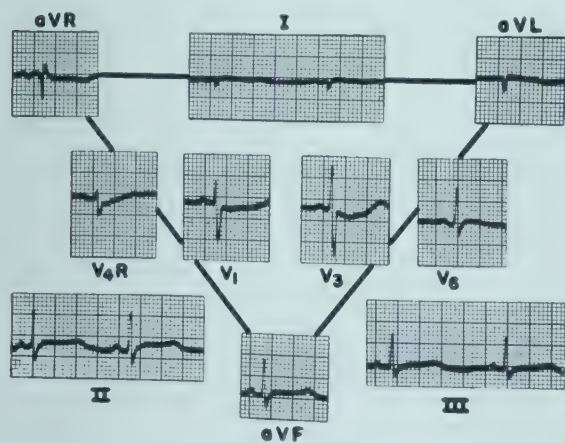


FIG. 244. Electrocardiogram in hypokalemia (serum potassium, 2.7 mEq./L.; serum calcium, 4.8 mEq./L. at time of tracing). Note the prolongation of electrical systole due to a widened TU wave, especially in leads II, III and aVF; also depression of the S-T segment in  $V_{4R}$ ,  $V_1$  and  $V_3$ .

interval). The normal Q-TC is variously given as 0.38 plus or minus 0.04. It is often lengthened in children with acute rheumatic carditis, myocarditis secondary to infections, hypokalemia and hypocalcemia (Figs. 243, 244). In hypokalemia and hypocalcemia prolonged electrical systole is due to a lengthened Q-U interval. A shortened Q-TC may be found after administration of digitalis and with pericarditis and hyperkalemia.

**S-T segment and T wave abnormalities.** In generalized pericarditis superficial epicardial involvement may cause elevation of

the S-T segment, which is later followed by abnormal T wave inversion as healing progresses. Administration of digitalis is associated with sagging of the S-T segment and abnormal inversion of the T wave. Depression of the S-T segment may also occur in conditions producing myocardial hypoxia, e.g., anemia and carbon monoxide poisoning.

A group of abnormalities of special interest which produce S-T segment depression and sharp inversion of the T waves and which usually cannot be differentiated by the electrocardiogram alone includes endocardial sclerosis, aberrant origin of the left coronary artery from the pulmonary artery, glycogen storage disease of the heart, myocardial tumors and gargoylism. Aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those seen in acute myocardial infarction in adults. Similar changes may occur in progeria with degenerative coronary artery lesions and calcinosis of the coronary arteries.

In any form of carditis, especially diphtheria, simple inversion of the T wave may occur. Hypothyroidism may produce flat or inverted T waves in association with a generalized low voltage graph. In hyperkalemia the T waves are commonly of high voltage and are tent-shaped (Fig. 245).

**Hematologic Data.** The normal variations of the blood picture in infancy should be borne in mind in evaluation of cardiovascular disease. These include the normal poly-

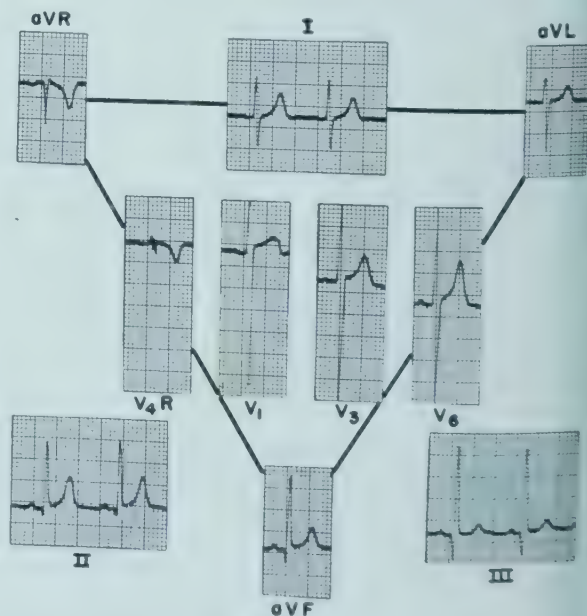


FIG. 245. Electrocardiogram in hyperkalemia. (Serum potassium, 6.5 mEq./L.; serum calcium, 5.1 mEq./L.) Note the tall, tent-shaped T waves, especially in leads I, II and  $V_6$ .



cythemia of the neonatal period and the relative anemia and leukocytosis of infancy. Persistent polycythemia after the first month of life is frequently associated with right-to-left shunts and cyanosis. Anemia and polymorphonuclear leukocytosis are often encountered in active rheumatic fever and in subacute bacterial endocarditis.

Patients with intense cyanosis may exhibit manifestations of an abnormal clotting mechanism. Laboratory studies may indicate any

combination of the following: prolonged bleeding and clotting times, decreased or abnormal platelets, decreased plasma fibrinogen or prolonged prothrombin time. These abnormalities frequently revert to normal after repeated venesection and have clinical importance when surgical therapy is being considered.

**Cardiac Catheterization.** The technique consists in passing a radiopaque catheter under sterile conditions into a peripheral vein

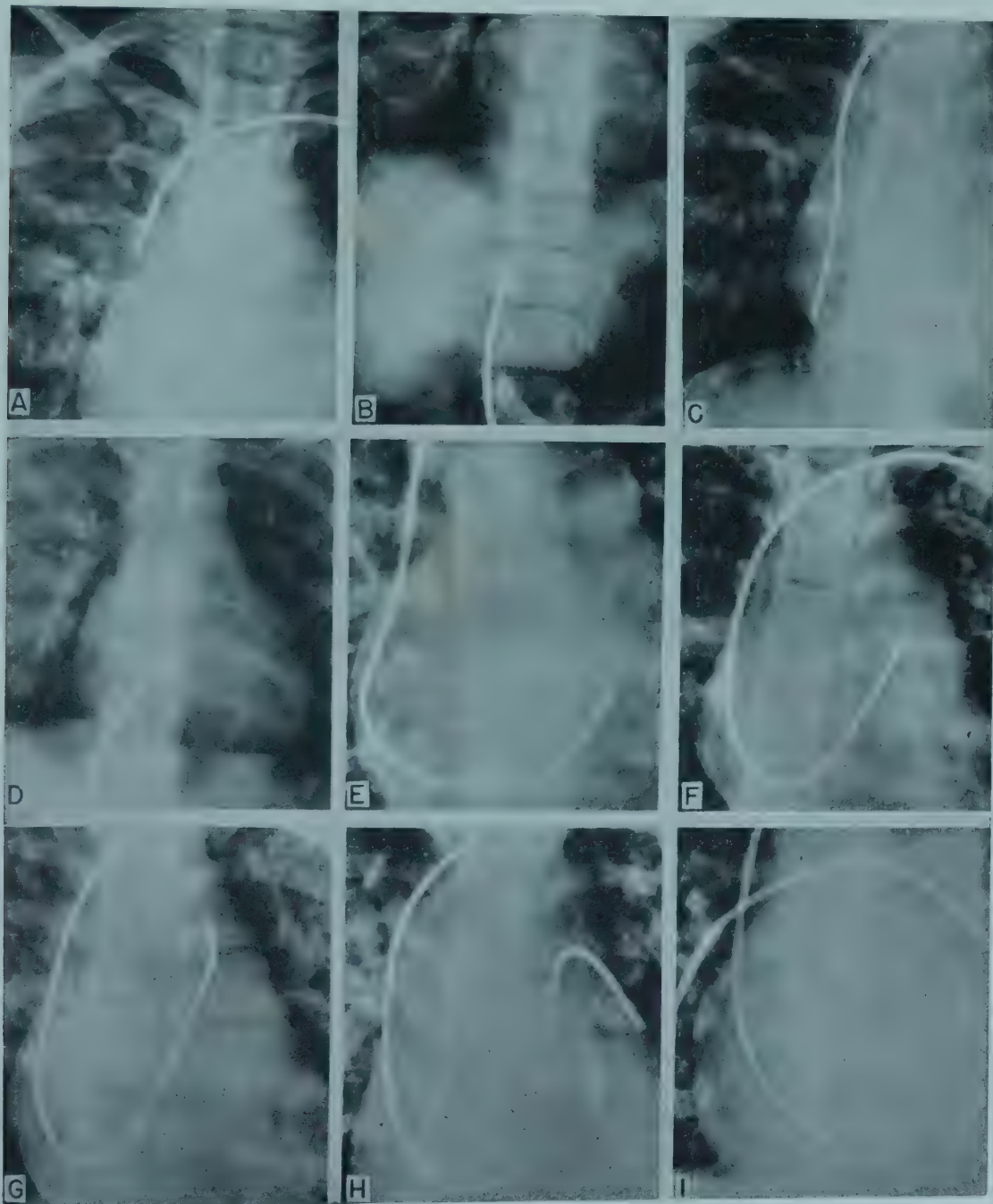
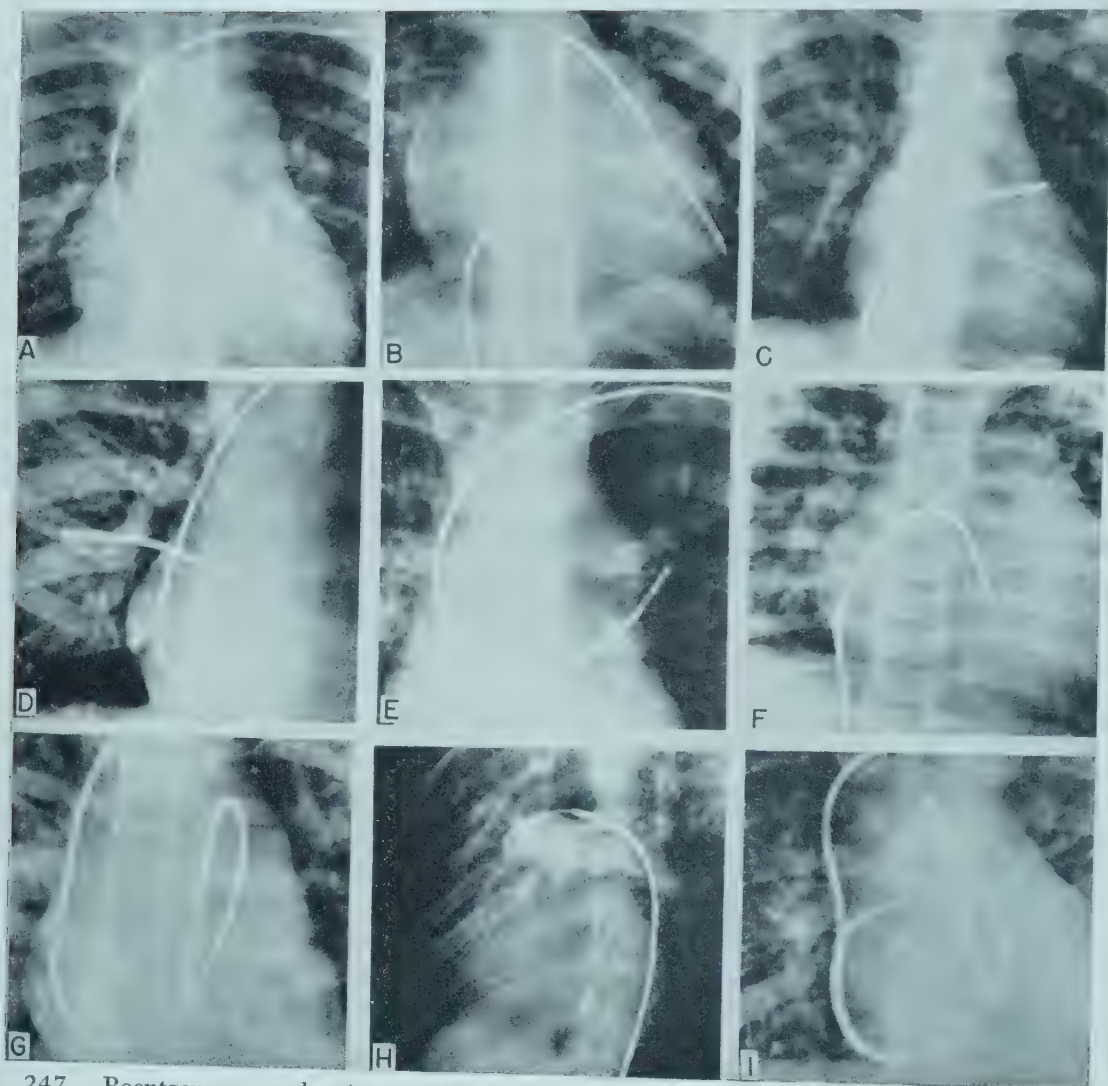


FIG. 246. Roentgenograms showing the positions of the cardiac catheter from which pressures and blood samples may be obtained. A, Superior vena cava. Catheter inserted from antecubital vein. B, Inferior vena cava. Catheter inserted from saphenous vein. C, Low right atrium. D, Right atrium in region of tricuspid valve. E, Low right ventricle. F, High right ventricle in region of outflow tract. G, Main pulmonary artery. H, Left pulmonary artery. I, Right pulmonary artery.



**FIG. 247.** Roentgenograms showing positions of the cardiac catheter. *A*, Coronary sinus: compare with Figure 246, *F*. *B*, Pulmonary wedge or "capillary" via left pulmonary artery. *C*, Catheter has passed from the right to left atrium across an atrial septal defect. *D*, Catheter has passed across an atrial septal defect and entered a right pulmonary vein. This picture is frequently confused with an anomalous pulmonary vein across an atrial septal defect. *E*, Catheter tip in a left pulmonary vein after passing from the right to left atrium across an atrial septal defect. *F*, Catheter has passed from the inferior vena cava into the right atrium, across an atrial septal defect into the left atrium, and then through the mitral valve into the left ventricle. *G*, Catheter has passed from the superior vena cava to the right atrium, right ventricle and pulmonary artery, through a patent ductus arteriosus and down the descending aorta. *H*, Retrograde catheterization of the aorta from the femoral artery. The catheter tip has passed across a patent ductus arteriosus into the pulmonary artery. *I*, After coiling in the right atrium the catheter has passed into the right ventricle, then through a ventricular septal defect into the aorta.

and guiding it with the aid of fluoroscopy into the great veins, the right heart chambers and pulmonary artery (Fig. 246). In some congenital cardiovascular abnormalities the catheter may pass through intracardiac defects or into abnormally placed vessels (Fig. 247). Samples of arterial blood may be obtained simultaneously from an indwelling needle in the brachial or femoral arteries. Oxygen consumption and carbon dioxide production may be calculated from samples of

expired air collected in Douglas bags. These studies are of value in determining the presence of intracardiac shunts and pressures, as well as measurements of cardiac outputs and indices. Calculations may also be made of the pulmonary and peripheral arteriolar resistances, the work of the heart, the volume of various shunts and the areas of intracardiac defects and valves.

Cardiac catheterization in infants and children presents many problems not encountered



in adults. In many instances it is necessary to sedate or even anesthetize the patient. Volatile gas mixtures such as ether should not be used, because manometric blood analyses done in the presence of these substances are inaccurate. The calculations of cardiac output, shunts, resistances and valve areas should be interpreted cautiously if the study is made during anesthesia because their validity depends upon the patient being in a "steady state," which is difficult to obtain during deep narcosis.

The majority of congenital cardiac lesions can be diagnosed after a careful clinical history and examination, and cardiac catheterization should not be used indiscriminately in young patients because of the hazards of injury and even of death. Suitable laboratory facilities which must be available before the study is undertaken include a fluoroscope, electrocardiograph and apparatus for recording blood pressures and for analysis of the oxygen and carbon dioxide content of blood.

Abnormal findings which may be encountered in patients with congenital heart disease are shown in Tables 98 and 99.

**Dye Dilution Curves.** Localization of intracardiac and extracardiac shunts may be facilitated by injection of an indicator dye at multiple sites in the heart and great vessels during cardiac catheterization. Dye dilution curves may be recorded by means of ear piece and cuvette oximeters. The shape of the dye dilution curve depends on the site of injection of the dye and the presence or absence of intracardiac and extracardiac shunts (Fig. 248).

The dye most frequently used is T-1824 (Evans blue). A disadvantage of this material is that multiple injections result in a blue discoloration of the skin. Other dyes are now available which overcome this problem. This technique can also be used for measurement of cardiac output and for the assessment of competence of the cardiac valves.

**Arterial Oxygen Saturation.** The arterial

Table 97. Normals and Formulas for Determination of Hemodynamics in Cardiac Catheterization

1. Cardiac index  $3.1 \pm 0.4$  liter/minute/square meter
  2. Arteriovenous oxygen difference  $4.5 \pm 0.7$  ml./100 ml.
  3. Oxygen consumption 160–180 ml./square meter/minute
  4. Arterial oxygen saturation 94–100%
  5. Difference in oxygen content between venae cavae and right atrium  $< 1.9$  vol. %
  6. Difference in oxygen content between right atrium and right ventricle  $< 0.9$  vol. %
  7. Difference in oxygen content between right ventricle and pulmonary artery  $< 0.5$  vol. %
  8. Normal mean left atrial pressure 4 to 8 mm. Hg
  9. Pulmonary arteriolar resistance 50–150 dyne sec. cm.<sup>-5</sup>
  10. Cardiac output ml./min. = 
$$\frac{\text{O}_2 \text{ intake (ml./min.)}}{\left\{ \begin{array}{l} \text{O}_2 \text{ content arterial blood (vols. \%)} \\ \text{minus O}_2 \text{ content of mixed venous blood} \end{array} \right\}} \times 100$$
  11. Cardiac index = cardiac output (L./min.) per square meter of body surface area
  12. Pulmonary artery flow = 
$$\frac{\text{O}_2 \text{ intake (ml./min.)}}{\left\{ \begin{array}{l} \text{O}_2 \text{ content of pulmonary venous blood (vols. \%)} \\ \text{minus O}_2 \text{ content of pulmonary arterial blood (vols. \%)} \end{array} \right\}} \times 100$$
  
If a pulmonary venous sample is not obtained, it is assumed to be saturated 95% of capacity
  13. Systemic flow = 
$$\frac{\text{O}_2 \text{ intake (ml./min.)}}{\left\{ \begin{array}{l} \text{systemic arterial O}_2 \text{ content (vols. \%)} \\ \text{minus mixed venous O}_2 \text{ content (vols. \%)} \end{array} \right\}} \times 100$$
  14. Effective pulmonary artery flow = 
$$\frac{\text{O}_2 \text{ intake (ml./min.)}}{\left\{ \begin{array}{l} \text{pulmonary venous O}_2 \text{ content (vols. \%)} \\ \text{minus mixed venous O}_2 \text{ content (vols. \%)} \end{array} \right\}} \times 100$$
  15. Total left-to-right shunt = pulmonary artery flow minus effective pulmonary artery flow
  16. Total right-to-left shunt = systemic flow minus effective pulmonary artery flow
  17. Pulmonary arteriolar resistance  $R = \frac{PA - PC}{PF} \times 1332$
- Where  $R$  = pulmonary arteriolar resistance in dyne seconds cm.<sup>-5</sup>  
 $PA$  = mean pulmonary artery pressure in mm. Hg  
 $PC$  = mean pulmonary "capillary" pressure in mm. Hg  
 $PF$  = pulmonary flow in ml./sec.

Table 98. Analysis of Oxygen Content in Blood (Cardiac Catheterization)

	Venae Cavae	Right Atrium	Right Ventricle	Pulmonary Artery	Arterial Oxygen Saturation	Remarks
Patent ductus arteriosus	←————Comparable————→		————→	Higher than R. V., R. A. and V. C.	Normal	(a) Rarely, with right-to-left shunt, arterial unsaturation present (b) If associated pulmonary valve insufficiency, high R. V. samples comparable to P. A.
Atrial septal defect	Lower than R. A., R. V. and P. A.	←————Comparable————→	————→	————→	Normal	
Ventricular septal defect	←————Comparable————→	————→	←————Higher than R. A. and V. C.————→		Normal	Rarely, direct shunt into P. A. without mixing in R. V. when P. A. higher than R. V., R. A. and V. C.
Anomalous pulmonary veins	(a) If empty into S. V. C., I. V. C. lower than S. V. C., R. A., R. V. and P. A. (b) If empty into I. V. C., S. V. C. lower than I. V. C., R. A., R. V. and P. A.	If empty into R. A., V. C. lower than R. A., R. V. and P. A.	←————Comparable————→		Normal	
Isolated pulmonary stenosis	←————Comparable————→	————→	————→		Normal	If right-to-left shunt, e.g., through foramen ovale, arterial unsaturation
Aorticopulmonary septal defect	←————Comparable————→	————→	————→	Higher than R. V., R. A. and V. C.	Normal	
Tetralogy of Fallot	←————Comparable————→	————→	————→		Usually gross unsaturation	In many instances R. V. and P. A. samples higher than R. A., and V. C. Venous blood grossly unsaturated
Tricuspid atresia	←————Comparable————→	————→	————→		Usually gross unsaturation	
Transposition of great vessels	Depends on presence of associated defects such as atrial defect, ventricular septal defect and patent ductus arteriosus				Gross unsaturation	Contents vary in same chamber because shunt is in both directions
Eisenmenger "physiology," i.e., pulmonary hypertension with bidirectional shunt	Depends on site of defect. Commonest is ventricular septal defect when R. V. and P. A. higher than R. A. and V. C.				Unsaturation	In atrial defect, V. C. lower than R. A., R. V. and P. A. In patent ductus P. A. higher than R. V., and brachial artery higher than femoral artery.

Normally the difference in oxygen content between the venae cavae and right atrium is less than 1.9 volumes per cent, between the right atrium and right ventricle less than 0.9 volume per cent, and between the right ventricle and pulmonary artery, less than 0.5 volume per cent.

P. A. = pulmonary artery, R. V. = right ventricle, R. A. = right atrium, V. C. = venae cavae, S. V. C. = superior vena cava, I. V. C. = inferior vena cava.



Table 99. Pressures during Cardiac Catheterization (mm. Hg)

	<i>Venae Cavae</i>	<i>Right Atrium</i>	<i>Right Ventricle</i>	<i>Pulmonary Artery</i>	<i>Pulmonary Capillary</i>	<i>Remarks</i>
Normal	0-5	0-5	18-30/0-5	18-30/6-12 Mean 13-17	6-12	Normal left atrial pressure, 4-8
Patent ductus arteriosus	Normal	Normal	Normal to increased	Normal to increased	Normal to increased	Right atrial and caval pressures increased in congestive failure
Atrial septal defect	Normal	Normal	Normal to increased	Normal to increased	Normal	
Ventricular septal defect	Normal	Normal	Normal to increased	Normal to increased	Normal to increased	Right atrial and caval pressures increased in congestive failure
Anomalous pulmonary veins (partial)	Normal	Normal	Normal to increased	Normal to increased	Normal	
Isolated pulmonary stenosis	Normal to increased	Normal to increased	Increased	Normal to decreased	Normal	Left atrial pressure normal, and right atrial pressure curve may show prominent "a" wave
Aorticopulmonary septal defect	Normal	Normal	Normal to increased	Normal to increased	Normal to increased	
Tetralogy of Fallot	Normal	Normal	Increased	Normal to decreased	Normal	Pressure differentials may be noted in con- tinuous tracing as catheter passes from pulmonary artery to infundibular cham- ber and to right ventricle
Tricuspid stenosis	Increased	Increased	_____	_____	_____	Left atrial pressure normal Right atrial pressure curve shows prom- inent "a" wave
Transposition of great vessels	Normal	Normal	Increased	Increased	Increased	Right atrial and caval pressures increased in congestive failure
Eisenmenger physiology	Normal to increased	Normal to increased	Increased	Increased	Normal	

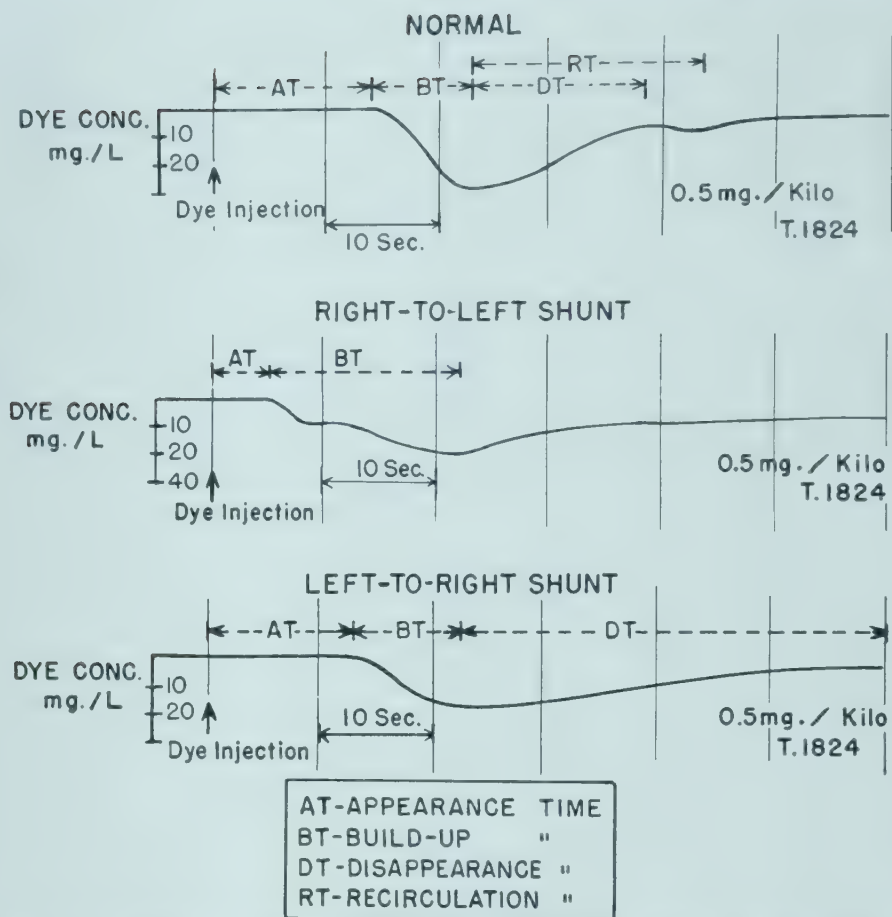


FIG. 248. Typical diagrams of dye dilution curves. T-1824 is injected into the antecubital vein, and photokymographic records of the dilution curve are obtained by oximetric readings of blood from a peripheral artery (e.g., radial artery). The upper curve shows the time components from a normal subject. The middle curve indicates a central right-to-left shunt. Note the decrease in appearance time and the abnormal hump on the build-up slope. The lower curve indicates a central left-to-right shunt. Note that the maximum concentration of dye is less than normal and that the disappearance time is prolonged. The peak concentration of dye is lower in both a left-to-right and a right-to-left shunt. In the majority of instances the indicator dye is injected selectively into specific cardiac chambers or blood vessels, depending on the site of suspected shunt.

oxygen saturation may be determined by analysis of blood obtained by direct puncture of the brachial or femoral artery or by oximetry. Normal arterial blood has an oxygen saturation between 94 and 98 per cent. These levels are reduced in veno-arterial shunts and in disease of the pulmonary epithelium or vasculature which results in failure of proper oxygenation of the blood. The response of arterial oxygen saturation to exercise is a measurable index of the incapacity of the patient. In cyanotic congenital heart disease (e.g., tetralogy of Fallot) the resting arterial oxygen saturation is low; it is further reduced on exercise, and the time taken for recovery to the control level is prolonged.

**Angiocardiography.** The great blood vessels and individual cardiac chambers may be visualized by injection of suitable contrast

media. It appears that venous angiocardiography (i.e., injection of contrast material into a peripheral vein) with serial roentgenograms taken at speeds of two to four per second has little to offer in the diagnosis of cardiovascular malformations. This technique has been superseded by the introduction of selective angiocardiography, i.e., injection of contrast material into specific cardiac chambers or great vessels. This method allows identification of specific abnormalities without the superimposition of the shadows of normal chambers. After contrast material has been injected, serial roentgenograms may be obtained in two planes at a rate of six to fourteen per second.

Image intensification and photofluorography have made possible cardiac catheterization and selective angiocardiography simultaneously. It has the distinct advantage of reducing



radiation to the patient by tenfold to fiftyfold during fluoroscopy. The method has been combined with a closed circuit television which monitors the fluoroscopic screen and allows visualization of the cardiac silhouette and the cardiac catheter without previous dark adaptation. The reaction of the patient to the various phases of the study can be seen because fluoroscopy is performed in a normally lighted room. After the cardiac catheter has been introduced into the specific chamber to be studied a small amount of contrast medium is rapidly injected, and moving pictures are exposed at thirty to sixty frames per second. The technique of recording the movement of contrast medium by motion pictures has been extremely helpful because each examination can be studied repeatedly by running the motion picture at various speeds.

The injection of contrast medium into the circulation is not without hazard and should be used discriminately. Deaths have been reported from iodine sensitivity, cardiac arrhythmia, cerebrovascular complications and pulmonary edema. However, the risk has been reduced by the introduction of better contrast agents. Also, in selective angiocardiology, the amount of contrast medium used is reduced as compared to that for venous angiocardiology.

"Idealized" diagrams of the normal angiogram are shown in Figure 236. The indications for this study are outlined under the individual congenital lesions described later in this section.

**Arteriography.** The aorta and its branches may be outlined by injecting a contrast medium intra-arterially and recording its course by rapid serial roentgenograms or moving pictures. In infants and young children the arterial circulation may be visualized after retrograde injection of dye through a cannula placed in the brachial artery (Keith and Forsyth). In older children and adolescents a catheter may be passed from the brachial artery into the first or second part of the aorta and the contrast medium injected for visualization of the aorta and its branches (Helmsworth and co-workers). This study may be of value in the diagnosis of patent ductus arteriosus, peripheral arterial aneurysms, some instances of coarctation of the aorta and arterial malformations (e.g., the study of the renal vessels in patients with suspected renal hypertension). The indications for arteriography have decreased with the introduction of combined cardiac cath-

terization and selective angiocardiology. The latter techniques allow the diagnosis of these anomalies and also may identify unsuspected associated malformations.

**Roentgenokymograms.** Roentgenokymograms are produced by interposing a slotted cassette between the film and the patient. During continuous exposure to the roentgen rays for about two seconds the film moves downward and records in one picture the variations of the cardiac size during systole and diastole. The excursion of pulsation of the heart and great vessels may also be measured with a photoelectric cell and recorded as a continuous tracing on a moving film. Such procedures provide permanent records of the activity of the heart as observed periodically in the fluoroscope.

**Circulation Time.** The circulation time may be determined by injection of a substance such as saccharin or sodium dehydrocholate in an arm vein and recording the time which elapses until the sensation of the characteristic taste occurs. Histamine, ether and radioactive substances have also been used. A sharp end point may be obtained with a sodium cyanide solution which makes the child gasp when it reaches the aortic body, or with fluorescein, which produces a green fluorescence of the lips when viewed under an ultraviolet lamp. The average time required for circulation of blood (as measured by the fluorescein method) from a peripheral arm vein to the heart through the lungs and finally to peripheral capillaries is about seven seconds in infants and eleven seconds in older children (Witzberger and Cohen). Many of the tests of circulation time depend on subjective sensations which are commonly difficult to evaluate in young patients.

**Phonocardiography.** Sound waves produced by the cardiac tones and murmurs may be recorded simultaneously with electrocardiographic and pulse waves. By this method the time at which murmurs occur in the cardiac cycle may be determined more accurately, and their duration, shape and other properties may be measured, and permanent records are provided.

**Arteriogram and Phlebogram.** Recordings of the arterial pulsations from a peripheral vessel may be obtained directly from an indwelling needle or indirectly by recording the movement of an expansile capsule over the surface of the artery. The former method is more accurate and is preferable. Most abnormal contours can be discerned by the palpating finger, but records of the peripheral

arterial wave are also helpful. Details of the peripheral venous pulsations (phlebogram) have already been described.

**Vital Capacity.** The amount of air which can be forcibly expired after a maximum inspiration represents the vital capacity and may be recorded on a spirometer. The capacity of a normal child is computed in terms of his age, height, weight or square meter of body surface. The results vary widely in young children, but repeated tests in the same child provide evidence of progress of his disease over a period of time.

**Standard Exercise Test.** The objective of this test is recognition of mechanical obstruction in the outflow tract of the right ventricle or in the pulmonary valve. In a normal person the pulmonary circulation increases sufficiently to meet the respiratory demands of exercise, and there is an increase in the ratio of oxygen consumed to the liters of ventilation. In patients with pulmonary stenosis mechanical obstruction limits the pulmonary blood flow, and the ratio falls. The standard exercise test, in which the patient steps up and down on a 20-cm. step thirty times in one minute, is positive in about 75 per cent of patients with pulmonary stenosis.

**Response to exercise.** Various tests have been devised to evaluate myocardial function. These tests depend on the response of the pulse and respiratory rates and variations in the level of blood pressure to a specific exercise (Master, Schneider). It is usually difficult to evaluate these results because they depend on the cooperation of the patient. The wide variation in results obtained in normal children must be borne in mind when patients with cardiac disease are tested. Fine grades of differences in myocardial function are not detectable by these methods.

The presence of *external dyspnea* is frequently difficult to ascertain in young patients, especially those with acyanotic congenital heart disease. Parents may deny the symptom of exercise intolerance and only appreciate the previous incapacity of the child when his activity has increased to normal after surgical therapy. In infants one of the early signs of dyspnea on exertion is manifest during feeding, since it is not possible to breathe and swallow simultaneously.

**Ballistocardiography.** Recoil of the body in the opposite direction to the ejection of blood from the heart may be recorded graphically if the subject is placed on a suitable table (Starr). Small tables for children have

been constructed to record body movements in "head-to-foot" and "side-to-side" directions. Coarctation of the aorta is associated with an absent or small K wave.

SAMUEL KAPLAN  
ROBERT A. LYON

## REFERENCES

### General

- Keith, J. D., Rowe, R. D., and Vlad, P.: *Heart Disease in Infancy and Childhood*. New York, Macmillan Company, 1958.
- Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: *Diagnosis of Congenital Heart Disease*. Chicago, Year Book Publishers, Inc., 1955.
- Nadas, A. S.: *Pediatric Cardiology*. Philadelphia, W. B. Saunders Company, 1957.
- Wood, P.: *Diseases of the Heart and Circulation*. 2nd ed. Philadelphia, J. B. Lippincott Company, 1956.

### Cardiac Sounds and Phonocardiography

- Leatham, A.: Systolic Murmurs. *Circulation*, 17: 601, 1958.
- Luisada, A. A.: *The Heart Beat. Graphic Methods in the Study of the Cardiac Patient*. New York, Paul B. Hoeber, Inc., 1953.
- McKusick, V. A.: Symposium on Cardiovascular Sound. *Circulation*, 16:270, 414, 1957.

### Blood Pressure

- Downing, M. E.: Blood Pressure of Normal Girls from Three to Sixteen Years of Age. *Am. J. Dis. Child.*, 73:293, 1947.
- Graham, A. W., Hines, E. A., and Gage, R. P.: Blood Pressures in Children between the Ages of Five and Sixteen Years. *Am. J. Dis. Child.*, 69: 203, 1945.
- Lambert, J. P.: Venous Pressure in Children. *Am. J. Dis. Child.*, 52:1088, 1936.

### Roentgen Examination

- Caffey, J.: *Pediatric X-Ray Diagnosis*. 3rd ed. Chicago, Year Book Publishers, Inc., 1956.
- Meyer, R. R.: A Method for Measuring Children's Hearts. *Radiology*, 53:363, 1949.

### Electrocardiogram

- Alimurung, M. M., Joseph, L. G., Nadas, A. S., and Massell, B. F.: The Unipolar Precordial and Extremity Electrocardiogram in Normal Infants and Children. *Circulation*, 4:420, 1951.
- Barker, J. M.: *The Unipolar Electrocardiogram. A Clinical Interpretation*. New York, Appleton-Century-Crofts, Inc., 1952.
- Cabrera, E., and Monroy, J. R.: Systolic and Diastolic Loading of the Heart. I. Physiologic and Clinical Data. II. Electrocardiographic Data. *Am. Heart J.*, 43:661, 669, 1952.
- Goodwin, J. F.: The Electrocardiogram in Normal Children and in Children with Right Ventricular Hypertrophy. *Brit. Heart J.*, 14:173, 1952.
- Sodi-Pallares, D., and Calder, R. M.: *New Bases of Electrocardiography*. St. Louis, C. V. Mosby Company, 1956.



- Taran, L. M., and Szilagyi, N.: The Duration of the Electrical Systole (Q-T) in Acute Rheumatic Carditis in Children. *Am. Heart J.*, 33:14, 1947.
- Yu, P. N. G., Joos, H. A., and Katsampes, C. P.: Unipolar Electrocardiogram in Normal Infants and Children. *Am. Heart J.*, 41:91, 1951.
- Ziegler, R. F.: Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill., Charles C Thomas, 1951.
- : Characteristics of the Unipolar Precordial Electrocardiogram in Normal Infants. *Circulation*, 3:438, 1951.
- Cardiac Catheterization*
- Bing, R. J.: Catheterization of the Heart; in *Advances in Internal Medicine*. Chicago, Year Book Publishers, Inc., 5:59, 1952.
- Broadbent, J. C., and Wood, E. H.: Indicator Dilution Curves in Acyanotic Congenital Heart Disease. *Circulation*, 9:890, 1954.
- Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterization in Congenital Heart Disease. New York, Commonwealth Fund, 1949.
- Holling, H. E., and Zak, G. A.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease. *Brit. Heart J.*, 12:153, 1950.
- McMichael, J.: Pharmacology of the Failing Human Heart. Oxford, Blackwell Scientific Publications, 1950.
- Swan, H. J. C., Zapata-Diaz, J., and Wood, E. H.: Dye Dilution Curves in Cyanotic Congenital Heart Disease. *Circulation*, 8:70, 1953.
- Wood, E. H., and others: General and Special Techniques in Cardiac Catheterization. *Proc. Staff Meet., Mayo Clin.*, 23:494, 1948.
- Angiocardiography and Arteriography*
- Astley, R., and Oldham, J. S.: The Clinical Applications of Image Intensification: A Symposium. *Brit. J. Radiol.*, 29:544, 1956.
- Dotter, C. T.: Motion in Cardiovascular Radiography. *Circulation*, 12:1034, 1955.
- Dotter, C. T., and Steinberg, I.: *Angiocardiography*. New York, Paul B. Hoeber, Inc., 1951.
- Fredzell, G., Lind, J., Ohlson, E., and Wegelius, C.: Direct Serial Roentgenography in Two Planes Simultaneously at 0.08 Second Intervals. *Am. J. Roentgenol.*, 63:548, 1950.
- Helmsworth, J. A., McGuire, J., and Felson, B.: Arteriography of Aorta and Its Branches by Means of the Polyethylene Catheter. *Am. J. Roentgenol.*, 64:196, 1950.
- Keith, J. D., and Forsyth, C. C.: Aortography in Infants. *Circulation*, 2:907, 1950.
- Rowe, R. D., Vlad, P., and Keith, J. D.: Selective Angiocardiography in Infants and Children. *Radiology*, 66:344, 1956.
- Wegelius, C., and Lind, J.: Diagnostic Evaluation of the Heart Dynamics by Angiocardiography; in McLaren, J. W., ed.: *Modern Trends in Diagnostic Radiology*. Second Series. New York, Paul B. Hoeber, Inc., 1953.
- Roentgenokymograms*
- Luisada, A., and Fleischner, F. G.: Fluorocardiography (Electrokymography). *Am. J. Med.*, 6:756, 1949.
- Schwarzschild, M. M.: The Physical Principles of Slit Kymography. *Radiology*, 33:90, 1939.
- Circulation Time*
- Witzberger, C. M., and Cohen, H. G.: Circulation Time in Infants and Young Children Determined by the Fluorescein Method. *J. Pediat.*, 22:726, 1943.
- Arteriogram and Phlebogram*
- Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice. Baltimore, Williams & Wilkins Company, 1945.
- Brofman, B. L., and Feil, H.: The Diagnosis of Congenital Subaortic Stenosis. Application of Hemodynamic Principles. *Circulation*, 6:817, 1952.
- Ballistocardiogram*
- Braunstein, J. R.: The Ballistocardiogram. Springfield, Ill., Charles C Thomas, 1953.
- Starr, I.: Clinical Studies with the Ballistocardiograph; In Congestive Failure, on Digitalis Action, on Changes in Ballistic Form and in Certain Acute Experiments. *Am. J. M. Sc.*, 202:469, 1941.

## CONGENITAL HEART DISEASE

**Fetal Circulation.** During fetal life, blood flows from the fetus by way of the umbilical artery to the placenta, where it exchanges carbon dioxide and other waste products for oxygen and nutritive material. The oxygenated blood returns to the fetus through the umbilical vein; part of it goes directly into the inferior vena cava by way of the ductus venosus, and the remainder passes through the liver on its way to the heart. The blood entering the heart from the inferior vena cava is therefore a mixture of oxygenated and deoxygenated blood. The blood from the

superior vena cava passes directly to the right ventricle through the tricuspid orifice, while the blood from the inferior vena cava divides into two streams, one directed into the right ventricle and the other through the open foramen ovale into the left atrium. In this way a part of the blood entering the right atrium is shunted directly to the left atrium and ventricle and out through the aorta without passing through the lungs. The blood which enters the right ventricle is directed toward the lungs, but, since the lungs are not expanded, most of it is shunted into the

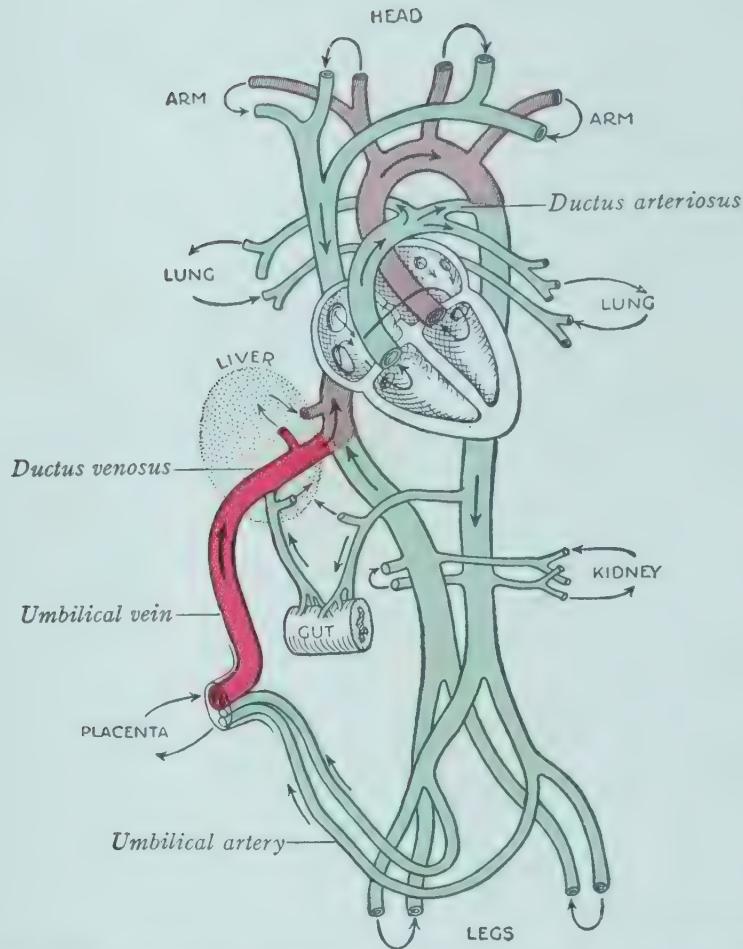


FIG. 249. Plan of the human circulation before birth (partly after Dodds). Colors show the quality of the blood, and arrows indicate its direction of flow (Arey).

aorta by way of the ductus arteriosus, which connects the pulmonary artery and aorta. Thus the blood in the aorta which circulates to all parts of the body is a mixture of partly oxygenated and deoxygenated blood. A portion flows by way of the hypogastric arteries to the umbilical arteries and then to the placenta (Fig. 249).

**Circulation in the Newborn Infant.** Changes in circulation occur rapidly after birth. When the cord is clamped and the lungs expand, the pulmonary circulation increases greatly in volume. The foramen ovale, the ductus arteriosus and ductus venosus are no longer needed, but their closure proceeds gradually. The foramen ovale is functionally closed by the third month of life, although it is possible to pass a probe through the overlapping flaps in 25 per cent of adults (Patton). In the studies of Christie the ductus was closed in 88 per cent of infants by the end of the eighth week, and the foramen ovale was closed in 87 per cent of infants by the end of the twelfth week. During this

period of adjustment there are rarely physical signs of patency of these structures. On rare occasions emboli to the abdominal aorta and its branches (especially mesenteric) may arise from thrombosis in the ductus arteriosus.

**Incidence of Congenital Heart Disease.** The two important conditions which produce cardiovascular diseases in children are congenital heart disease and rheumatic fever. The introduction of antimicrobial agents for the treatment and prophylaxis of streptococcal infections has resulted in a large decrease in the incidence of acute rheumatic fever within the last decade. Simultaneously great advances have been made in the diagnosis and surgical treatment of congenital cardiovascular diseases. In centers where diagnostic and surgical facilities are available new patients with congenital heart disease are almost ten times more frequent than those with acute rheumatic fever.

MacMahon found an incidence of congenital heart disease of about three per 1000 at birth and one per 1000 at the age of ten



years. In a study of 60,000 infants Richards and her associates found that 0.83 per cent had congenital heart disease. Cardiovascular malformations account for about 50 per cent of the deaths caused by congenital defects in the first year of life. It is difficult to establish the frequency of various lesions from published reports because these data depend on the source of the material, e.g., the age of the patient and whether the study was based on pathologic or clinical material (Table 100).

**Etiology.** *Maternal disease* influences the bodily structures of the fetus. German measles in the mother during the early weeks of pregnancy may interrupt development of the fetus with resulting deformities of the heart, eyes, ears and other tissues. The offspring of rats maintained on diets deficient in vitamin A often have defects of the heart and great vessels as well as of other structures (Warkany and Wilson). It seems possible that other infections and nutritional disorders of the mother may be factors causing congenital heart disease.

The role of *heredity* as an etiologic factor is not understood. Congenital heart lesions are recorded in two and even three generations of a family (Taussig); Abbott observed congenital heart disease more frequently in sibships than in their preceding or succeeding generations. From the data available it would seem unwise to discourage parents of

a child with congenital heart disease from having additional children.

The *incidence of other congenital defects* among patients with congenital heart disease is apparently greater than among those with normal hearts. Mongolism is frequently associated with persistent atrioventricular canal or ostium primum defects. Coarctation of the aorta occurs in Turner's syndrome. Diseases of the aorta and the aortic valve occur frequently in Marfan's syndrome and may result in dissecting aneurysm of the aorta in adult life. Cataracts, deafness and skeletal defects have been noted with increasing frequency in patients with congenital cardiac lesions. Among the 1000 patients with congenital heart disease reported by Abbott, 188 patients had anomalies elsewhere in the body, and Vierordt noted that 80 of a group of 700 patients with congenital heart disease had multiple congenital lesions. A knowledge of the types of defects which tend to occur in combinations may help in diagnosis and in a better understanding of the etiologic factors.

**Diagnosis of Congenital Heart Disease.** The development of surgical procedures effective for certain of the congenital cardiovascular defects has made it incumbent to make as accurate a diagnosis as possible. Most often the diagnosis can be established from the history, physical findings and customary roentgenographic and electrocardi-

Table 100. Relative Frequency of Congenital Cardiac Defects

Defect	Per Cent Incidence			
	Abbott	Wood	Nadas	Ober and Moore
Pulmonic stenosis with ventricular septal defect.....	11.5	20.0	9.5	4
Patent ductus arteriosus.....	10.5	14.5	17.5	—
Coarctation of the aorta.....	8.5	8.0	10.9	11
Ventricular septal defect.....	6.2	12.0	11.8	18
Transposition of the great vessels.....	4.9	1.0	6.2	27
Pulmonic stenosis with intact ventricular septum.....	3.5	12.0	14.4	—
Atrial septal defect.....	3.3	17.5	16.8	—
Dextrocardia.....	2.9	—	—	—
Cor biloculare or triloculare.....	2.7	—	—	12
Aortic stenosis.....	2.3	3.0	—	—
Truncus arteriosus.....	2.1	—	1.9	—
Tricuspid atresia.....	1.6	3.0	2.9	—
Aortic atresia.....	1.2	—	—	—
Aortopulmonary septal defect.....	1.0	—	—	—
Anomalous pulmonary venous return.....	0.4	—	2.2	—
Miscellaneous.....	37.4	9.0	5.9	28

Abbott's series is based on 1000 autopsies, Wood's on 200 clinically studied cases, Nadas' on 577 cases (clinical and autopsy), and Ober and Moore's on 100 autopsies in infants dying in the first month of life.

ographic examinations. When doubt exists, cardiac catheterization, angiocardiology and aortography often supply the necessary confirmatory information. The greatest difficulty is encountered in young infants and children suffering from such severe circulatory failure that intricate diagnostic procedures might threaten life.

**Classification of Congenital Heart Disease.** Abbott established the custom of dividing congenital heart diseases into two groups: (1) those with cyanosis at rest, and (2) those without cyanosis or who manifest it only under certain adverse conditions, e.g., high pulmonary resistance. Taussig makes a similar division on the basis of malformations which do or do not permit an adequate supply

of oxygen to the body. This classification has been criticized, and other more complicated ones have been suggested; they depend on hemodynamic and anatomic factors, including the direction of shunt. In congenital heart disease persistent cyanosis is usually caused by the shunting of venous blood from the right to the left side of the heart, so that it passes into the systemic circulation without being oxygenated in the lungs. In this text the following classification of the more common anomalies will be used: (1) right-to-left shunts (i.e., with cyanosis), (2) left-to-right shunts (i.e., without cyanosis), (3) no shunt at all. It is appreciated that there is overlapping in these groups.

## CONGENITAL CARDIAC DISEASE WITH CYANOSIS (DOMINANT RIGHT-TO-LEFT SHUNT)

### TETRALOGY OF FALLOT

The combination of (1) pulmonary stenosis, (2) ventricular septal defect, (3) dextroposition of the aorta, and (4) right ventricular hypertrophy constitutes the tetralogy of Fallot. It is the most common condition accompanied by persistent cyanosis and accounts for 75 per cent of cyanotic congenital heart disease in patients over the age of one year. The most common site of stenosis is in the outflow tract of the right ventricle (infundibular), but not infrequently it is valvular or both infundibular and valvular (Brock). The outflow tract of the right ventricle and pulmonary artery are usually smaller than normal. The ventricular septal defect is located in the membranous portion of the ventricular septum in close proximity to the aortic valve. Dextroposition of the aorta indicates that its root is displaced to the right, so that it appears to override both ventricles. The aorta, which is usually large, has a right-sided arch in 20 to 25 per cent of cases (Taussig). A persistent left superior vena cava has been described in 20 per cent (Wood).

**Hemodynamics.** Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts, it meets resistance at the pulmonary stenosis and shunts some of its blood across the ventricular septal defect into the aorta. This results in persistent arterial unsaturation and cyanosis. The pulmonary blood flow is re-

stricted by the obstruction at the pulmonary valve, but may be supplemented by bronchial collateral circulation and occasionally by a patent ductus arteriosus. The systolic and diastolic pressures in each ventricle are similar, as well as the mean pressures in the atria. A measurable gradient of pressure is always detected across the outflow of the right ventricle, owing to the pulmonary stenosis.

It appears that the two major defects in the tetralogy of Fallot are the pulmonary stenosis and the ventricular septal defect. When these conditions exist without right-to-left shunt, the anomaly has been termed *acyanotic Fallot* (see *Pulmonary Stenosis with Ventricular Septal Defect*, p. 870).

**Clinical Manifestations.** *Cyanosis*, one of the outstanding manifestations of the tetralogy, may not be present at birth. It appears that as long as the ductus arteriosus remains open, sufficient blood passes through the lungs to prevent cyanosis. As it closes during the first months of life, cyanosis may become apparent gradually or develop suddenly when the infant has an infection. The cyanosis is most prominent in the mucous membranes of the lips and mouth and in the fingernails and toenails, but the entire skin surface has a dusky, bluish color. The scleras are gray, and the blood vessels at the periphery are likely to be engorged, giving the appearance of a mild conjunctivitis. The blood vessels of the retina are large and dark. The mucous membranes of the pharynx



are purple, and the tongue is deep blue and often large and fissured, with prominent papillae. The gums are frequently inflamed and bleed easily from light pressure. The teeth are normal in size and shape, but their eruption may be delayed; histologic examination reveals dilatation and engorgement of the capillaries in the dental pulp and poor calcification of the dentin. *Clubbing* of the ends of the fingers and toes is a conspicuous sign; the underlying bone may be involved. *Hemoptyses* may be recurrent, some of which may be due to thromboses of the smaller pulmonary arteries.

*Dyspnea* occurs on exertion. Infants and young children will play actively for a short time and then sit or lie down. Older children may be able to walk a block or so before stopping to rest; many of them rest by *squatting* for a few moments or by sitting with their feet elevated. The capacity for exercise depends on the severity of the cardiac lesion, which is often reflected by the intensity of the cyanosis. Young children may have syncopal attacks lasting for a few moments to a few hours after exercise or emotional excitement, possibly the result of cerebral anoxia. The child usually learns his capacity for exertion, and these attacks occur less often with advancing age.

*Paroxysmal dyspneic attacks* are a particular problem during the first two years of life. They may occur spontaneously or follow feeding or a spell of crying. The child becomes dyspneic and intensely cyanotic, cries weakly or loudly as if in pain and may soon lose consciousness, with or without convulsions. Some infants have been noted to clutch or scratch over the anterior chest as if they had precordial pain, somewhat reminiscent of hypercyanotic angina pectoris of older patients. The attacks may last from a few minutes to several hours and are occasionally fatal. Spontaneous recovery from these attacks is followed by deep sleep for a few hours. Depending on the frequency and severity of the attacks, one or all of the following procedures should be tried in sequence: (1) placement of the infant on his abdomen in the knee-chest position, making certain that there is no constricting clothing; (2) administration of oxygen; (3) injection of morphine in doses of 1 mg. per 10 pounds of body weight; this is especially effective.

*Growth and development* may be delayed. The stature and nutritional status are usually below the average for the age, and the

muscles and subcutaneous tissues are flabby and soft. Puberty is delayed.

The *pulse* is usually normal, as are the venous and arterial pressures. The left anterior chest may bulge forward. The heart is usually normal in size, and the apical impulse is tapping in nature. A *systolic thrill* is felt in 50 per cent of cases along the left sternal border in the third and fourth parasternal spaces. Owing to the pulmonic stenosis, the normal pulmonary artery pulsation in the second left interspace is commonly absent.

The *systolic murmur* heard along the left sternal border is usually loud and harsh, and maximal in the third and fourth left parasternal spaces. The systolic murmur is an ejection type and finishes before the aortic element of the second sound. The second sound at the base is single, owing to the absence of the pulmonary element. In a small number of cases the systolic murmur may be followed by a blowing diastolic murmur heard over any part of the precordium or in the back between the scapulae. This diastolic murmur is produced by enlarged bronchial collateral vessels and rarely by persistence of a patent ductus arteriosus, but occurs most frequently in pulmonary atresia.

*Polycythemia* and an elevated *hematocrit* value are usual. The defects in coagulation have been described (p. 831).

The *exercise test* devised by Bing demonstrates that there is no increase in oxygen consumption per liter of ventilation during exercise. This test, positive in about 75 per cent of cases, suggests the presence of pulmonary stenosis, which prevents an adequate increase of the pulmonary circulation during exercise.

**Roentgen Examination.** The typical configuration in the anteroposterior position consists of a narrow base, concavity of the left border in the area usually occupied by the pulmonary artery and a normal heart size. The rounded apical shadow situated rather high above the diaphragm is produced chiefly by the hypertrophied right ventricle and has been likened to the shape of a sheep's nose; the entire cardiac silhouette, to that of a wooden shoe (*coeur en sabot*) (Fig. 250). In the right anterior oblique view the configuration is accentuated. The shadow of the large right ventricle approaches and may touch the anterior chest margin, and there is a deep concavity immediately above it where the pulmonary artery is usually seen in the normal patient. In the



FIG. 250. Teleroentgenogram of a patient with tetralogy of Fallot. Note the pulmonary undervascularity, normal heart size, elevation of the apex of heart and a concavity in the region of the main pulmonary artery.

left anterior oblique view the right ventricle tends to encroach upon the anterior chest wall, the left ventricle may be clear of the vertebral column, and the pulmonary window is clear. In many patients the hypertrophied right ventricle displaces the normal left ventricle posteriorly so that the latter chamber partly overlies the spine.

The aorta is usually large, and its position is important. In about 20 per cent of instances the aorta arches to the right instead of the left; this may be clearly visible in the anteroposterior view or may be confirmed by displacement of the barium-filled esophagus to the left. In the left oblique view a right aortic arch may indent the esophagus.

The hilar areas of the lungs are relatively clear and usually pulsate little or not at all, owing to the absence of normal pulmonary vessels. The lung fields are remarkably clear for the same reason; this constitutes an important diagnostic sign which may be detected either by fluoroscopy or in roentgenograms.

Variations from the typical radiographic picture include exaggeration of the shadow of the pulmonary artery usually associated with valvular pulmonic stenosis (Fig. 251). Occasionally pulmonary vascularity is made prominent by a reticular pattern of collateral bronchial circulation which radiates from the hilus of the lungs (Fig. 252). In the oblique projections the right ventricular shadow may be normal or recede in a manner suggestive of an underdeveloped right ventricle. The electrocardiogram is much more accurate in

the assessment of ventricular dominance than is the roentgenographic examination.

**Electrocardiography.** The electrocardiogram reveals evidence of right ventricular hypertrophy, clockwise rotation and often tall, spiked P waves. Evidence of right ventricular dominance, without which the diagnosis of tetralogy of Fallot is unlikely, is found in the right precordial chest leads and in the unipolar right arm lead (Figs. 239, 240).

**Other Tests.** In the majority of instances the diagnosis of tetralogy of Fallot can be made with the aid of the foregoing studies, but doubtful cases would require cardiac catheterization or angiocardiology to help elucidate the anatomic anomalies.

**Cardiac catheterization** reveals systolic hypertension in the right ventricle and a sudden fall of pressure as the catheter enters the infundibular chamber or pulmonary artery. Serial pressure determinations taken from the region of stenosis of the right ventricular outflow tract may in some instances differentiate between valvular and subvalvular stenosis. In valvular stenosis the change in pressure from the pulmonary artery to the right ventricle is abrupt, whereas in infundibular stenosis the change is less abrupt, but may show three pressure differentials as the catheter tip is withdrawn from the pulmonary artery, the infundibular chamber and right ventricle, respectively (Fig. 253). The systolic pressure in the right ventricle is



FIG. 251. One of the variants in the teleroentgenogram in tetralogy of Fallot. The stenosis was localized to the pulmonary valve, and poststenotic dilatation of the pulmonary artery is evident. The intrapulmonary vascularity is decreased.



usually between 60 and 90 mm. of mercury.

The mean pulmonary artery pressure is commonly between 5 and 10 mm. of mercury, and the right atrial pressure is usually normal. The aorta may be entered from the right ventricle through the ventricular septal defect (Fig. 247, I). Samples of blood from the venae cavae, right atrium, right ventricle and pulmonary artery are frequently similar in oxygen content, indicating absence of a left-to-right shunt. In many patients, how-

ever, a left-to-right shunt is demonstrated at the ventricular level (Table 98).

*Selective angiocardiology* is of great value. The injection of contrast material into the right ventricle demonstrates the outflow tract and identifies the site of stenosis. The presence and location of infundibular and/or valvular stenosis are clearly visualized, and their behavior can be studied during systole and diastole. Simultaneous opacification of the aorta by the passage of contrast medium



FIG. 252. Aortogram in tetralogy of Fallot demonstrating the possible collateral circulation to the lung. A, The thoracic and abdominal aorta and their branches are visualized. The left pulmonary artery fills from a patent ductus arteriosus. The right pulmonary artery is absent, and the right lung is supplied by a large bronchial artery arising from the third intercostal artery. This patient had a gratifying clinical improvement after a left Blalock-Taussig operation. B, Same aortogram as in A. The details of the descending thoracic aorta, left pulmonary artery and large bronchial artery are demonstrated.

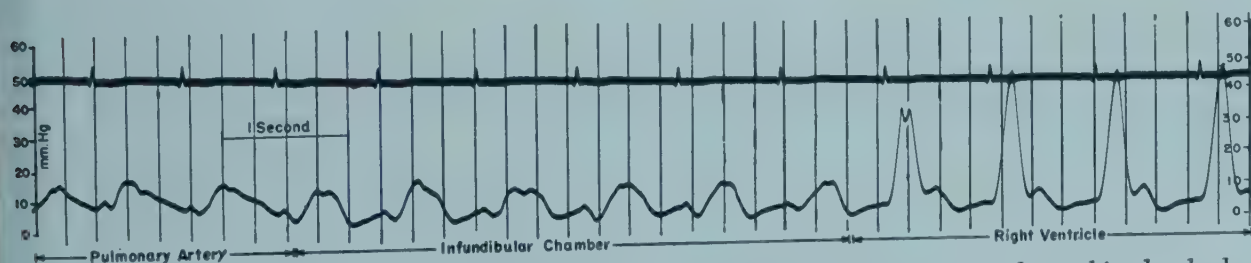


FIG. 253. Pressure curve obtained during cardiac catheterization in a patient with combined valvular and infundibular pulmonary stenosis and a ventricular septal defect. The upper tracing is the electrocardiogram. The lower tracing is a continuous record of pressure as the catheter was withdrawn from the pulmonary artery to the right ventricle. Three pressure differentials are noted, corresponding to the pulmonary artery, infundibular chamber and right ventricle. The right ventricular pressure is higher than that in the infundibular chamber and pulmonary artery and indicates the presence of pulmonary stenosis. Infundibular stenosis is recognized because the diastolic pressure in this area is lower than that in the pulmonary artery and the same as in the right ventricle. In many patients the systolic pressure in the infundibular chamber exceeds the pulmonary artery systolic pressure, but is lower than the right ventricular systolic pressure.

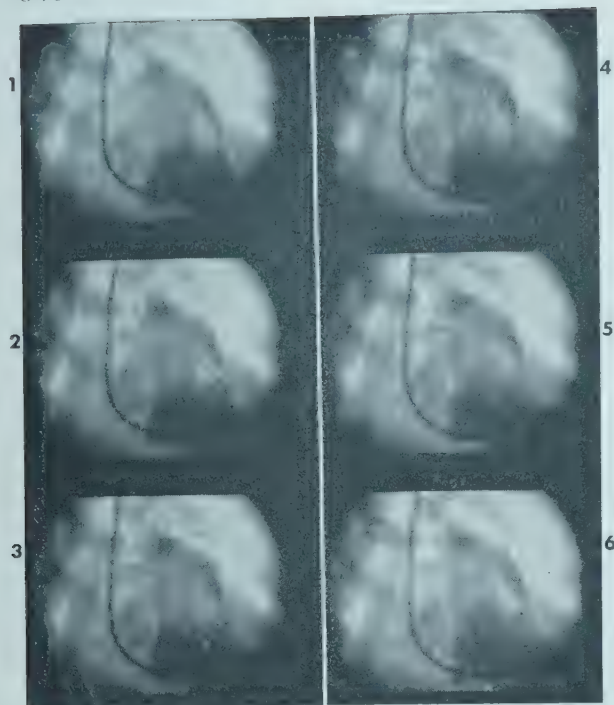


FIG. 254. Selective cine-angiogram in a patient with tetralogy of Fallot. Film speed is 60 frames per second. The tip of the catheter is in the right ventricle, and the patient is in the left posterior oblique projection. The contrast medium in the lower right of each frame is in the cavity of the right ventricle. A constant obstruction to the outflow of the right ventricle is seen anteriorly, and the infundibular chamber is visualized. Simultaneous opacification of the aorta from the right ventricle is confirmed by the presence of contrast medium in the descending aorta anterior to the vertebral column.

through the ventricular defect is also clearly identified.

The *circulation time* from arm to tongue is shortened because the blood entering the right ventricle is shunted into the systemic circulation through the overriding aorta.

**Prognosis.** Without operation the prognosis varies with the severity of the pulmonary stenosis and the amount of collateral circulation. Deeply cyanotic children who have dyspnea on slight exertion rarely live until late childhood. Others may succumb during the adolescent period, and a few may live beyond the third decade. In early childhood fainting and paroxysmal dyspnea may occur after exertion or excitement. Some children die in such attacks; anoxia or thrombosis of a vessel in a vital organ, usually the brain, may be the terminal event. The incidence of a variety of disorders is higher than in average children; these include pulmonary tuberculosis, pyogenic respiratory infections, pulmonary artery thromboses, sub-

acute bacterial endocarditis and brain abscess. Congestive heart failure is unusual.

**Treatment. General management.** Although the majority of patients require surgical treatment, astute management is necessary prior to surgery. The prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. The treatment of paroxysmal dyspneic attacks has been described (p. 843). Intercurrent infections should be vigorously treated with suitable antibiotics. Nadas and Rudolph have shown that correction with iron therapy of a "relative hypochromic anemia" may improve the exercise tolerance and general well-being. It appears that the safest level of the hematocrit is between 55 and 65 per cent. Cautious repeated venesection may be indicated if the hematocrit value is above 70 per cent, because at this level there is a high incidence of thromboses, especially cerebral.

**Surgical. ANASTOMOTIC PROCEDURES.** Taussig observed that the prognosis was better when the ductus arteriosus was patent. She and Blalock devised the operation whereby an artificial ductus is created by anastomosis of a branch of the aorta to the homolateral branch of the pulmonary artery. The most common procedure is an end-to-side anastomosis of a subclavian artery to the pulmonary artery. Potts and his associates achieved the same objective by side-to-side anastomosis of the aorta to the pulmonary artery.

There are no rigid criteria for choosing between a Blalock-Taussig or Potts procedure. In the former the inner opening of the anastomosis depends on the inner diameter of the subclavian artery, whereas in the Potts procedure the size of the side-to-side anastomosis does not depend on the caliber of the vessels and therefore may be preferable in children under the age of two or three years. If the aorta arches to the right, the Potts procedure is not technically possible. When tetralogy of Fallot is associated with dextrocardia, the vessels for anastomosis should be identified by angiocardiography, and the operation of choice would depend on the relationship of these arteries. During the Potts procedure mobilization of the aorta may require sacrificing precious bronchial vessels, which would be undesirable in patients in whom a large bronchial collateral flow is suspected.

The *operative risk* varies with the age of



the patient, the mortality rates being higher in infants and adults. The best results are obtained in children between the ages of two years and puberty. However, if incapacitating symptoms occur before the age of two years, operation is urgently indicated. The surgical mortality rate in patients between the ages of two and twelve years is less than 5 per cent, whereas in infants and adults the rate may be as high as 20 per cent.

The *postoperative course* of 90 per cent of patients with a successful anastomosis is smooth, and the child should be ambulatory within three to seven days. In addition to the usual postoperative complications following a thoracotomy, chylothorax, Horner's syndrome and postoperative cardiac failure may occur. Chylothorax is due to trauma to the thoracic duct or its tributaries and is treated with repeated thoracenteses. Horner's syndrome is usually temporary and does not require treatment. Postoperative cardiac failure may be due to the large size of the anastomosis; its treatment is described on page 897. Other rare complications include endothelialization of the anastomotic site with the obstruction of blood flow, subacute bacterial endarteritis and vascular changes in the upper extremity supplied by the subclavian artery which has been used for anastomosis.

After a successful anastomosis there is a striking improvement in symptoms. Exercise tolerance is increased, and the habit of squatting is discontinued. The degree of cyanosis and clubbing diminishes. A machinery-type murmur, sometimes accompanied by a thrill, is detected after operation. This murmur is indicative of a functioning anastomosis and is permanent.

**BROCK PROCEDURE.** Brock has suggested a direct surgical attack on the pulmonary stenosis by pulmonary valvotomy if the stenosis is valvular, or infundibular resection if the outflow tract of the right ventricle is stenosed. With these procedures about two thirds of patients are greatly improved, one sixth are benefited and nearly one sixth die, the mortality rate being higher with infundibular resection (Campbell, Deucher and Brock).

**DIRECT-VISION INTRACARDIAC SURGERY (WITH A PUMP OXYGENATOR).** Theoretically, the ideal surgical therapy is relief of pulmonary stenosis and closure of the ventricular septal defect. This form of therapy is now being utilized with the aid

of a pump oxygenator. While the patient's circulation is temporarily maintained by an artificial heart-lung machine, the right ventricle is opened extensively, the infundibular stenosis resected, coexistent valvular pulmonary stenosis is relieved, and the ventricular septal defect is closed. If indicated, the outflow tract of the right ventricle is enlarged by placing a plastic prosthesis anteriorly at and below the pulmonary valve.

**CHOICE OF SURGICAL PROCEDURE.** Before parents can be advised which of the foregoing procedures should be undertaken for the child, the physician must be aware of the immediate surgical risks as well as the expected long-term results. It has been pointed out that operative risk with the anastomotic procedures is low and the immediate clinical improvement gratifying. However, some incapacity frequently remains, and, although cyanosis, clubbing and polycythemia are greatly reduced, they are seldom abolished. Some years after the anastomosis the clinical condition may deteriorate, requiring a second anastomosis, on the opposite side. A complication which is now becoming apparent is the development of severe pulmonary hypertension many years after the anastomosis was made.

The Brock procedure has a higher mortality rate than the anastomotic operation, but the immediate clinical improvement is better, especially after infundibular resection. Adequate relief of pulmonary stenosis leaves the patient with a ventricular septal defect which in later years may result in severe pulmonary hypertension and heart failure.

There appears to be little doubt that the theoretic procedure of choice is direct-vision, open heart surgery. This results in relief or improvement of the pressure gradient from the right ventricle to the pulmonary artery and abolishes the right-to-left shunt across the ventricular septal defect. In successful cases the results are spectacular with disappearance of symptoms and signs of anoxia. However, at this time, the mortality rate is still high (10 to 30 per cent), the lower mortality rate comprising selected cases. Further, sufficient time has not elapsed for evaluation of long-term results. It may be argued that anastomotic procedures could be used as temporizing therapy while the results of the direct approach are being improved and evaluated. However, the risk of surgery with the pump oxygenator may be higher if a patient has had a previous thoracotomy.

Therefore at present the choice of the surgical procedure is still not clear, but direct-vision surgery holds the most promise.

### PULMONARY ATRESIA

Complete obliteration of the main pulmonary artery and the pulmonary valve is always associated with a ventricular septal defect and usually with dextroposition of the aorta. The hemodynamics are similar to those of tetralogy of Fallot except that the pulmonary blood flow is dependent on the bronchial collateral flow or, in some instances, on a large patent ductus arteriosus.

The *clinical manifestations* are much the same as those of the tetralogy with the following exceptions: Cyanosis usually appears within a few days after birth in contrast to later in the first year in the tetralogy. The systolic murmur is absent or is softer and is not characteristic. The second sound at the base is moderately loud and never split. Continuous murmurs due to bronchial collateral flow may be heard anywhere in the chest, anteriorly or posteriorly, but are usually heard best under the clavicles. The heart may be enlarged, and the deep indentation of the left border is the same as that produced by the tetralogy. The reticular pattern of the bronchial collateral flow is shown roentgenographically.

The diagnostic study of choice is *selective angiocardiology* with injection of contrast medium into the right ventricle. Although the main pulmonary artery is atretic, its two primary branches may be of sufficient caliber to allow an anastomotic procedure. Either the left or the right pulmonary artery may be absent in association with other defects of tetralogy of Fallot. This is suspected when the pulmonary vascularity is heavy on one side and decreased on the other. These patients can be benefited by a Blalock-Taussig anastomosis on the side of the pulmonary artery.

### TRICUSPID ATRESIA

Atresia or stenosis of the tricuspid valve is accompanied by underdevelopment of the right ventricle and pulmonary stenosis or atresia. Little or none of the blood entering the right atrium can gain access to the right ventricle and must escape to the left atrium by way of the foramen ovale or a gross defect in the interatrial septum. In the left atrium the mixture of blood passes into the left



FIG. 255. Teleroentgenogram in tricuspid atresia with underdeveloped right ventricle (see text).

ventricle, and through the aorta to the systemic circulation. The pulmonary circulation is derived from the systemic blood, which reaches the lungs either through a ventricular septal defect, patent ductus arteriosus or enlarged bronchial arteries.

**Clinical Manifestations.** Cyanosis, polycythemia, exertional dyspnea and anoxic hypercyanotic (paroxysmal dyspneic) attacks develop early. After infancy, clubbing and squatting are usually present. Owing to the tricuspid stenosis, the pressure in the right atrium is increased, resulting in a prominent jugular venous "a" wave. In a similar way, the liver is frequently enlarged and may exhibit an intrinsic presystolic pulsation. The heart may or may not be enlarged with a heaving left ventricular apical impulse. In very ill small infants, murmurs may not be prominent, but in the majority of instances a harsh systolic murmur is audible maximally down the left sternal border. The second heart sound is single, owing to absence of the pulmonary element.

*Roentgenographic studies* demonstrate pulmonary undercirculation and deficiency of shadows of the pulmonary artery segment (Fig. 255), but the shape of the cardiac silhouette is not always distinctive and in some cases may resemble that of tetralogy of Fallot. Although the right ventricle is small, its shadow may or may not be decreased in the oblique projections. In fact, the positional displacement caused by the hypertrophied left ventricle may produce a radiologic picture of an enlarged right ventricle.

The *electrocardiogram* is a much more



sensitive index of the state of the ventricles. In normal infants a prominent R wave in the right ventricular surface leads is produced by a summation of the electrical activity of the interventricular septum and right ventricle. In tricuspid atresia with underdeveloped right ventricle the r wave in the right ventricular surface leads is produced by activation of the interventricular septum only and is therefore small and is followed by a deep S wave. Left ventricular dominance is suggested by S-T segment and T wave abnormalities in the left ventricular surface leads. The electrical position is also unusual in these patients, and aVR commonly shows a Q-S pattern. The heart is commonly horizontal, but may on occasion be vertical. The P waves are usually tall and spiked.

*Cardiac catheterization* shows an elevated right atrial pressure with a prominent "a" wave in the pressure curves taken from the right atrium and cavae. If the catheter is introduced from the saphenous vein into the inferior vena cava and right atrium, it usually passes with ease across the foramen ovale or atrial septal defect into the left atrium or pulmonary veins (Fig. 247, C, E.).

With *selective angiocardiology* there is immediate opacification of the left atrium from the right atrium followed by left ventricular filling and visualization of the aorta (Fig. 256). The pulmonary artery or its branches may be demonstrated because these

structures receive blood from a patent ductus arteriosus or from the left ventricle across a ventricular septal defect. On occasion the diminutive right ventricular chamber is visualized.

**Prognosis and Treatment.** The prognosis is poor, and many infants fail to survive the first few months of life unless collateral circulation to the lungs is adequate. Improvement may occur from anastomosis of the aorta or one of its branches to the pulmonary artery, but the results are not as gratifying as with the treatment of tetralogy of Fallot. Disappointing postoperative results may occur, owing to inadequacy of the defect between the atria or because of left ventricular failure. With good results the postoperative clinical course is similar to that described under Tetralogy of Fallot (p. 847).

### EISENMENGER SYNDROME

The term "Eisenmenger syndrome" is used here for the combination of pulmonary hypertension with reversed shunt either through a ventricular septal defect, atrial septal defect or patent ductus arteriosus (or other communications between the aorta and lesser circulation). This concept implies that the major physiologic abnormality is elevation of the pulmonary vascular resistance. In normal infants at, or soon after, birth the pulmonary vascular resistance is high, probably owing

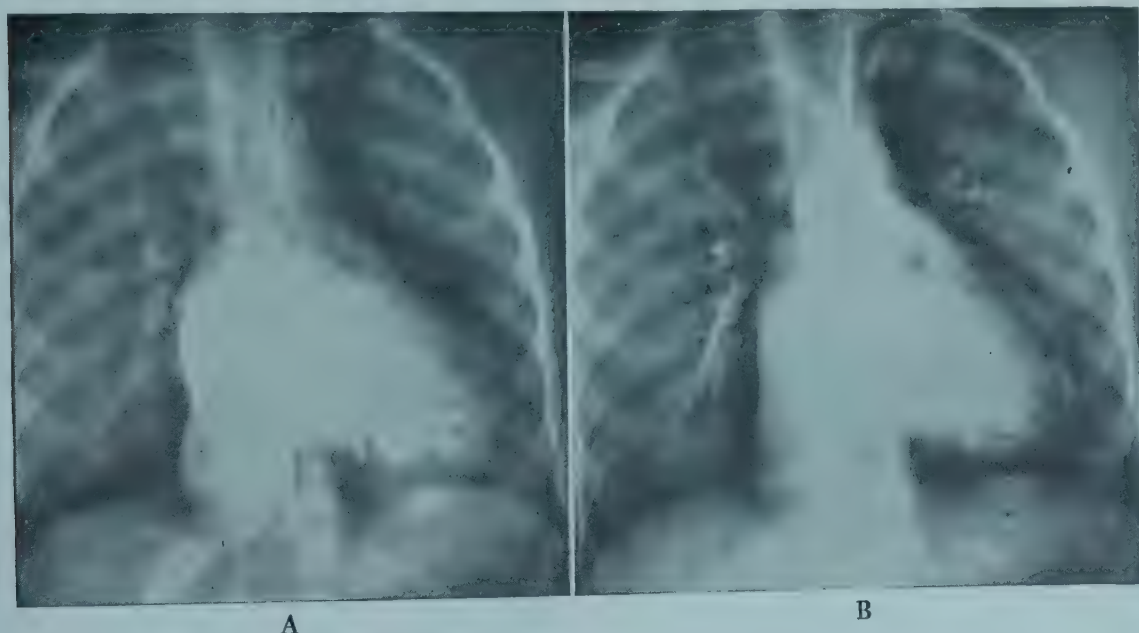


FIG. 256. Angiogram in tricuspid atresia with underdeveloped right ventricle. A, 1.5 seconds after injection of contrast medium. The contrast substance has opacified the right atrium and passed across an atrial septal defect into the left atrium and left ventricle. B, 2 seconds after injection of contrast medium. Note opacification of the aorta and its branches and the pulmonary artery. The right ventricle was not visualized.



FIG. 257. Teleroentgenogram in Eisenmenger syndrome due to a ventricular septal defect. Note the dilatation of the pulmonary artery and gross pulmonary overvascularity.

to relatively small lumens of the arterioles. Within a few months the structure of the pulmonary arterioles changes to that of the adult pattern with a thin wall and a large lumen, and the pulmonary vascular resistance falls to normal adult levels. In the Eisenmenger syndrome the pulmonary vascular resistance remains high; this abnormal resistance is probably present from birth (Edwards, Dammann).

**Clinical Manifestations.** Symptoms are usually present within the first year of life, especially in patients with ventricular septal defect. These include dyspnea, feeding difficulties, fatigue, failure to gain weight and recurrent attacks of pneumonia. As the child gets older effort dyspnea is obvious, especially when there are ventricular and atrial septal defects. Squatting, angina pectoris, hemoptysis and episodes of syncope occur occasionally. Cyanosis, which may be present early, increases in intensity as the child approaches puberty and is associated with clubbing and polycythemia. In patent ductus arteriosus, venous blood from the pulmonary artery is shunted down the descending aorta. This may result in differential cyanosis (blue lower extremities and pink upper extremities), but this sign is not common in children.

The venous pressure is increased when congestive heart failure or functional tricuspid insufficiency is superimposed. The heart size is extremely variable, being normal in many cases with ventricular defect, but usually enlarged with atrial defect. A conspicu-

ous left parasternal, right ventricular heave with palpable pulmonary artery pulsations is frequent. Although a systolic murmur is usual, it varies in intensity, but there may be none. The second heart sound is closely split or single in many cases of ventricular defect, but is widely split in atrial defect. Functional incompetence of the pulmonary valve (Graham Steell murmur) resulting in a blowing diastolic murmur down the left sternal border is common and is associated with a normal peripheral pulse.

*Roentgenographically*, the heart is found to vary in size from normal to greatly enlarged. The larger hearts are seen with atrial defects and the smaller ones with ventricular defects, but there is a large overlap. The pulmonary artery is usually enlarged. The pulmonary vessels are enlarged in the hilar areas and diminish in caliber in the peripheral branches. The right ventricle and atrium are prominent.

The *electrocardiogram* frequently shows right ventricular hypertrophy, occasionally associated with incomplete right bundle branch block. The P wave may be tall and spiked. Sometimes the electrocardiogram is balanced and does not reveal the ventricular hypertrophy.

*Cardiac catheterization* usually shows a bidirectional shunt at the site of the defect; e.g., in patients with a ventricular septal



FIG. 258. Teleroentgenogram in Eisenmenger syndrome due to a patent ductus arteriosus. The heart size is normal, the pulmonary artery segment is dilated, and the pulmonary vascularity is normal or slightly increased.



defect a left-to-right shunt is demonstrated at the ventricular level and is associated with a decrease in the arterial oxygen saturation due to the right-to-left shunt. There is, of course, a definite decrease in arterial oxygen saturation when there is only a right-to-left shunt. The catheter frequently traverses the defect, especially in patent ductus arteriosus and in atrial septal defect. The systolic pressures are usually equal in the systemic and pulmonary circulations. The pulmonary vascular resistance is elevated. *Dye dilution curves* demonstrate the bidirectional shunts or the unidirectional right-to-left one. *Selective angiocardigraphy* is helpful in locating the site of the shunt. In patent ductus arteriosus contrast medium enters the descending aorta from the pulmonary artery.

**Treatment.** The presence of the Eisenmenger syndrome contraindicates surgical closure of the defect. The results of attempts at surgical correction have most often been disastrous. However, it should be understood that pulmonary hypertension with increased pulmonary blood flow, but without a right-to-left shunt, is not the Eisenmenger syndrome and does not contraindicate surgery. In these patients surgery is lifesaving. Medical treatment of the Eisenmenger syndrome is entirely symptomatic.

### TRANSPOSITION OF THE GREAT VESSELS (ARTERIES)

In this condition the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. The systemic veins return to the right atrium, and the pulmonary venous return is to the left atrium. Thus the blood from the right side of the heart passes to the aorta. The pulmonary venous blood is returned to the lungs. The two independent circuits do not support life unless the foramen ovale or the ductus arteriosus remains open or unless there is a defect in the atrial or ventricular septum to permit some mixture of blood. This condition accounts for the majority of deaths in infants under the age of one year with cyanotic congenital heart disease (Ober and Moore).

**Clinical Manifestations.** Dyspnea, retardation of growth and signs of congestive heart failure are frequent. Cyanosis makes its appearance shortly after birth. Differential cyanosis occurs in some patients in whom the lower extremities are less cyanotic than the rest of the body. The difference in color may be obvious if the child's hand is placed by

the side of his foot. This difference is due to patency of the ductus arteriosus and not uncommonly is associated with coarctation of the aorta above the entry of the ductus. Because the pulmonary artery pressure may be higher than that of the descending aorta, oxygenated blood enters the aorta from the ductus and is carried only to the lower part of the body. Anoxic, paroxysmal dyspneic attacks may occur, but not as frequently as in the tetralogy of Fallot. Murmurs are of no diagnostic significance and are absent in about 30 per cent of cases in early life. If present, the murmur is usually systolic in time and is heard over most of the precordium. The second heart sound is split. Polycythemia and arterial unsaturation are usual.

*Roentgenograms* reveal that, although the heart is enlarged, the base is comparatively narrow in the anteroposterior view, because the aortic shadow is superimposed upon that of the pulmonary artery segment (Fig. 259). In the left anterior oblique position both ventricles are found to be enlarged, and the great vessels, now lying side by side, greatly increase the basal shadows. The pulmonary vascularity is usually grossly increased. These characteristics may not appear in the early days of life, especially if the basal shadows are obscured by the thymus.

In *electrocardiograms* there is clockwise rotation, right ventricular hypertrophy and, not uncommonly, tall, spiked P waves.

*Cardiac catheterization* shows right ventricular hypertension. The catheter enters the aorta directly from the right ventricle; it may pass across the foramen ovale or an atrial



FIG. 259. Teleroentgenogram in complete transposition of the great vessels (arteries), showing cardiac enlargement and gross pulmonary overvascularity.

septal defect, or across a ventricular septal defect, into the pulmonary artery. The blood in the pulmonary artery has a higher oxygen content than that in the aorta. The shunt is usually bidirectional if there is an associated ventricular septal defect. At the atrial level the shunt is usually from right to left. If the ductus remains patent, the shunt is usually from pulmonary artery to aorta.

*Selective angiocardiography* by injection of contrast material into the right ventricle is diagnostic. It demonstrates the origin of the anteriorly placed aorta from the right ventricle and the presence or absence of an associated ventricular defect or patent ductus.

**Prognosis and Treatment.** The majority of patients succumb during infancy. The occasional child who survives to adolescence usually has an associated pulmonary stenosis and a large ventricular septal defect.

*Treatment* is symptomatic and directed toward relief of congestive cardiac failure, paroxysmal dyspneic attacks and intercurrent pulmonary infections. Surgical treatment has been attempted without much success. These procedures include the following: (1) creation of an atrial septal defect and subclavian to pulmonary anastomosis, (2) redirection of venous blood (i.e., vena caval anastomosis to the left atrium and pulmonary veins to the right atrium), (3) end-to-end anastomosis of the origin of the pulmonary artery to the aorta and the origin of the aorta to the pulmonary artery, (4) insertion of a new atrial septum to direct systemic venous blood to the left ventricle and pulmonary venous blood to the right ventricle.

#### TRANSPOSITION OF THE GREAT VESSELS (ARTERIES) IN ASSOCIATION WITH OTHER DEFECTS

**With Pulmonary Stenosis.** This condition assumes some importance because it may mimic abnormalities which are surgically treatable, e.g., tetralogy of Fallot. The time of onset of symptoms is variable from soon after birth to late infancy and depends largely on whether a ventricular septal defect is present. In such cases oxygenated blood from the left ventricle meets the resistance of the pulmonary stenosis and may result in a shunt of arterialized blood into the aorta. Manifestations include cyanosis, hypercyanotic (paroxysmal dyspneic) episodes, poor physical development and sometimes congestive heart failure. The cardiac findings are similar to those described under Tetralogy of Fallot. However, the cyanosis is usually more in-

tense, and the heart is usually larger. In contradistinction to uncomplicated transposition of the great vessels (arteries), pulmonary undercirculation is usual. During the first few months of life the electrocardiogram may resemble that found in tricuspid atresia. However, in older patients right ventricular hypertrophy, occasionally combined with left ventricular hypertrophy, is common. Selective angiocardiography is of help in making the correct diagnosis.

Patients with transposition and pulmonary stenosis benefit from a Blalock-Taussig or Potts anastomosis, but some arterial unsaturation is usual postoperatively.

**With Tricuspid Atresia.** The clinical picture is similar to that described under Tricuspid Atresia with underdeveloped right ventricle. However, because the pulmonary artery arises from the left ventricle, pulmonary overcirculation is frequent. The prognosis is extremely poor, and these patients usually succumb during infancy.

**With Single Ventricle.** The clinical picture is similar to that described under Transposition of the Great Vessels. In some instances these patients may survive to early childhood or even adolescence. Treatment is entirely symptomatic.

#### TRANSPOSITION OF AORTA AND OVERRIDING PULMONARY ARTERY (TAUSSIG-BING SYNDROME)

In this rare malformation the aorta arises from the right ventricle, and the pulmonary artery, which is large, overrides the ventricular septum. A ventricular septal defect is always present. Cyanosis is usually present from birth. A systolic murmur is usual down the left sternal border and is followed by a loud split second sound. The heart is large, the pulmonary artery prominent and the pulmonary vascularity is increased. The diagnosis is established by selective injection of contrast material into the right ventricle. The prognosis is poor, and the treatment symptomatic.

#### EBSTEIN'S DISEASE

This abnormality consists in the displacement of an abnormal tricuspid valve into the right ventricle. The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are attached to the wall of the right ventricle. The latter chamber is divided into two parts by the abnormal valve; the first is continuous with the cavity of the



right atrium, and the second consists of a thin-walled right ventricle. The right atrium is huge, and the tricuspid valve may or may not be competent.

*Symptoms* are frequently mild. Cyanosis is usually absent, but may be present with an associated atrial septal defect. Paroxysmal tachycardia may occur. The venous pressure is normal or, if there is associated tricuspid insufficiency, increased. The heart is usually greatly enlarged, but on palpation the precordium is quiet. A systolic murmur, sometimes accompanied by a thrill, is audible over most of the anterior left chest. Gallop rhythm is common, as is a diastolic murmur down the left sternal border. This murmur is superficial and may mimic a pericardial friction rub.

The *electrocardiogram* shows incomplete or complete right bundle branch block, normal or tall P waves and normal or prolonged P-R interval. *Roentgen examination* shows cardiac enlargement due to right atrial and ventricular dilatation, pulmonary undercirculation and a small aorta. This clinical picture is characteristic and does not require further study for confirmation; *cardiac catheterization* and *angiocardiography* are dangerous in these patients. In the reported cases of successful cardiac catheterization the pressures in the right heart are normal and of small amplitude. Right atrial and ventricular pressures are similar and frequently indicate the presence of tricuspid insufficiency. The arterial oxygen saturation varies and depends on the degree of right-to-left shunt across the foramen ovale; it is frequently between 85 and 90 per cent.

The *prognosis* is extremely variable, and *treatment* is entirely symptomatic.

## TRUNCUS ARTERIOSUS

This condition is due to failure of development of the aortico-pulmonary septum, resulting in persistence of the fetal common arterial trunk. A single large vessel arises from both ventricles and overlies a ventricular septal defect; the valve between the heart and the truncus is quadricuspid or bicuspid. The pulmonary arteries arise from the truncus, usually in its ascending portion.

Much confusion has arisen concerning the anatomy and hemodynamics of truncus arteriosus. The definition given above is that of *true* truncus arteriosus. When a single artery arises from the ventricles and the pul-

monary flow is supplied by enlarged bronchial vessels, this condition is pulmonary atresia and not truncus arteriosus. True truncus arteriosus in which the lungs are supplied by both pulmonary and bronchial arteries is rare.

**Hemodynamics.** Both ventricles empty their blood at systemic pressure into the truncus. In the presence of a normal pulmonary vascular resistance, the blood flow to the lungs is greatly increased, the arterio-venous oxygen difference small and cyanosis is minimal or absent. When the pulmonary resistance is high, the pulmonary circulation is inadequate, and cyanosis is intense.

**Clinical Manifestations.** Owing to the extremely variable hemodynamics, the clinical picture varies. In the presence of a large pulmonary blood flow symptoms may be mild. However, in the majority of patients dyspnea, fatigue, heart failure and poor physical development are frequent. Cyanosis, polycythemia and clubbing may be absent, minimal or intense. If the pulmonary blood flow is large, the pulse pressure is wide with the resultant peripheral signs of a water-hammer pulse. The heart is usually enlarged, and the precordium is hyperdynamic. A systolic ejection murmur, sometimes accompanied by a thrill, is usual down the left sternal border. The second heart sound is loud. Basal diastolic murmurs may be audible. These are due to insufficiency of the valve between the ventricles and the truncus or to collateral bronchial circulation, when the murmur is continuous. In the latter instance the differentiation from pulmonary atresia may be difficult. The electrocardiogram is variable and shows pure right, pure left or combined ventricular hypertrophy. Roentgen examination shows a prominent large vessel which takes the usual course of the aorta (Fig. 260). Cardiac enlargement is due to prominence of both ventricles. The shadow of the main pulmonary artery is absent. The pulmonary vascularity is increased in the presence of a normal pulmonary resistance; it decreases as the resistance rises.

The *diagnosis* is confirmed by cardiac catheterization and by selective angiocardiography with injection of contrast medium into the right ventricle. The catheter may enter the pulmonary arteries from the truncus. A left-to-right shunt is demonstrated at the ventricular level, and the systolic pressures in both ventricles, truncus and pulmonary arteries are similar. Angiocardiography



FIG. 260. Teleroentgenogram in truncus arteriosus. The bizarre supracardiac shadow is produced by the truncus (see text).

reveals the large truncus arteriosus and the origin of the pulmonary arteries from its ascending portion.

The *prognosis* is variable. Although many patients succumb during infancy, some survive to adolescence or even later. *Treatment* is symptomatic.

### SINGLE VENTRICLE

#### (COR TRILOCULARE BIATRIATUM)

Absence of the ventricular septum with normal atria is usually associated with other cardiac anomalies. These consist of one or any combination of the following: (1) transposition of the aorta and pulmonary artery, (2) a rudimentary outflow chamber giving rise to the aorta, pulmonary artery or both, (3) pulmonary stenosis.

The clinical picture is variable. Dyspnea, fatigue, poor physical development, varying degrees of cyanosis and episodes of heart failure are usual. The pulse and blood pressure are normal. The heart is usually enlarged. A loud ejection systolic murmur is audible down the left sternal border and may be followed by a mid or late diastolic murmur.

The electrocardiogram may show left or right ventricular hypertrophy, or the precordial leads across the chest may show a single pattern. Roentgen examination confirms the cardiac enlargement. The rudimentary outflow chamber is sometimes visible on the left cardiac border in the anteroposterior projec-

tion above the ventricular shadow. The pulmonary vascularity may be increased; it is decreased in the presence of pulmonary stenosis.

Cardiac catheterization reveals a left-to-right shunt at the ventricular level. The pressure in the single ventricle is high, and a gradient may be demonstrated between it and the rudimentary outflow tract or the pulmonary artery in the presence of pulmonary stenosis. Selective angiocardiology by injection of contrast medium in the single ventricle shows absence of the ventricular septum and identifies the associated abnormalities.

A large number of these patients succumb during infancy from congestive heart failure and superimposed pulmonary infection. The prognosis appears to be better if there is associated pulmonary stenosis. Treatment is symptomatic.

### AORTIC ATRESIA

Aortic atresia is a severe congenital malformation consisting in underdevelopment of the ascending aorta and its arch, the left ventricle and left atrium. The right ventricle and atrium are enlarged, and the ductus arteriosus is widely patent. It has been suggested that this malformation is produced in some instances by premature closure of the foramen ovale during fetal life.

Venous blood returning to the right atrium passes into the right ventricle and pulmonary artery. The larger part of the venous blood passes through the patent ductus arteriosus to the descending aorta and retrograde to the arch of the aorta. The aortic valve is usually atretic or has a small opening, the mitral valve is small, and the ascending aorta is hypoplastic but patent. Associated endocardial sclerosis of the left ventricle is common.

Signs of heart failure appear within the first few weeks of life and include dyspnea and hepatomegaly. Cyanosis of varying intensity is usual. Differential cyanosis may be striking if the aortic valve has a small opening. In these patients oxygenated blood from the left ventricle enters the ascending aorta and innominate artery, resulting in a normal color in the right arm and right side of the head and neck with a contrasting cyanosis in the rest of the body. Cardiac enlargement is usual. In many cases murmurs are not audible and, if present, are not characteristic. Roentgen studies confirm the cardiac enlargement and show an increase in the pulmonary vascular markings. The electrocardiogram



shows evidence of right ventricular hypertrophy.

The majority of patients succumb during the first month of life. Treatment is symptomatic.

### DEXTROCARDIA WITH SITUS INVERSUS

Dextrocardia indicates that the heart is in the right hemithorax, the apex pointing to the right. This condition is frequently associated with situs inversus with abdominal and thoracic organs transposed to opposite sides of the body. Bronchiectasis and paranasal sinusitis may complicate dextrocardia with situs inversus (Kartagener's syndrome).

In infancy the bedside diagnosis of dextrocardia may be difficult. The apical impulse is in the right side of the chest, and the heart sounds may be louder on the right. Fluoroscopic examination localizes the position of the heart clearly, and with barium the stomach is demonstrated under the right diaphragm. The electrocardiogram is characteristic. Lead I is the mirror image of the normal tracing with inverted P and T waves, and these waves are upright in aVR.

Structural cardiac defects are less frequent than with dextrocardia without situs inversus, and the heart may be functionally normal.

The *prognosis* depends on the presence or absence of associated cardiac defects. Conditions, such as left diaphragmatic hernia or eventration, agenesis or collapse of the right lung, emphysema or cysts of the left lung, left pleural effusion, and the like, which displace the heart into the right chest seldom produce problems in *differential diagnosis*.

### ISOLATED DEXTROCARDIA

In this condition the heart is in the right hemithorax, but the abdominal viscera are in their normal positions. In the majority of instances there are severe cardiac malformations. The commonest ones are tricuspid stenosis or atresia with transposition of the great vessels or single ventricle and transposition of the great vessels (Keith, Rowe and Vlad); tetralogy of Fallot is rare.

The clinical picture is dominated by the dextrocardia and the associated cardiac anomalies. The prognosis is poor; most patients succumb during infancy. However, when there is a pulmonary stenosis, an anastomotic procedure may be beneficial.

### LEVOCARDIA WITH SITUS INVERSUS

The heart is in its normal anatomic position, but the abdominal viscera are totally or partially transposed. In the majority of instances severe cardiac malformations coexist, the commoner ones being (1) a single ventricle with atrioventricular canal, transposition of the great vessels and pulmonary stenosis or atresia, (2) atrioventricular canal with transposition of the great vessels and pulmonary stenosis or atresia, (3) anomalous systemic and pulmonary venous return (Keith, Rowe and Vlad). Splenic abnormalities are common and consist of congenital absence, rudimentary spleen or multiple small spleens.

The clinical picture is generally dominated by the coexisting cardiac malformations. The prognosis is usually poor; the majority of patients succumb during infancy. If the pulmonary blood flow is reduced owing to associated pulmonary stenosis, anastomotic shunts can be advised.

### PULMONARY ARTERIOVENOUS FISTULA

Congenital localized or multiple fistulous communications may occur in the vasculature of the lungs. Such an anomaly produces a shunting of venous blood from the pulmonary artery to the pulmonary veins. Cyanosis, clubbing and polycythemia usually result from the veno-arterial communication.

Exertional dyspnea is often present, and there is a history of recurrent hemoptysis in about 50 per cent of patients. The heart is usually normal in size and contour. Systolic and diastolic bruits are often heard over the



FIG. 261. Teleroentgenogram in pulmonary arteriovenous fistula, showing a localized increase in pulmonary vascularity in the right lung.

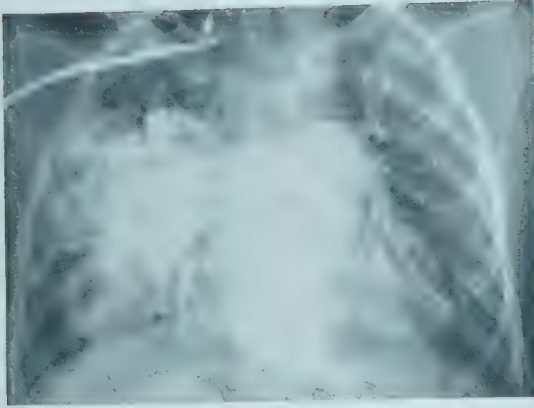


FIG. 262. Angiocardiogram in pulmonary arteriovenous fistula. (Same patient as Fig. 261.) The contrast medium has delineated the extent of the fistula in the right lung.

site of a fistulous communication. The pulmonary lesions may be single or multiple and may be associated with widely distributed aneurysms, especially in the skin and in the mucous membranes of the nasopharynx.

Roentgen studies show areas of localized increase in vascular markings, which at times may be confused with chronic pulmonary infection (Fig. 261). On fluoroscopy the

vascular lesions may be seen to pulsate. Angiocardiography demonstrates the location and extent of the lesion (Fig. 262). The electrocardiogram is normal in all respects.

Excision of localized fistulas by lobectomy results in a dramatic disappearance of cyanosis and other symptoms.

### ECTOPIA CORDIS

This is a rare malformation in which the heart is in an abnormal location. In the commonest form, thoracic in type, the sternum is split, and the heart protrudes outside the chest. In others the heart protrudes through the diaphragm into the abdominal cavity, or it may be situated in the neck. Death occurs in the first few days of life in the majority of instances.

### DIVERTICULUM OF THE LEFT VENTRICLE

This is a rare anomaly protruding through a defect in the diaphragm into the epigastrium. A pulsating mass is visible and palpable in the upper part of the abdomen. Such a diverticulum has been successfully excised.

## CONGENITAL HEART DISEASE WITH LITTLE OR NO CYANOSIS (DOMINANT LEFT-TO-RIGHT SHUNT OR NO SHUNT)

### VENTRICULAR SEPTAL DEFECT

Defects in the ventricular septum are among the commonest malformations of the heart. The opening may be situated anywhere in the ventricular septum, and occasionally there is more than one defect. These defects are most frequently situated in the membranous portion of the ventricular septum and may be closely related to the aortic valve and to the septal leaflet of the tricuspid valve.

**Hemodynamics.** In the majority of instances the systolic pressure in the left ventricle exceeds that in the right ventricle. This results in a large pressure gradient, and during left ventricular systole blood is shunted across the defect into the right ventricle. Thus the normal right ventricular output is supplemented by the increment of the shunt across the ventricular defect. Therefore the pulmonary arterial flow is increased, as is the return of pulmonary venous blood to the left atrium and ventricle. The right ventricular and pulmonary artery pressures as well as the pulmonary arteriolar resistance may be nor-

mal or moderately or greatly increased. The factor or factors which determine the presence or absence of pulmonary hypertension are not clear. The amount of left-to-right shunt is not the cause of pulmonary hypertension because in atrial septal defect there may be a huge pulmonary blood flow with normal pulmonary pressures. Other factors to be considered in the etiology of pulmonary hypertension in ventricular septal defect include the size of the defect, the fact that the right ventricle and pulmonary artery are exposed to left ventricular pressures during systole and the persistence of the neonatal high pulmonary arteriolar resistance (see also Eisenmenger Syndrome, p. 849).

**Clinical Manifestations.** These are extremely variable. In some patients there are none; in others heart failure and death may occur at any time, but especially during infancy. The factor which determines the presence or absence of symptoms is the degree of elevation of the pulmonary artery pressure and pulmonary arteriolar resistance.

In the asymptomatic child the lesion is



generally detected during a routine physical examination, and the parents are surprised to learn that the child has congenital heart disease. In other patients the history includes recurrent episodes of pulmonary infection frequently complicated by heart failure during infancy, poor physical development, fatigue and dyspnea on exertion. The history of unusual dyspnea with exercise may be difficult to elicit and may require repeated and careful questioning.

On physical examination the venous pressure is normal unless there is congestive heart failure. The pulse and blood pressure are not unusual. Cyanosis is absent. In asymptomatic patients with normal pulmonary artery pressures the heart is not enlarged and there is no abnormal apical thrust. In others the heart is moderately or greatly enlarged. In the latter group palpation of the precordium reveals a hyperdynamic left ventricular apical thrust, a left sternal border right ventricular lift and pulsations in the second left parasternal space due to an enlarged pulmonary artery. These signs indicate biventricular hypertrophy. In the majority of instances a systolic thrill is palpable maximally at the lower left sternal border, but may radiate widely over most of the precordium. The murmur is loud, pansystolic and maximal down the left sternal border, especially in the third, fourth and fifth interspaces. The second heart sound is split, and the pulmonary element is accentuated, especially in the presence of pulmonary hypertension. A functional, apical, low-pitched mid-diastolic murmur is frequent and is probably due to the large blood flow across the mitral valve. In patients with pulmonary hypertension, a functional pulmonary diastolic murmur (Graham Steell) may be audible.

*Roentgen examination* in the asymptomatic patient with normal pulmonary pressures is usually normal. In the symptomatic group the heart is enlarged, owing to left and right ventricular prominence. The pulmonary artery is enlarged and the intrapulmonary vascularity increased with or without a hilar dance. The aorta may be small, normal or prominent.

The *electrocardiogram* is normal in the asymptomatic patients. In others the tracing shows left and right ventricular hypertrophy with or without incomplete right bundle branch block. Some patients show isolated left or right ventricular hypertrophy. In the majority of instances the graph shows right axis deviation with a vertical heart. However,

in others the axis is left, and the heart is horizontal. In the latter instance, especially if there is associated biventricular hypertrophy and incomplete right bundle branch block, the graph may simulate that seen in ostium primum defect.

*Cardiac catheterization* reveals a left-to-right shunt at the ventricular level due to the entry of arterialized left ventricular blood into the right ventricle. The pressures in the lesser circulation vary from normal to elevated ones approaching systemic levels. In some instances a small gradient of pressure is measured across the outflow of the right ventricle which is probably due to functional hypertrophy of the crista supraventricularis. If the catheter passes across a patent foramen ovale and enters the left ventricle from the left atrium, injection of contrast medium into the left ventricle demonstrates the location of the ventricular defect. The left-to-right shunt is also demonstrable by dye dilution techniques.

**Prognosis and Complications.** Ventricular defect is a serious abnormality. The previously suggested good prognosis of ventricular defect is probably related to the fact that many accidental murmurs and those of slight pulmonary or aortic stenosis were misdiagnosed as ventricular defect. In Selzer's series of 88 fatal cases 29 per cent of patients died during the first year of life, and 20 per cent between the ages of one and five years. The complications of severe pulmonary hypertension with bidirectional or reversed shunt have



FIG. 263. Teleroentgenogram in ventricular septal defect. Note the cardiac enlargement, prominent pulmonary artery segment and pulmonary overcirculation. This radiographic picture may be simulated by atrial septal defect and partial anomalous pulmonary venous return.

been described under the Eisenmenger syndrome. Subacute bacterial endocarditis may complicate ventricular defects in about 10 to 20 per cent of cases (Wood). The vegetations may be found on the defect, the opposite wall of the right ventricle, the wall of the left ventricle or the aortic valve. Owing to the direction of flow across the defect, pulmonary emboli are common. Congestive heart failure may occur at any age, but is most frequent during infancy and is usually precipitated or accompanied by pulmonary infection.

**Treatment.** With the advent of direct-vision, open-heart surgery with the use of a pump oxygenator, ventricular septal defects can be repaired; the left-to-right shunt is obliterated, the hyperdynamic heart becomes quiet, thrills and murmurs are abolished, and the pressures in the lesser circulation are returned to normal. In some instances after successful surgery, systolic ejection murmurs of low intensity persist for some months, owing to turbulence in the pulmonary artery.

The indications for surgery are not clearly defined. The ideal candidate is the symptomatic patient over the age of two years whose systolic pressure in the pulmonary artery is between 50 and 70 mm. of mercury and who has a large left-to-right shunt. In these patients the surgical mortality rate is 5 per cent or less. Patients who have pulmonic systolic pressures at or approaching the systemic level, but without demonstrable right-to-left shunt and large left-to-right shunts, are still good candidates for surgery, but the surgical mortality rate is higher. It appears at present that patients with demonstrable right-to-left shunts and small left-to-right shunts are inoperable (see Eisenmenger Syndrome). Infants with symptomatic ventricular defects present a difficult problem in management, since open-heart surgery has a higher mortality rate during the first year of life. In spite of the apparent high mortality rate with medical management in this age group, it is often possible to revert episodes of heart failure and pulmonary infection with diligent and careful treatment. If these measures fail, surgery can be considered; the risk of delay must be weighed against the operative risk. Before the advent of surgery the authors observed patients who had recurrent episodes of heart failure, pulmonary infection and poor weight gain (e.g., weight of 10 pounds at the age of one year) who survived to be successfully treated with surgery in later years. When patients are asymptomatic, have

a normal-sized heart, normal electrocardiogram and normal pressures in the lesser circulation, it is preferable to defer surgery.

Medical management in the years prior to surgery is important. The therapy in the symptomatic infant has been mentioned. As a protection against subacute bacterial endocarditis, the child should receive large doses of penicillin for forty-eight hours before and seventy-two hours after dental extractions, tonsillectomy and adenoidectomy. Similarly, intercurrent infections should be treated diligently with suitable antibiotics.

#### **VENTRICULAR SEPTAL DEFECT WITH AORTIC INSUFFICIENCY**

In rare instances ventricular septal defect is complicated by prolapse of the aortic valve and aortic insufficiency. The physical signs are those of ventricular septal defect and aortic insufficiency. The diastolic murmur is clearly due to aortic insufficiency, because it is associated with the peripheral signs of a wide pulse pressure. These defects may be confused with patent ductus arteriosus.

#### **VENTRICULAR SEPTAL DEFECT WITH LEFT VENTRICULAR, RIGHT ATRIAL SHUNT**

Ventricular defects may be closely associated with an abnormal septal leaflet of the tricuspid valve. Thus, during left ventricular systole, arterialized blood is ejected through the defect into the right atrium. The physical signs are those of ventricular septal defect or ostium primum defect. In addition, the high right atrial pressure is manifest as a large systolic venous pulsation in the neck. Cardiac catheterization reveals a left-to-right shunt at the atrial level and may result in a misdiagnosis of atrial septal defect. However, the right atrial pressure curve shows a large "c" wave and, in contrast to ostium secundum atrial defects, the right ventricular and pulmonary artery pressures are usually elevated. These patients are treated surgically by closure of the ventricular defect as described above.

#### **OTHER DEFECTS ASSOCIATED WITH VENTRICULAR SEPTAL DEFECT**

With the advent of surgery for ventricular septal defects the correct diagnosis of associated cardiovascular malformations becomes of paramount importance. These associated defects include the following:

**Patent Ductus Arteriosus.** During cardiopulmonary bypass for the repair of ventricular



defects arterialized blood from the heart-lung apparatus is returned to a branch of the aorta. If there is an associated patent ductus arteriosus, there is a leak of blood into the pulmonary artery which results in flooding the surgical field with blood, and may contribute to postoperative pulmonary complications. In some instances the physical signs are dominated by those of the ventricular septal defect, and the murmur of the patent ductus is inaudible. In these patients the diagnosis is established by the passage of the cardiac catheter from the pulmonary artery, through the ductus and into the descending aorta.

In other instances the signs are dominated by those of patent ductus arteriosus, although a systolic murmur and thrill are often present along the lower left sternal border. In these cases cardiac catheterization and selective angiocardiography reveal the left-to-right shunt at the ventricular level as well as the patent ductus arteriosus.

Both the ventricular defect and the patent ductus are treated surgically at the same operation. If the presence of the open ductus is appreciated, the surgical risk is the same as that for uncomplicated ventricular defect.

**Multiple Ventricular Septal Defects.** In rare instances there is more than one ventricular septal defect. Because this cannot be appreciated clinically or by cardiac catheterization, exploration of the whole ventricular septum is indicated during open cardiomy to ensure that all defects have been treated.

**Atrial Septal Defect.** In patients with a ventricular defect and an ostium secundum atrial defect the physical signs are usually dominated by the ventricular defect. This combination of defects may be suspected during cardiac catheterization if a left-to-right shunt is demonstrated at the atrial level and another at the ventricular level. During right ventriculotomy for closure of ventricular defects the atrial septum is easily explored through the tricuspid valve, and, if both defects are present, they can be treated during the same surgical procedure.

**Coarctation of the Aorta.** The signs of coarctation of the aorta are clear, but those of the ventricular defect may be confused with the signs produced by the collateral circulation secondary to the coarctation. It is frequently difficult to treat both abnormalities through the usual incision for cardiopulmonary bypass, and it may be necessary to repair these lesions at separate surgical procedures.

**Persistent Left Superior Vena Cava.** This condition is not diagnosable clinically. It is proved by cardiac catheterization when the catheter enters the persistent left superior vena cava from the coronary sinus. Surgical treatment of ventricular defects with cardiopulmonary bypass requires occlusion of the venous inflow. If the left superior vena cava is not occluded, large volumes of venous blood enter the heart during cardiomy. The persistent left superior vena cava in itself does not require treatment.

**Endocardial Sclerosis.** Thickened white areas are frequently found in the endocardium of the right ventricle in patients with ventricular septal defect. These areas are presumably produced by the jet of blood shunting across the defect to the opposite right ventricular wall. Endocardial sclerosis involving the left atrium and ventricle is not frequently associated with ventricular defect.

**Complete Heart Block.** This arrhythmia is rare in patients with ventricular septal defect, although systolic murmurs of varying intensity are not unusual in patients with complete heart block. They are produced by the turbulence associated with the large stroke volume. If patients with complete heart block are to have a ventricular septal defect corrected, transposition of the great vessels should also be suspected. These abnormalities do not contraindicate surgical closure of the ventricular defect.

## ATRIAL SEPTAL DEFECT

### PATENT FORAMEN OVALE

The foramen ovale is an important structure during intrauterine life allowing the shunting of inferior vena caval blood from the right atrium to the left atrium. At or soon after birth the foramen ovale closes. In about 80 per cent of normal hearts the closure is permanent; in the remainder a small slitlike opening remains patent.

An isolated patent foramen ovale is of no clinical significance. If the right atrial pressure is increased (e.g., secondary to pulmonary stenosis or pulmonary hypertension), venous blood may be shunted across the patent foramen ovale into the left atrium and result in cyanosis. A cardiac catheter introduced from the saphenous vein into the inferior vena cava and right atrium may pass easily across a patent foramen ovale into the left atrium.

Because of the anatomic structure at the

valve of a patent foramen ovale, blood cannot be shunted from the left atrium to the right atrium.

An isolated patent foramen ovale does not require treatment.

### OSTIUM SECUNDUM DEFECT

The ostium secundum type of atrial septal defects are large openings and are associated with normal atrioventricular valves. The anatomic location of these defects depends on the time of arrested development of the septum primum or secundum. They may be situated anywhere in the atrial septum, including the lower anterior part of the septum, the region of the fossa ovalis or posteriorly. Occasionally ostium secundum defects are multiple.

**Hemodynamics.** A considerable shunt of oxygenated blood flows from the left to the right atrium. This blood is added to the normal venous return to the right atrium and is pumped by the right ventricle to the lungs. The large blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilatation of the pulmonary artery. In spite of the large pulmonary blood flow, the pulmonary arterial pressure is usually normal or moderately elevated. The left ventricle and aorta are small, owing to the relatively small amount of blood that they carry. Progressive dilatation of the right ventricle leads to heart failure. Cyanosis is extremely rare; it is seen occasionally with congestive heart failure or with the complicating features of the Eisenmenger syndrome.

**Clinical Manifestations.** In many children the condition is asymptomatic and discovered during routine physical examination. Ostium secundum defects rarely produce heart failure in infancy. The history in older children usually includes recurrent episodes of bronchopneumonia frequently complicated by segmental pulmonary collapse, varying degrees of exercise intolerance and poor physical development. In many instances the patients are completely asymptomatic during the first two decades of life.

The pulse is normal or small and the venous pressure normal unless there is associated tricuspid insufficiency or heart failure. The heart may be normal in size or moderately or greatly enlarged. A hyperdynamic right ventricular systolic lift is usually palpable and extends from the left sternal border to the mid-clavicular line. On auscultation a mid-systolic ejection murmur usually of low

intensity, but occasionally accompanied by a thrill, is audible maximally over the pulmonary area and radiates down the left sternal border. The murmur is preceded by a loud first heart sound. The second heart sound is widely split, does not vary with respiration and is due to prolongation of the right ventricular systole (Wood). A mid-diastolic murmur may be audible at the apex and/or at the lower left sternal edge. The diastolic murmur of pulmonary incompetence may be heard, but is rare. Leatham and Gray ascribe the systolic murmur to the large pulmonary flow and the loud first sound and mid-diastolic murmur to the increased tricuspid flow.

Associated abnormalities which may be found on physical examination include pigeon chest, kyphoscoliosis, high arched palate and arachnodactyly. Congenital or rheumatic mitral stenosis with atrial septal defect (*Lutembacher syndrome*) is rare, and its frequency has been overemphasized.

*Roentgen examination* shows varying degrees of cardiac enlargement due to prominence of the right ventricle and atrium. The pulmonary artery is large, the pulmonary vascularity greatly increased, and hilar dance is not unusual. The left ventricle and aorta are small. These signs vary and in the less advanced cases may not be conspicuous.

The *electrocardiogram* is abnormal in nearly all instances, revealing evidence of incomplete right bundle branch block (Fig. 242), of right ventricular hypertrophy or of



FIG. 264. Teleroentgenogram in atrial septal defect (ostium secundum). Note the cardiac enlargement, prominent pulmonary artery segment, pulmonary overcirculation and small aorta.



a combination of both these signs. Occasionally complete right bundle branch block is present.

The diagnosis may be confirmed by *cardiac catheterization*, which demonstrates a significantly higher oxygen content of the blood from the right atrium as compared to samples from the venae cavae. This finding is not diagnostic of atrial septal defect and may be found with anomalous pulmonary venous return to the right atrium, with ventricular septal defect with tricuspid insufficiency and with ventricular septal defects associated with left ventricular right atrial shunts.

*Dye dilution curves* with injection into the pulmonary artery, right side of the heart and venae cavae usually help to distinguish the foregoing abnormalities from atrial septal defect. The catheter frequently enters the left atrium from the right atrium. *Selective angiocardiology* with injection of contrast material into the left atrium demonstrates the shunt at the atrial level. The pressures in the right side of the heart are variable; they are frequently normal or may show moderate right ventricular and pulmonary hypertension. The pulmonary arteriolar resistance is usually normal, but occasionally may be increased. The shunt across the defect is also variable, but is usually considerable (as high as 20 liters per minute per square meter of body surface.)

**Complications and Prognosis.** Atrial septal defects may be associated with partial anomalous pulmonary venous return or pulmonary stenosis. Functional tricuspid incompetence secondary to dilatation of the right ventricle is not infrequent in the presence of congestive heart failure. Subacute bacterial endocarditis is rare; if it occurs, it suggests the presence of associated abnormalities, e.g., pulmonary stenosis. Eisenmenger and Lutembacher syndromes complicating atrial septal defect have been described.

The *prognosis* is extremely variable. Occasionally death occurs in the first few years of life because of uncontrollable pulmonary infections and congestive heart failure. However, in many instances little disability is experienced until the third decade. The major guides to prognosis appear to be the presence or absence of symptoms and of continuing cardiac enlargement.

**Treatment.** Although many forms of surgical therapy have been introduced to close atrial septal defects, direct-vision, open-heart surgery allows accurate closure. This type of surgery may be accomplished by hypothermia

or with the use of a pump oxygenator and cardiopulmonary bypass. We have preferred the latter form of treatment because the defect may be closed leisurely and because associated defects may be treated during the same procedure. The mortality rate from surgery is less than 2 per cent.

#### OSTIUM PRIMUM DEFECT AND COMMON ATRIOVENTRICULAR CANAL

##### (ENDOCARDIAL CUSHION DEFECTS)

These abnormalities have been grouped together because they have a common embryologic relationship and the clinical pattern may be similar.

*Ostium primum defect* is an atrial septal defect, the lower border of which is formed by the mitral and tricuspid valves. In the majority of instances there is a cleft in the anterior mitral valve leaflet with resultant mitral regurgitation.

*Common atrioventricular canal* is a continuous communication consisting of an ostium primum defect in association with a high ventricular septal defect. In addition, the mitral and tricuspid leaflets are abnormal. They may remain undifferentiated, forming a common atrioventricular valve, or may fuse together through the defect with clefts in either the mitral or tricuspid valve or both.

*Transitional varieties* of these defects also occur, which include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets, but without a ventricular septal defect, and, less commonly, ostium primum defects with normal atrioventricular valves.

**Hemodynamics.** The shunt of blood across the defect is usually from left to right. In contradistinction to ostium secundum defects, the right ventricular and pulmonary artery systolic pressures are frequently elevated, as is the pulmonary arteriolar resistance. Of great importance is the presence of the mitral valve cleft with resultant mitral insufficiency. Elevation of the pulmonary artery pressure to systemic levels results in a bidirectional shunt and cyanosis (Eisenmenger syndrome).

**Clinical Manifestations.** Endocardial cushion defects are more common among children with mongolism than among other children; mongolism is also associated with a variety of other congenital heart defects. Symptoms, which include recurrent episodes of bronchopneumonia with or without segmental atelectasis, effort dyspnea and poor physical development, may appear at any age from infancy to the second decade or later. The

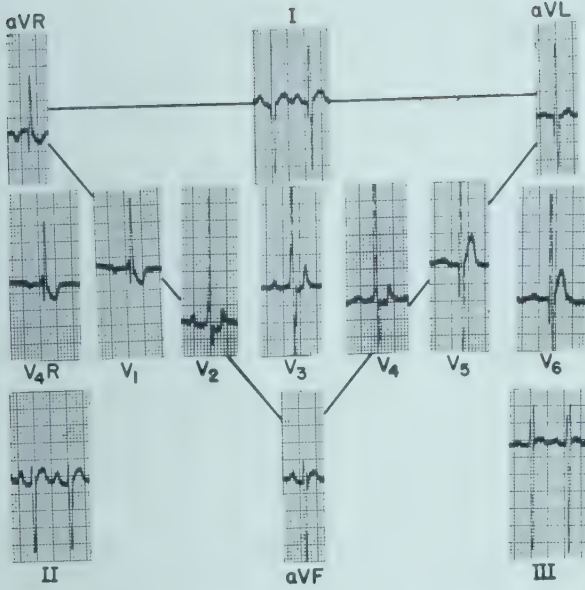


FIG. 265. Electrocardiogram in ostium primum atrial septal defect. Note the prolongation of the P-R interval, left axis deviation, horizontal electrical position and evidence of biventricular hypertrophy.

jugular venous pressure is increased with congestive heart failure, with tricuspid insufficiency and at times with pulmonary hypertension. The heart is usually enlarged to some degree. The apical impulse is manifest by a left ventricular heave and is associated with a right ventricular sternal and parasternal lift. A systolic murmur sometimes accompanied by a thrill is usually audible. At the apex the murmur is pansystolic (regurgitant), owing to the mitral insufficiency. The systolic murmur along the left sternal border is ejection in type and is probably due to the ventricular septal defect or to turbulence produced by the large pulmonary artery flow. Apical mid-diastolic rumbling murmurs are common. The second heart sound is split, but the degree of it varies from wide to narrow.

*Roentgen examination* confirms the cardiac enlargement, which is due to prominence of both right and left ventricles. The pulmonary artery is large; pulmonary vascularity is increased, and hilar dance is not unusual. The aorta is small or normal in size. The *electrocardiogram* is unusual and frequently diagnostic (Fig. 265). The abnormalities consist in prolongation of the P-R interval, left axis deviation and biventricular hypertrophy. Right ventricular hypertrophy is frequently associated with a slurred R wave in  $V_4R$  and  $V_1$ . Sometimes the pattern in the right ventricular surface leads is that of incomplete

right bundle branch block. Left ventricular hypertrophy is indicated by tall R waves in  $V_5$  and  $V_6$  followed by either tall, flat or inverted T waves.

*Cardiac catheterization* demonstrates a left-to-right shunt at the atrial level as indicated by a high oxygen content of the right atrial blood as compared to the caval blood. A further shunt may be shown at the ventricular level, or sometimes the demonstrable shunt is only at the ventricular level. The pulmonary artery and right ventricular systolic pressures are usually elevated. If they reach systemic levels, the shunt is bidirectional as indicated by arterial oxygen unsaturation and by dye dilution curves. The right atrial pressure is increased in the presence of congestive heart failure or tricuspid insufficiency. The catheter passes across the atrial defect with ease. Selective angiocardiology with injection of contrast material into the left atrium and left ventricle also demonstrates the left-to-right shunt.

**Differential Diagnosis.** Endocardial cushion defects may simulate ostium secundum defects as well as ventricular septal defects. In endocardial cushion defects the symptoms frequently appear early, signs of mitral insufficiency and biventricular hypertrophy are common, and the electrocardiographic changes are usually definitive, although the changes of isolated ventricular septal defect may at times closely simulate them.

The *prognosis* is variable and appears to depend on the degree of mitral insufficiency and the elevation of the pulmonary arteriolar resistance. Death from congestive cardiac failure during infancy is not uncommon. However, many patients with ostium primum defects are asymptomatic or have only minor nonprogressive symptoms until they reach the third or fourth decade of life.

**Treatment.** Direct-vision intracardiac surgery with an artificial heart-lung machine and cardiopulmonary bypass is now a feasible form of treatment for endocardial cushion defects. The defect is approached from an incision in the right atrium. The cleft in the mitral valve is visualized through the atrial defect and is repaired by direct suture. If a cleft is present in the tricuspid valve, it is also treated by direct suture. The defects in the atrial and ventricular septa are usually closed by insertion of a prosthesis; they cannot be treated successfully with blind techniques or during hypothermia. The surgical mortality is higher than that for ostium secundum defects, but is not prohibitive.



## PATENT DUCTUS ARTERIOSUS

During fetal life a large percentage of pulmonary arterial blood is shunted through the ductus arteriosus into the aorta; functional closure of the ductus normally occurs soon after birth. However, if the ductus remains patent, aortic blood is shunted into the pulmonary artery. The aortic end of the ductus is opposite and usually distal to the origin of the left subclavian artery, and it enters the pulmonary artery at its bifurcation. Patent ductus arteriosus is peculiar among congenital cardiac defects in that it occurs frequently as an isolated anomaly. It occurs about twice as frequently in females as in males and is one of the commonest congenital cardiovascular anomalies associated with maternal rubella during early pregnancy.

**Hemodynamics.** The blood flow through the ductus is from the aorta to the pulmonary artery as a result of the higher aortic pressure. The degree of shunt depends on the size of the ductus and the pressure gradient between the aorta and the pulmonary artery. In extreme cases one half to two thirds of the left ventricular output may be shunted through the ductus, and the oxygenated blood recirculates through the pulmonary circulation. In the majority of instances the pressures within the pulmonary artery and the right ventricle and right atrium are normal, but the pulmonary artery and right ventricular systolic pressures may be elevated to moderate or even to systemic levels (see Eisenmenger Syndrome). There is a wide pulse pressure. Cassels and Morse have shown that the total blood volume is increased and that it returns to normal limits after surgical closure of the ductus.

**Clinical Manifestations.** There are usually no symptoms; the lesion is often detected during a routine physical examination. However, symptoms may develop at any age and include slowly progressive exertional dyspnea, followed by left ventricular failure or frank congestive cardiac failure. Retardation of physical growth may be the main complaint. Other, rarer symptoms include precordial pain, probably due to complicating neurocirculatory asthenia, and hoarseness from involvement of the adjacent recurrent laryngeal nerve.

The paucity of symptoms contrasts with the striking physical signs. Dynamically, a patent ductus arteriosus is an arteriovenous shunt of considerable extent; and signs of a large pulse pressure are produced, including

water-hammer radial pulsations and conspicuous arterial Corrigan pulsations in the neck. The low diastolic blood pressure may fall further after exertion. The heart is usually normal in size, but may be moderately or grossly enlarged. The apical impulse is normal or left ventricular and, with cardiac enlargement, is heaving. A thrill, situated maximally in the second left interspace, is present in many instances and may radiate toward the left clavicle and somewhat down the left sternal border or toward the apex. The thrill is usually systolic in time, often extends into diastole and, in some instances, may be palpated throughout the cardiac cycle. The classic murmur has been variously described as machinery, humming top, millwheel or rolling thunder in quality. The murmur begins soon after the onset of the first sound, reaches a maximum intensity at the end of systole and wanes in late diastole. It may be localized to the second left intercostal space or radiate down the left sternal border or to the left clavicle. The murmur is harsh and does not have the blowing quality commonly found in acquired lesions. A few patients have atypical murmurs, especially if there is a large ductus or pulmonary hypertension. If there is pulmonary diastolic hypertension associated with the usual low systemic diastolic pressure, there may be a small or negligible flow across the ductus during diastole. Under these conditions only a systolic murmur is present. Rarely the murmur is confined to diastole; this is probably due to pulmonary valve insufficiency. In patients with a large left-to-right shunt a low-pitched mitral diastolic murmur may be audible and is probably due to the large blood flow across the mitral valve.

The *electrocardiogram* is normal in the majority of instances. If the ductus is large, left ventricular hypertrophy may be present. The diagnosis of uncomplicated patent ductus arteriosus is untenable in the presence of electrocardiographic evidence of right ventricular hypertrophy.

*Roentgenographic studies* commonly reveal evidence of a prominent and vigorously pulsating pulmonary artery. The intrapulmonary vascular markings are increased and sometimes exhibit an intrinsic pulsation or hilar dance. The cardiac size depends on the degree of left-to-right shunt; it may be normal, moderately or grossly enlarged (Fig. 266). The chambers involved are the left atrium and ventricle. The aortic knob is normal or prominent and pulsates vigorously. Rarely,

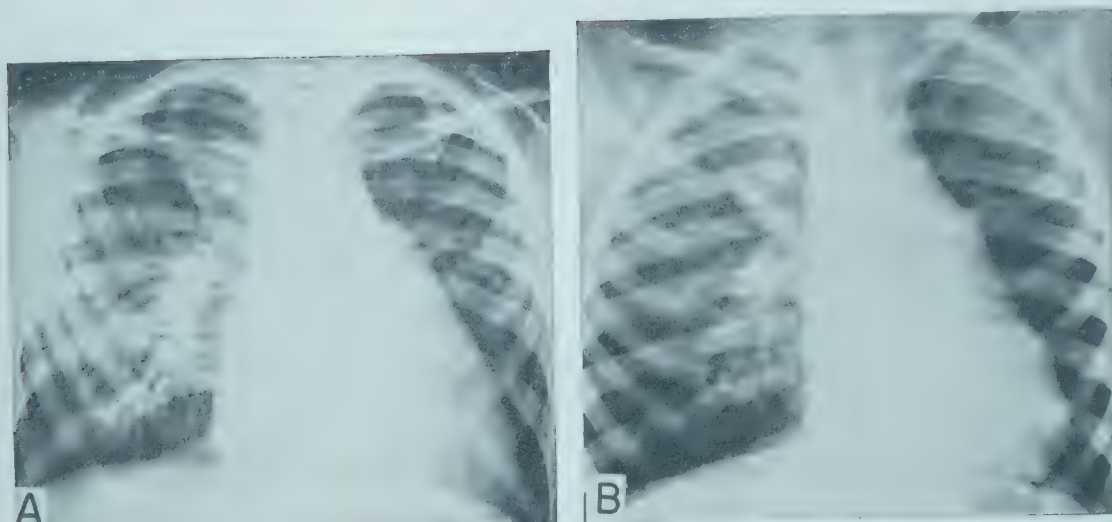


FIG. 266. Teleroentgenograms in patent ductus arteriosus. *A*, Preoperative. Note the cardiac enlargement, prominent pulmonary artery segment and pulmonary overvascularity. *B*, One year postoperative. The heart size and pulmonary vascularity have decreased. Some prominence of the pulmonary artery segment persists.

calcification may be demonstrated in the wall of the ductus.

The clinical pattern is sufficiently distinctive to allow an accurate diagnosis in the majority of patients. However, in patients with atypical murmurs further confirmatory studies are indicated.

*Cardiac catheterization* reveals a normal or increased pressure in the right ventricle and pulmonary artery. Continuous pressure recordings taken as the catheter is withdrawn from a branch of the pulmonary artery to the main pulmonary artery may show an increase in pressure as the catheter tip passes through the jet of blood shunted from the aorta. Oxygenation of the blood in the pulmonary artery confirms the diagnosis of a left-to-right shunt, but does not exclude an aorticopulmonary septal defect. Samples of blood from the venae cavae, right atrium and right ventricle have a comparable oxygen content. With pulmonary insufficiency some oxygenation of the right ventricular blood may be present. The catheter may pass through the ductus into the descending aorta (Fig. 247, *G*). Angiocardiographic studies may also be of value. Injection of contrast material into the ductus demonstrates the anatomy and the left-to-right shunt. Injection into the outflow tract of the right ventricle may show a washing away of the dye in the pulmonary artery by the shunt of blood from the aorta. Retrograde aortography by injection of contrast medium into the brachial artery shows opacification of the pulmonary artery from the aorta. A localized dilatation of the descending aorta just below the isthmus

may be visualized, possibly produced by the aortic end of the ductus or by a traction aneurysm of the aorta.

**Patent Ductus Arteriosus in Infancy.** An uncomplicated patent ductus arteriosus may on occasion produce symptoms of left-sided heart failure or severe congestive failure during the first two years of life. These symptoms are frequently precipitated by respiratory infections to which these patients are prone. They may also exhibit the other symptoms described above.

It has been said that the typical machinery murmur of patent ductus arteriosus generally appears between the ages of three and five years and that before this time only a systolic murmur over the pulmonary area is audible. As in older children, the presence or absence of the diastolic component of the murmur depends on the pressure relationship between the aorta and the pulmonary artery. If secondary pulmonary hypertension has developed, there is little or no flow of blood during diastole, and only a systolic murmur is present. However, if the pulmonary artery pressure is normal or only moderately elevated, the typical machinery murmur is present early, even in infants a few weeks of age. In addition, the pulse pressure is wide, and the heart is moderately to grossly enlarged, the main chambers involved being the left ventricle and atrium.

*Roentgen examination* confirms the enlargement of the chambers and also reveals prominent pulmonary arteries and increased pulsations in the aorta. The *electrocardiogram* may be normal or may show evidence of left



ventricular dominance or biventricular hypertrophy.

This clinical pattern is sufficiently well recognized so that a diagnosis of uncomplicated patent ductus arteriosus can be made at any age. In atypical cases the diagnosis may be confirmed by the methods described above.

The diagnosis of symptomatic uncomplicated patent ductus arteriosus in infancy is important because surgical treatment of the lesion produces dramatic relief of symptoms and normal cardiovascular dynamics. Surgical therapy is indicated in all symptomatic patients irrespective of age and has been successfully performed in infants as young as two months of age.

**Differential Diagnosis of Patent Ductus Arteriosus.** The diagnosis of uncomplicated patent ductus arteriosus is usually not difficult. However, there are other conditions which produce systolic and diastolic murmurs in the pulmonary area which may be misinterpreted. The characteristics of a *venous hum* have been described elsewhere. *Aortico-pulmonary septal defect* may be clinically indistinguishable from a patent ductus. Similarly, difficulty in diagnosis may occur in patients with a *ruptured sinus of Valsalva into the right side of the heart or pulmonary artery* and in patients with *coronary arteriovenous fistulas*. In these three conditions the dynamics are those of an arteriovenous fistula with a machinery type of murmur and a wide pulse pressure. Sometimes the murmur is not maximal in the pulmonary area, but is heard along the lower left sternal border. Pulmonary arteriovenous fistulas may give rise to a machinery type of murmur (see p. 855).

*Ventricular septal defect with aortic insufficiency and combined rheumatic aortic and mitral insufficiency* may be confused with patent ductus arteriosus because the combination of murmurs produced by these lesions superficially resembles those of patent ductus arteriosus. Careful auscultation and the absence of pulmonary overcirculation usually resolves the diagnostic problem.

**Prognosis and Complications.** Because many patients with patent ductus arteriosus are asymptomatic, the impression may be gained that this lesion is benign. Keys and Shapiro estimated that a patent ductus was responsible for an average reduction of life expectancy of about twenty-three years in men and twenty-eight in women. There are occasional instances of patients living a nor-

mal span with little or no cardiac embarrassment. However, children and young adults who have this anomaly are subject to complications (see below), the frequency of which is great enough to make it clear that the lesion is not an innocuous one. Spontaneous closure of the ductus after infancy is extremely rare.

It has been mentioned that infants may succumb to congestive cardiac failure. This complication, which is not infrequently preceded by attacks of left ventricular failure, may occur at any age, but is most common in the third decade of life. Cardiac failure is treated along the usual medical lines, but it is an urgent indication for operation when the patient's condition permits.

Subacute bacterial endarteritis, the most frequent complication in late childhood or early adult life, may occur at any age. Pulmonary emboli are common, and, when the ductus is involved, systemic emboli may occur. This complication should be vigorously treated with suitable antibiotics and surgical closure of the ductus. The mortality and morbidity rates are much lower if the blood stream can be sterilized before operation. The optimum time for surgical treatment is about three months after cure of the infective process.

Rarer complications include aneurysmal dilatation of the pulmonary artery and/or the ductus, noninfective thrombosis of the ductus with embolization, paradoxical emboli and acquired rheumatic heart disease. Patent ductus arteriosus with pulmonary hypertension (Eisenmenger syndrome) has been described (p. 849).

**Treatment.** Irrespective of the age group, patients with manifestations of a patent ductus arteriosus will derive great benefit from surgical closure of the abnormal shunt (see above). If congestive cardiac failure should develop, surgical treatment should not be postponed for too long a time after adequate digitalis, diuretic and low salt diet therapy, even if some signs of failure persist.

Because the mortality rate of surgical treatment is less than 1 per cent, and the risk otherwise is greater, ligation or division of the ductus is indicated in the asymptomatic patient, preferably between the ages of three and ten years. Surgical therapy in this age group is performed with relative facility, whereas in older persons the regional vessels are more rigid or associated with degenerative changes, and the cardiac reserve is reduced

(Gross). The upper age limit for surgical repair in the asymptomatic patient is about thirty-five years. However, if important symptoms develop at any age, there should be no hesitation to operate. Pulmonary hypertension is not a contraindication to operation if it can be demonstrated that the shunt is from aorta to pulmonary artery and not reversed.

Surgical closure is either by ligation or by division and suture of the ductus; the choice is an individual one.

After closure, symptoms of frank or incipient cardiac failure rapidly disappear. If the patient was physically stunted, there is usually an improvement in physical development within a year or two. The pulse and blood pressure return to normal, and the machinery murmur is replaced by two normal heart sounds. In a small number of patients a grade 1 systolic murmur over the pulmonary area may persist; the murmur may be due to turbulence in a persistently dilated pulmonary artery or rarely to an unsuspected associated ventricular or atrial septal defect. The roentgenographic signs of cardiac enlargement and pulmonary overcirculation also disappear (Fig. 266), and the electrocardiogram becomes normal. If pulmonary hypertension was associated with a left-to-right shunt, the pressure returns to normal.

### AORTICOPULMONARY SEPTAL DEFECT

This communication between the aorta and main pulmonary artery close to their origins is indistinguishable clinically and rarely by technical means from patent ductus arteriosus. Occasionally the murmur is heard maximally in the third and fourth left parasternal spaces, but this is not the rule. If the condition is suspected, the course of the catheter during cardiac catheterization may give the correct diagnosis. In patent ductus arteriosus the catheter enters the pulmonary artery and passes across the ductus into the descending aorta. In aorticopulmonary septal defect the catheter enters the ascending aorta from the pulmonary artery. In many instances the diagnosis is made at thoracotomy undertaken for the erroneous diagnosis of patent ductus arteriosus.

Aorticopulmonary defects can be cured by surgical treatment. In the majority of instances the defect is in the intracardiac portion of the aorta, and cardiopulmonary bypass with a heart-lung machine is necessary for the surgical repair.

### FISTULA OF A CORONARY ARTERY

A congenital fistula may exist between a coronary artery and vein, or a coronary artery may empty directly into the right ventricle. In both instances the signs are similar to those of patent ductus arteriosus, but the machinery murmur may be more diffuse. In patients with *coronary arteriovenous fistula* arterialized blood enters the coronary veins, which in turn empty into the coronary sinus. In such cases the right atrial blood has a higher oxygen content than samples from the cavae. When a *coronary artery empties directly into the right ventricle*, there is a left-to-right shunt at the ventricular level. Treatment consists in surgical abolition of the fistula.

### RUPTURED SINUS OF VALSALVA

One of the sinuses of Valsalva of the aorta may be weakened by congenital or acquired disease and result in aneurysmal formation and rupture, usually into the right atrium or ventricle. The clinical manifestations are similar to those of patent ductus arteriosus, except that the machinery type of murmur may be in an unusual site. Cardiac catheterization demonstrates the level of the left-to-right shunt at the atrial or ventricular level. Retrograde aortography with injection of contrast medium into the ascending aorta demonstrates the site of aneurysm and rupture. Surgical obliteration of the shunt with the use of a heart-lung machine is now feasible.

### PULMONARY STENOSIS (WITH NORMAL AORTIC ROOT)

Although the clinical manifestations of this abnormality were described only recently, it probably comprises about 10 per cent of all congenital heart diseases. Pulmonary stenosis may exist as an isolated abnormality or with defects in the atrial or ventricular septa. However, in all instances the origin of the aorta is normal. This distinction aids in separating the malformation under discussion from tetralogy of Fallot, in which the aorta is dextroposed. However, experience gained from direct-vision open-heart surgery indicates that in many instances dextroposition of the aorta (even in tetralogy of Fallot) may be more apparent than real.

The following is a modification of the



classification of pulmonary stenosis with normal aortic root as suggested by Abrahams and Wood:

1. Simple pulmonary stenosis
  - a. Valvular
  - b. Infundibular
  - c. Combined valvular and infundibular
2. Pulmonary stenosis (valvular or infundibular or both) with arteriovenous shunt
  - a. Pulmonary stenosis with atrial septal defect
  - b. Pulmonary stenosis with ventricular septal defect (acyanotic Fallot)
  - c. Pulmonary stenosis with patent ductus arteriosus
3. Pulmonary stenosis (valvular or infundibular or both) with veno-arterial shunt
  - a. Pulmonary stenosis with ventricular septal defect (hemodynamically similar to tetralogy of Fallot)
  - b. Pulmonary stenosis with reversed interatrial shunt (through patent foramen ovale or atrial septal defect)

#### SIMPLE VALVULAR PULMONARY STENOSIS

In this, the commonest type of isolated pulmonary stenosis, the valve cusps exist as a dome-shaped membrane of varying thickness with a small central or eccentric opening. The ventricular and atrial septa are intact.

**Hemodynamics.** The obstruction to the passage of blood from the right ventricle to the pulmonary artery results in increased systolic pressure and hypertrophy of the right ventricle. The degree of these changes depends on the degree of the pulmonary stenosis. In severe cases the right ventricular pressure may be much higher than the systemic systolic pressure. The pulmonary artery pressure is low or normal. The arterial oxygen saturation is normal, and in severe cases the cardiac output is low and fixed.

**Clinical Manifestations.** Symptoms vary with the degree of stenosis. With mild or moderate pulmonary stenosis there are usually no symptoms. If the stenosis is severe, there is usually some degree of effort dyspnea, and the exercise tolerance may be reduced to walking a few yards. Squatting may occur, but is not as common as with tetralogy of Fallot. Substernal pain and effort syncope are rare manifestations in severe cases.

The physique is frequently normal, and many patients are robust. The facies of patients with a severe type of pulmonary stenosis have been described as being round, bloated or moon-shaped.

With stenosis of a mild degree the venous pressure and pulse are normal. The heart is not enlarged; the apical impulse is normal,

and the right ventricle is not palpable. A loud ejection pulmonary systolic murmur, frequently accompanied by a thrill, is audible maximally over the pulmonary area. The second heart sound may be widely split with a delayed pulmonary element of normal intensity. The electrocardiogram is normal or reveals incomplete right bundle branch block. The only abnormality on roentgen examination is poststenotic dilatation of the pulmonary artery. The heart size, the right ventricle and the pulmonary vascularity are within normal limits.

In stenosis of a moderate degree the physical signs are those described above with variable degrees of exaggeration. The venous pressure may be slightly elevated with an intrinsic "a" wave. A right ventricular sternal lift may be palpable. The electrocardiogram reveals varying degrees of right ventricular hypertrophy (systolic overload), sometimes with a prominent spiked P wave. Roentgen examination reveals the heart to be normal in size or mildly enlarged, owing to prominence of the right ventricle, and the intrapulmonary vascularity may be decreased.

In *stenosis of a severe degree* peripheral cyanosis is sometimes present, owing to a small cardiac output, to compensatory vasoconstriction and to sluggish blood flow through the skin. The arterial oxygen saturation is normal. The venous pressure is usually elevated, owing to a large presystolic jugular "a" wave, which is sometimes transmitted to the liver as a presystolic pulsation. Occasionally a large jugular "c" wave is evident and is due to functional tricuspid incompetence. The heart is moderately or greatly enlarged with a conspicuous sternal and parasternal right ventricular lift which frequently extends to the mid-clavicular line. A loud ejection systolic murmur, frequently accompanied by a thrill, is audible maximally in the pulmonary area and may radiate widely over the whole precordium, into the neck and to the back. The systolic murmur extends into the second sound, making its evaluation difficult. The pulmonary element of the second sound is either inaudible or very late and soft. A right atrial presystolic gallop is usually heard in the presence of a large venous "a" wave (Wood). The electrocardiogram shows gross right ventricular hypertrophy frequently accompanied by a tall spiked P wave (P pulmonale). Roentgen studies confirm the moderate or gross cardiac enlargement with prominence of the right ventricle and atrium.

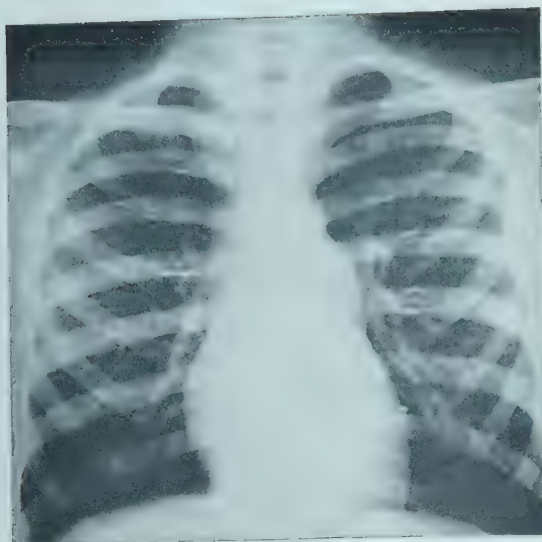


FIG. 267. Teleroentgenogram in valvular pulmonic stenosis with normal aortic root. The heart size is within normal limits, but there is post-stenotic pulmonary artery dilatation and pulmonary undervascularity.

The pulmonary artery segment is prominent, owing to poststenotic dilatation. The intrapulmonary vascularity is decreased.

Cardiac catheterization demonstrates an abrupt gradient of pressure across the pulmonary valve, the magnitude of which depends on the severity of obstruction. The pulmonary artery pressure is normal or low. The right ventricular systolic pressure is about 30 to 50 mm. of mercury in mild cases, about 50 to 100 mm. in moderate cases, and in severe cases is frequently higher than the systemic systolic pressure. In severe and in some moderate cases the right atrial pressure shows a prominent, frequently giant "a" wave. *Selective angiocardiology* with injection of contrast medium into the right ventricle clearly demonstrates the obstruction. The flow of contrast medium through the stenotic valve in ventricular systole produces a jet of dye which fills the dilated pulmonary artery. The abnormal pulmonary valve is frequently visualized.

**Complications.** Congestive cardiac failure, the most common complication, occurs only in severe cases and may occur at any age, even during the first month of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is described elsewhere. Subacute bacterial endocarditis is not common.

**Course and Prognosis.** Children with mild stenosis can lead a normal life without specific treatment, as may many with moderate

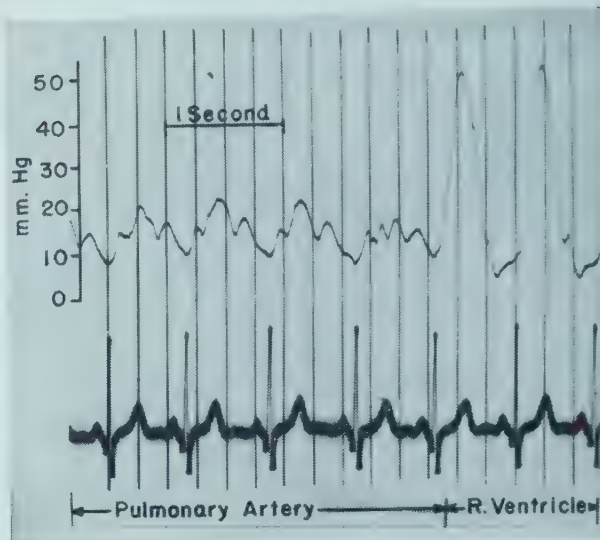


FIG. 268. Pressure curve obtained during cardiac catheterization in a patient with isolated pulmonary valvular stenosis. The lower tracing is the electrocardiogram. The upper curve is the pressure record as the catheter was withdrawn from the pulmonary artery to the right ventricle. Note the abrupt pressure gradient between the right ventricle and pulmonary artery. Compare with Figure 253.

stenosis, although their progress should be evaluated at regular intervals. With severe stenosis the course is rapidly downhill with the development of congestive cardiac failure.

**Treatment.** As indicated above, mild cases and many of moderate severity do not require specific treatment, and such patients should be encouraged to lead normal lives. Dental, ear, nose and throat surgery must be covered with prophylactic penicillin as described elsewhere.

All patients with severe isolated pulmonary stenosis require surgical therapy (*pulmonary valvotomy*). The valve can be cut and dilated blindly through a transventricular approach (Brock procedure); it can be approached through the pulmonary artery with inflow and outflow occlusion of the heart during hypothermia (Swan), or the valvotomy can be performed with the use of an artificial heart-lung machine (the authors' preference). Associated defects such as infundibular stenosis, atrial or ventricular defects which may be unrecognized preoperatively can be repaired at the same time.

Good results should be obtained in the majority of instances. The gradient across the pulmonary valve is reduced or abolished. A pulmonary diastolic murmur due to a surgically created pulmonary valve incompetence is not unusual, but appears to have little clinical significance.



**INFUNDIBULAR STENOSIS**

This condition is due to failure of involution of the bulbus cordis, resulting in a muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an infundibular chamber is present between the right ventricular cavity and the pulmonary valve. The pulmonary valve is also often abnormal (*combined valvular and infundibular stenosis*).

The *hemodynamics* and *clinical manifestations* are similar to those described under Valvular Pulmonary Stenosis with the following exceptions: (1) The systolic thrill and murmur are frequently maximal in the third and fourth left parasternal spaces, but radiate widely. (2) Poststenotic dilatation of the pulmonary artery may be present, but is not usual. (3) With an infundibular chamber and valvular pulmonary stenosis two pressure gradients may be noted during cardiac catheterization: between the right ventricle and the infundibular chamber and between it and the pulmonary artery. (4) Selective angiography can be diagnostic in the majority of instances. When contrast material is injected into the right ventricle, the site of the infundibular stenosis is demonstrated, the presence of an infundibular chamber is visualized, and associated abnormalities of the pulmonary valve are shown.

The *complications*, *course* and *prognosis*

are similar to those described under valvular pulmonary stenosis.

In severe cases surgical *treatment* is indicated. This is accomplished with the use of an artificial heart-lung machine. The infundibular stenosis is excised under direct vision and a pulmonary valvuloplasty performed, if there is associated pulmonary stenosis. In patients who have a small pulmonary valve ring, attempts are being made to enlarge the outflow of the right ventricle by the insertion of a plastic prosthesis. After surgery the pressure gradients are reduced or abolished.

**PULMONARY STENOSIS WITH ARTERIOVENOUS SHUNT**

Valvular or infundibular pulmonary stenosis or both may be associated with a left-to-right shunt across an atrial septal defect, a ventricular septal defect or a patent ductus arteriosus. The clinical features depend on the degree of stenosis and the magnitude of the left-to-right shunt.

**Pulmonary Stenosis and Atrial Septal Defect.** In patients with dominant valvular pulmonary stenosis and a small left-to-right shunt across an atrial septal defect the clinical picture is indistinguishable from that described under Valvular Pulmonary Stenosis. If the shunt across the atrial defect is large and the pulmonary stenosis slight, the clinical manifestations are similar to those described under Atrial Septal Defect, but the systolic murmur

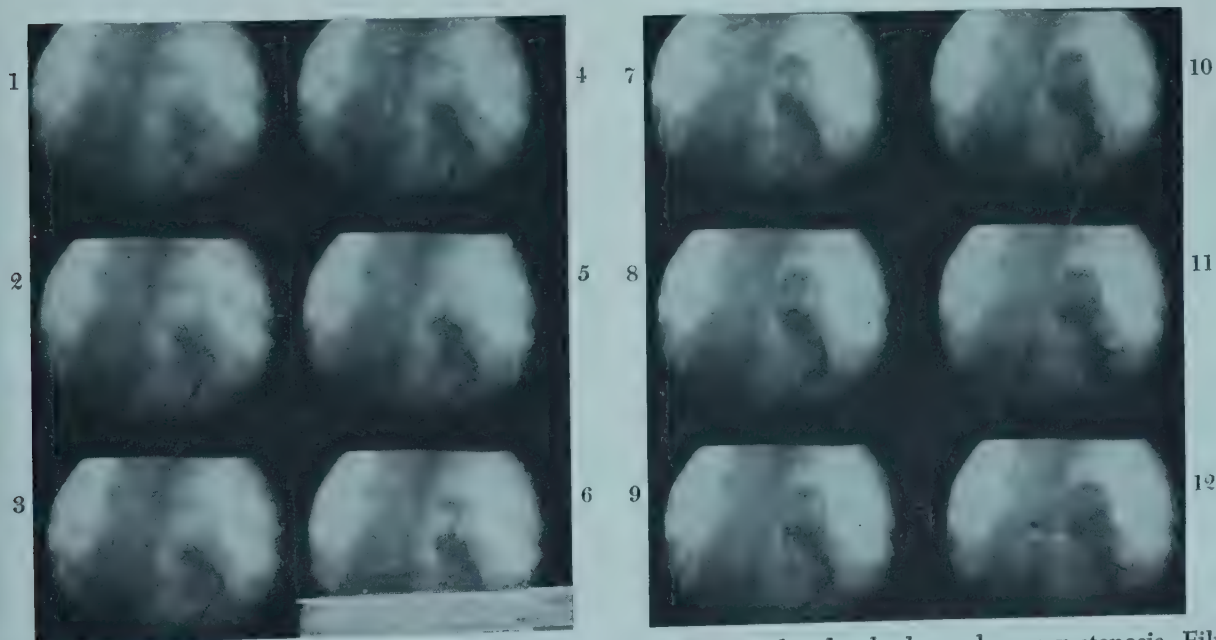


FIG. 269. Selective cine-angiogram in a patient with isolated valvular pulmonary stenosis. Film speed is 60 frames per second. The tip of the catheter is in the outflow of the right ventricle. The patient is in a slight left posterior oblique projection. The contrast material enters the outflow of the right ventricle and shows the pulmonary valve in diastole. During the next ventricular systole a jet of contrast material passes through the valve and mushrooms into a dilated pulmonary artery.

is harsh and frequently accompanied by a thrill. The diagnosis can be made during cardiac catheterization when a left-to-right shunt is demonstrated at the atrial level, and the pulmonary stenosis is shown by the presence of a pressure gradient across the valve. Selective angiocardiology also shows the presence of pulmonary stenosis, and dye dilution curves confirm the left-to-right shunt across the atrial defect.

**Pulmonary Stenosis and Ventricular Septal Defect.** When the ventricular septal defect is dominant and the pulmonary stenosis is slight, the clinical picture is that of ventricular septal defect, and the presence of pulmonary stenosis is not recognizable. However, during cardiac catheterization a gradient is measured across the pulmonary valve, and the left-to-right shunt is demonstrated at the ventricular level. The recognition of a small ventricular septal defect with dominant valvular or infundibular pulmonary stenosis is also difficult. Even during cardiac catheterization the small shunt across the ventricular defect may not be demonstrated, and the diagnosis of isolated pulmonary stenosis made erroneously.

**Pulmonary Stenosis and Patent Ductus Arteriosus.** In addition to the signs of pulmonary stenosis, a machinery type of murmur is audible over the pulmonary area. This combination of anomalies is suspected in patients with the signs of patent ductus arteriosus and right ventricular hypertrophy. Pulmonary atresia is excluded by the absence of cyanosis and the poststenotic dilatation of the pulmonary artery.

**Treatment of Pulmonary Stenosis with Arteriovenous Shunt.** This group of anomalies is treated by direct-vision surgery during cardiopulmonary bypass with an artificial heart-lung machine. The defects in the atrial or ventricular septa are closed and the pulmonary stenosis treated by infundibular resection or pulmonary valvuloplasty. If the ductus is patent, it is divided during the same procedure. Surgery is recommended only in the severe or progressive cases. After successful surgery the left-to-right shunt is obliterated, and the gradient across the valve is reduced or abolished.

#### PULMONARY STENOSIS WITH VENO-ARTERIAL SHUNT

**With Atrial Septal Defect or Patent Foramen Ovale (Trilogy of Fallot).** As indicated above, patients with moderate or severe

valvular or infundibular stenosis have right ventricular systolic hypertension. If, in addition, the right atrium has difficulty in emptying during right ventricular diastole (which occurs during right atrial systole), the right atrial pressure rises. This results in reversal of the shunt to a right-to-left one across the atrial septal defect and in cyanosis. A similar sequence of events occurs if the foramen ovale is patent.

Cyanosis may be present at birth or appear later, frequently during adolescence, and is accompanied by clubbing and polycythemia. The jugular venous pressure is increased in many instances with an intrinsic "a" wave. Other physical signs and technical data are similar to those described under severe valvular pulmonic stenosis. The right-to-left shunt produces arterial oxygen unsaturation.

Surgical therapy is required in all cases and preferably consists in pulmonary valvotomy and closure of the atrial septal defect with an artificial heart-lung machine.

**With Ventricular Septal Defect.** This condition is similar to that of tetralogy of Fallot (see p. 842).

#### COARCTATION OF THE AORTA

Constrictions of varying length may occur at any point between the arch and the bifurcation of the aorta, but 98 per cent of them occur as a localized stricture just below the origin of the left subclavian artery and about twice as often in males as in females.

**Hemodynamics.** Owing to the mechanical obstruction of the aorta, extensive collateral circulation usually develops, chiefly from the branches of the subclavian artery: the superior intercostal artery and the internal mammary with its intercostal, superior epigastric and musculophrenic branches. The thoracic and subscapular branches of the axillary artery may also enlarge as collateral channels. These vessels unite with the intercostal branches of the descending aorta and inferior epigastric branches of the femoral artery, thus creating a channel for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation become enormously enlarged and tortuous.

The blood pressure is elevated in the vessels arising proximal to the coarctation; below it the amplitude of pulsation is diminished, and the pressure below the constriction is lower than that above it. The basis for the



hypertension is not clear. It does not appear to be due to the mechanical obstruction alone, nor does renal ischemia play a major role.

**Clinical Manifestations.** Although incapacitating symptoms are not usual during the first decade of life, they may develop at any age and are the result of the hypertensive state, myocardial weakness and/or a deficient circulation in the lower extremities. Hypertension may result in epistaxes and throbbing headaches, and the symptoms of left ventricular or frank congestive cardiac failure may occur secondary to the hypertensive state. Cerebral hemorrhages are not uncommon. Deficient circulation to the lower extremities may be evidenced by cold feet and occasionally by intermittent claudication.

The classic sign of coarctation of the aorta is the disparity in pulsations and blood pressures between the upper and lower extremities. The femoral, popliteal, posterior tibial and dorsalis pedis pulsations are weak and delayed or absent, in contrast with the bounding pulses of the upper extremities and carotid vessels. In normal persons the systolic blood pressure in the legs as obtained by the cuff method is about 20 to 40 mm. of mercury higher than that in the arms. In coarctation of the aorta the blood pressure in the legs is much lower than that obtained in the arms; frequently it cannot be obtained. Elevation of blood pressure in the upper extremities may appear at any age from infancy, but hypertension of some degree is the rule in older patients. There is also a rise of blood pressure in response to exercise. It is essential to determine the blood pressure in both upper extremities; a difference of more than 30 mm. between the right and left arms suggests involvement of the left subclavian artery in the area of coarctation.

The collateral arterial circulation may give rise to visible and palpable pulsations and to systolic murmurs, especially in the back between the scapulae and at their angles. These signs are usually more striking after the first decade of life, as is enlargement of the heart with a left ventricular apical impulse. Murmurs are variable in location, intensity and quality and are not diagnostic. The common murmur is systolic in time, maximal over the base of the heart and radiates down the sternum to the apex and to the interscapular area; sometimes it is loudest in the back. The murmur may be produced by the coarctation, by tortuous collateral vessels, by abnormalities of the aortic valve or by associated structural anomalies of the heart such as septal

defects. Occasionally there is also a diastolic element, which may be due to associated congenital or rheumatic aortic insufficiency; it is heard best over the base of the heart and down the left sternal border. A continuous murmur over the pulmonary area radiating to the left clavicle suggests an associated patent ductus arteriosus. Rarely a diastolic murmur is heard in the back, presumably owing to collateral circulation. A rumbling apical diastolic murmur of uncertain origin may also be present; at times it may be due to coincident rheumatic mitral stenosis.

The findings on *roentgen examination* depend on the age of the patient and on the effects of hypertension and collateral circulation. In infancy there are usually no changes except cardiac enlargement if congestive cardiac failure develops. During childhood the findings are not striking except on occasion when the left ventricle is prominent. After the first decade the heart tends to be mildly or moderately enlarged, owing to left ventricular prominence. The enlarged left subclavian artery commonly produces a prominent shadow in the left superior mediastinum. Notching of the inferior border of the ribs due to pressure erosion from enlarged collateral vessels is common by late childhood, except in the upper or lower two or three ribs. Rarely erosion is unilateral and is due to one of the subclavian arteries arising below the area of coarctation. In the majority of instances there is an area of poststenotic dilatation of the descending aorta. This may be manifest by displacement of the barium-filled esophagus and by discontinuity of the lateral margin of the aorta below the arch (Fig. 270). Prominent serrations on the posterior aspect of the barium-filled esophagus suggest the presence of large intercostal arteries entering the aorta below the coarctation. Occasionally scalloping in the soft tissues may be visualized retrosternally; it is due to dilated internal mammary arteries.

The *electrocardiogram* is commonly normal in children, but may reveal evidences of left ventricular hypertrophy and occasionally of left bundle branch block. Other coexisting cardiovascular anomalies should be suspected if right ventricular hypertrophy is present. The pattern of incomplete right bundle branch block may be present in the absence of associated anomalies. The *ballistocardiogram* is usually abnormal, showing a shortened J-K stroke due to a small or absent K wave.

Most often the diagnosis can be made by

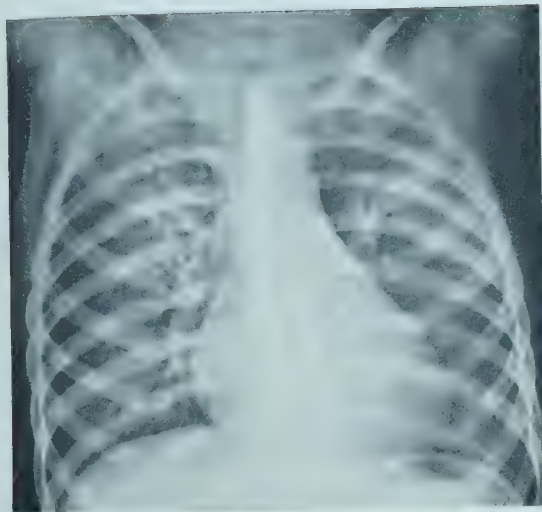


FIG. 270. Teleroentgenogram in a 6-year-old boy with coarctation of the aorta. The left ventricle is prominent, but there is no evidence of rib notching. The barium-filled esophagus is indented by the poststenotic dilatation. (Compare with retrograde aortogram, Fig. 271.)

physical examination. Routine examination of all hypertensive subjects and of all infants in whom cardiovascular defects are suspected should include palpation of all the major accessible peripheral arteries. This simple maneuver will make the correct diagnosis obvious. The segment of coarctation can be demonstrated by retrograde aortography or angiocardiology (Fig. 271), but these studies are seldom indicated except when the site of coarctation is considered to be unusual.

**Associated Abnormalities.** Associated defects are not uncommon and may produce gross physical signs which allow a correct diagnosis. Bicuspid aortic valves are relatively common, but usually do not produce any signs unless aortic incompetence or stenosis develops. Rheumatic mitral stenosis and aortic insufficiency are rare complications. The association of patent ductus arteriosus and coarctation of the aorta is discussed later. Ventricular and atrial septal defects may be suspected by the additional signs of left-to-right shunt.

Severe neurologic damage or even death may occur from associated cerebral vascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, of other vessels with defective elastic and medial tissue or of normal vessels; these accidents are secondary to the hypertensive state. Abnormalities of the subclavian arteries may also occur and include involvement of the left subclavian artery in the area of coarctation,

stenosis of the orifice of the left subclavian artery and anomalous origin of the right subclavian artery.

**Prognosis and Complications.** Although some patients with coarctation of the aorta live well into middle life without serious handicap, this is not the usual course. The majority succumb between the ages of twenty and forty years. Symptoms may appear in infancy and are nearly always present by the age of twenty-five years. The common serious complications are those related to the hypertensive state which may result in congestive cardiac failure or intracranial hemorrhage. If heart failure develops, the coarctation is frequently complicated by other anomalies, e.g., bicuspid aortic valve with aortic stenosis and/or insufficiency. Subacute bacterial endocarditis or endarteritis is also a frequent complication and most commonly involves abnormal aortic valves. Rupture of the aorta is also common and is due to defective elastic and medial tissue. Aneurysms of the descending aorta or of the enlarged collateral vessels are not unusual. The natural course in the individual case is unpredictable.

**Treatment.** In view of the natural course of coarctation of the aorta, most patients should be treated surgically. The optimum age for surgery is between eight and fifteen years, because at this time the aorta has a good elasticity with little or no degenerative changes, and the lumen after anastomosis is adequate to carry the patient through adult life (Gross). The mortality rate at this age is less than 2 per cent. After the second decade the operation is more hazardous, owing to a decreased cardiac reserve and de-



FIG. 271. Retrograde aortogram in coarctation of the aorta. (Same patient as Fig. 270.) The areas of coarctation and poststenotic dilatation are visualized.



generative changes or even aneurysms around the area of coarctation. However, if the cardiac reserve is sufficient, the condition can be satisfactorily repaired well into mid-adult life. The mortality rate in this age group is about 5 per cent.

Associated valvular lesions producing severe hemodynamic changes greatly increase the hazards of surgery. Surgical treatment is probably contraindicated in the presence of severe aortic insufficiency, but not in mild insufficiency.

The operation of choice is excision of the area of coarctation and primary anastomosis. If the length of aortic constriction does not allow primary anastomosis, aortic grafts may be used (Gross). Sympathectomy is of no value in the treatment of hypertension due to coarctation. Anastomosis of the left subclavian artery and the aorta below the coarctation (Blalock and Park) has generally been abandoned.

After operation there is a striking improvement in the amplitude of pulsations in the femoral artery. Patients may note a definite increase in the temperature of their legs. Headaches and epistaxes disappear, and symptoms of cardiac failure are improved. The relief of hypertension may be delayed for three or four weeks. Murmurs may not disappear after operation; they are probably due to persistent enlargement of the collateral vessels or aortic valve disease.

Hypertension with abdominal pain may occur in the immediate postoperative period. The abdominal pain varies in severity and may subside without treatment. In other instances it is associated with anorexia, nausea, vomiting, leukocytosis and even signs of small bowel obstruction. These patients usually respond to therapy with antihypertensive drugs, but in some instances surgical treatment for intestinal obstruction is indicated. This complication is due to mesenteric arteritis, but its cause is unknown.

**Coarctation of the Aorta in Infancy.** In rare instances coarctation of the aorta is complicated by severe congestive cardiac failure during infancy. Gross suggests that failure at this early age is due to closure of the ductus arteriosus in the absence of a well developed collateral circulation; Nadas suggests that it results from severe degrees of coarctation at birth. Endocardial sclerosis is not infrequently associated with coarctation of the aorta and may also be the mechanism of the heart failure (Bonham-Carter). It is also apparent that

uncomplicated coarctation may produce heart failure in infancy.

Symptoms usually appear within the first three months of life. The infant is severely ill and irritable and has tachypnea. Heart failure is manifest by hepatomegaly, rales in the chest and increased venous pressure. Absent or weak femoral arterial pulsations contrast with normal or bounding radial pulses. The heart is greatly enlarged, and a systolic murmur over the whole precordium with gallop rhythm is frequent. Roentgen studies confirm the cardiac enlargement; the heart shape is globular. The electrocardiogram reveals left ventricular hypertrophy, frequently with T wave inversion over the left precordium. Right ventricular hypertrophy may be associated.

Vigorous therapy for congestive heart failure is indicated. This includes digitalis, mercurial diuretics, low-salt diet and oxygen. In the majority of instances there is a slow but definite response over a period of weeks. These patients tend to do well after infancy, and surgery is undertaken between the optimal ages of eight and fifteen years. Surgery is indicated during infancy only in rare instances.

#### COARCTATION OF THE AORTA AND PATENT DUCTUS ARTERIOSUS

Many anatomic and physiologic classifications have been devised in an attempt to describe the nature of these coexisting abnormalities. The anatomic classifications depend on the site and length of coarctation, the site of the aortic opening of the ductus and the size of the aorta proximal to the coarctation. The direction of blood flow across the ductus depends primarily on the pulmonary vascular resistance. In the majority of instances the pulmonary vascular resistance is lower than the systemic resistance, so that the shunt is from aorta to pulmonary artery. This occurs irrespective of the site of aortic opening of the ductus in relation to the coarctation. In these patients the signs of patent ductus arteriosus are superimposed on those of coarctation of the aorta, and both lesions may be treated surgically simultaneously.

In infancy a large patent ductus arteriosus entering below a coarctation may be associated with a high pulmonary vascular resistance. This results in a reversal of blood flow across the ductus, so that the aorta below the coarctation is supplied with venous blood from the pulmonary artery. In this age group

these lesions are associated frequently with other complex cardiac malformations such as endocardial sclerosis with or without mitral and aortic valvular disease, transposition of the aorta and pulmonary artery and ventricular septal defect. Symptoms occur early and include dyspnea, cyanosis, superimposed pulmonary infections and feeding difficulties. Congestive cardiac failure also occurs early. Because the descending aorta is supplied with venous blood, differential cyanosis may be expected with cyanosis below the pelvic brim and a normal color of the upper half of the body. Unfortunately this sign is not always conspicuous, even if carefully looked for. The femoral pulses are present, but are sometimes weak. Although the heart is enlarged, murmurs are not diagnostic. The murmur is systolic, is heard over the whole precordium and is usually followed by a loud second sound. The electrocardiogram shows right ventricular hypertrophy. Roentgen examination confirms the cardiac enlargement and also reveals increased pulmonary vascularity. The prognosis is usually poor, and therapy is symptomatic.

### ANOMALOUS PULMONARY VENOUS RETURN

Abnormal development of the pulmonary veins may result in their anomalous drainage into the systemic venous circulation. The position of abnormal entry may be into the right atrium, into the superior or inferior vena cava or one of their major tributaries or into a persistent left superior vena cava, which opens into the coronary sinus. Rarely, the pulmonary veins may enter the portal vein. An associated atrial septal defect is frequently present. All or only part of the pulmonary venous return may empty into the systemic venous circulation.

#### PARTIAL ANOMALOUS PULMONARY VENOUS RETURN

A varying number of pulmonary veins may enter the systemic venous circulation or right atrium. This results in a left-to-right shunt of oxygenated blood, which is enhanced if there is an associated atrial septal defect. Partial anomalous pulmonary venous return usually involves some or all of the veins of only one lung, more frequently the right. The history, physical signs, electrocardiogram and roentgen findings are indistinguishable from those of atrial septal defect (ostium secundum). Occasionally an anomalous vein



FIG. 272. Teleroentgenogram in partial anomalous pulmonary venous return with an atrial septal defect. Note the cardiac enlargement, prominent pulmonary artery and pulmonary overvascularity. (Compare with Fig. 273.)

is visible radiologically as a crescentic shadow of vascular density along the right border of the cardiac silhouette.

During *cardiac catheterization* the catheter may enter the anomalous pulmonary vein from the superior vena cava or right atrium or may traverse the associated atrial septal defect. The site of left-to-right shunt depends on the point of entry of the pulmonary veins and may be found in the superior vena cava or right atrium. Frequently the oxygen content and saturation of the caval and right atrial blood are indistinguishable from those of atrial septal defect. Dye dilution curves are valuable to demonstrate the presence of anomalous pulmonary veins. The indicator dye is injected first into one and then the other pulmonary artery, and the circulation time measured from the blood of a peripheral artery or with an ear oximeter. The lung with anomalous venous drainage has a significantly longer circulation time. Anomalous pulmonary veins may also be demonstrated by *selective angiocardiology*.

The *prognosis* is similar to that described under atrial septal defect (ostium secundum).

In symptomatic patients surgical *therapy* is indicated. This is usually undertaken during cardiopulmonary bypass or hypothermia. If there is an associated atrial septal defect, it should be closed in such a way as to direct the pulmonary venous return to the left atrium.

#### TOTAL ANOMALOUS PULMONARY VENOUS RETURN

There is no venous connection with the left atrium, and all the blood returning to the



heart (the systemic and pulmonary venous blood) enters and mixes in the right atrium. Some of the blood passes into the right ventricle and pulmonary artery, and the remainder passes through an atrial septal defect or patent foramen ovale to the left atrium.

Usually the pulmonary veins form a single trunk before entering the systemic venous circulation at one of the following sites: left superior vena cava (43 per cent), coronary sinus (19 per cent), right atrium (14 per cent) and right superior vena cava (12 per cent) (Keith et al.). The remainder enter the portal vein or ductus venosus.

Most often symptoms occur during the first two years of life and include tachypnea, poor weight gain and congestive heart failure. Cyanosis may not be definite in many patients, especially in early life, but in others the sign may be striking. The left side of the chest is frequently protuberant and the heart enlarged. On auscultation gallop rhythm is usual. In early life murmurs may not be audible, but in the majority of instances a systolic murmur is heard maximally down the left sternal border and may be followed by a diastolic murmur. A continuous murmur with the quality of a venous hum may be audible over the pulmonary area and sometimes under the right clavicle.

The *electrocardiogram* demonstrates right ventricular hypertrophy, and the P waves are frequently tall and spiked. The roentgen examination is pathognomonic if the pulmonary veins enter the innominate vein and persistent left superior vena cava (Fig. 273). It consists of a large supracardiac shadow producing a "figure-of-eight" or "snowman" appearance. The supracardiac shadow is produced by the dilated left superior vena cava, left innominate vein and right superior vena cava. If the pulmonary veins drain elsewhere, the heart is enlarged, the pulmonary artery and right ventricle are prominent, and the pulmonary vascularity increased.

*Cardiac catheterization* shows that the oxygen saturation of blood in both atria, both ventricles and the aorta is more or less similar and higher than that of peripheral systemic venous blood. In older patients the pulmonary arterial and right ventricular pressures may be only moderately elevated, but in infancy pulmonary hypertension is usual. The catheter may enter the left superior vena cava. *Selective angiocardiology* after injection of contrast medium into the pulmonary artery shows the anatomy of the pulmonary

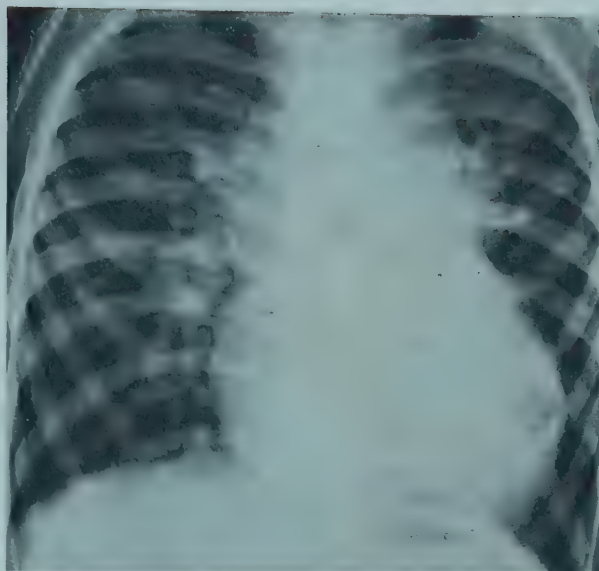


FIG. 273. Teleroentgenogram in a patient with total anomalous pulmonary venous return, showing the "snowman" or "figure-of-8" configuration (see text).

veins and their point of entry into the systemic venous circulation.

The *prognosis* is usually poor, and survival beyond infancy is unusual; death is due to congestive heart failure. Patients who survive beyond two years of age may have surprisingly few symptoms. Surgical *treatment* is now possible and is undertaken preferably with the heart-lung machine. The common pulmonary venous trunk is anastomosed to the left atrium, the atrial septal defect is closed, and the connection to the systemic venous circuit is obliterated. Although the surgical results are good in older children, the risk is high in infancy.

## CONGENITAL AORTIC STENOSIS

Congenital aortic stenosis accounts for about 3 per cent of all cardiac malformations; it is more common in males (3:1). In the majority of instances the stenosis is valvular, the leaflets thickened and the commissures fused in varying degrees. In others the stenosis is subvalvular (subaortic) with a fibrous obstruction to the left ventricular outflow below the aortic valves.

Most often the child is asymptomatic, the physical development is good and the abnormality is discovered during routine physical examination. Fatigue and dyspnea are present in some patients. In contradistinction to aortic stenosis in adults, children seldom experience angina pectoris, syncope or left ventricular failure. The pulse is usually nor-

mal; it sometimes has a small volume, and it is anacrotic in the minority of patients. The heart size and apical impulses are usually normal. A coarse, harsh systolic ejection murmur, usually accompanied by a thrill, is audible maximally in the aortic area and radiates down the left sternal border and toward the apex. In some patients the systolic murmur may be maximal down the left sternal border or even at the apex. Diastolic murmurs are not infrequent. Concomitant aortic insufficiency produces an aortic blowing diastolic murmur, and in some patients an apical mid-diastolic rumbling murmur is audible in the presence of a normal mitral valve. The normal splitting of the second heart sound is usually present, but it may be single.

The electrocardiogram is frequently a reliable guide to the severity of the stenosis. If the gradient of pressure across the aortic valve is small, the electrocardiogram is normal. In severer cases there is evidence of left ventricular hypertrophy even with inversion of T in V<sub>6</sub>. Roentgen studies confirm that the cardiac size is unusually normal. The ascending aorta is frequently prominent, but the aortic knob is normal.

Right cardiac catheterization does not reveal any abnormalities. In severe cases the gradient across the aortic valve may be measured by the simultaneous recording of left ventricular and aortic or brachial artery pressures. Because the left atrium is normal in size, left ventricular pressures are usually obtained by direct left ventricular puncture.

The *prognosis* is good in the majority of children; however, in a small number sudden death, frequently precipitated by severe physical exertion, has been reported. In these patients there is usually evidence of gross left ventricular hypertrophy. The prognosis is also affected by associated malformations, including ventricular and atrial septal defects, coarctation of the aorta and pulmonary stenosis. A small group of patients with aortic stenosis succumb during infancy from congestive heart failure. In these patients associated endocardial sclerosis of the left ventricle and atrium and mitral valve may be found.

*Surgical treatment* is indicated in patients with dyspnea and fatigue and with electrocardiographic evidence of gross left ventricular hypertrophy. The aortic valvotomy is performed under direct vision during cardiopulmonary bypass or hypothermia. Postoperative evaluation is difficult, owing to the paucity of symptoms prior to surgery, and

because aortic insufficiency may be produced by the valvotomy. However, the electrocardiographic improvement with alleviation of the signs of left ventricular hypertrophy indicates that the gradient across the aortic valve has been abolished or improved. Surgery is not indicated in the absence of definite evidence of left ventricular hypertrophy. There is probably some danger in allowing these patients to participate in active competitive sport, but otherwise they should lead normal lives. The status of each patient should be reviewed annually, and surgery advised if progression of signs is definite. Since subacute bacterial endocarditis may develop in these patients, penicillin prophylaxis is indicated at the time of tonsillectomy, dental extractions and oral surgery.

### CONGENITAL MITRAL STENOSIS

This relatively rare anomaly is usually associated with other defects, the commonest ones being patent ductus arteriosus, aortic stenosis and coarctation of the aorta. The role of endocardial sclerosis in the etiology of this anomaly is not clear. The mitral valve is funnel shaped, its leaflets are thickened, and the chordae tendineae are shortened and deformed.

Symptoms usually appear within the first two years of life. The infants are underdeveloped and usually have obvious dyspnea, and cyanosis is not infrequent. Episodes of congestive heart failure are common. The heart is usually enlarged, owing to dilatation and hypertrophy of the right ventricle. Although a variety of murmurs have been described (mainly systolic in time), our four cases all had rumbling diastolic murmurs followed by a loud first sound. The second sound is loud and split. The electrocardiogram reveals right ventricular hypertrophy, with normal, bifid or spiked P waves. Roentgen studies usually show generalized cardiac enlargement, pulmonary congestion and increased hilar markings. Cardiac catheterization demonstrates an increase in right ventricular, pulmonary artery and pulmonary wedge pressures and may also demonstrate the presence of such associated anomalies as patent ductus arteriosus. Angiocardiography may show delayed emptying of the left atrium.

The *prognosis* is usually poor; the majority of children succumb during the first two years of life. *Surgical treatment* has been attempted, but the results have been poor.



## ANOMALIES OF THE AORTIC ARCH

### RIGHT AORTIC ARCH

In this abnormality the aorta curves to the right and descends on the right side of the vertebral column; it is usually associated with other cardiac malformations. It is found in 20 per cent of cases of tetralogy of Fallot and is common in truncus arteriosus. A right aortic arch without other anomaly is asymptomatic. It can be demonstrated roentgenographically; the aortic arch is delineated to the right of the sternum. The barium-filled esophagus is indented on its right border at the level of the aortic arch.

### VASCULAR RINGS

Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression on these structures. The following are the more common anomalies: (1) double aortic arch (Figs. 274, 275), (2) right aortic arch with left ligamentum arteriosum, (3) anomalous right subclavian artery arising as the last major thoracic branch of a normally placed aorta (Fig. 276), (4) anomalous innominate artery arising further to the left on the arch than usual, (5) anomalous left carotid artery arising further to the right than usual and passing anterior to the trachea.

The clinical patterns are extremely variable. In some instances, and especially with anomalous right subclavian artery, the condi-

tion is asymptomatic. If the vascular ring produces compression of the trachea and esophagus, symptoms are frequently present during infancy. Respirations are wheezing in quality and aggravated by crying, feeding and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Vomiting is frequent. There may be a brassy cough, and complicating pneumonia is common. The diagnosis is established by examination of the barium-filled esophagus during fluoroscopy and on roentgenograms (Figs. 275, 276) and by observation of the air- or Lipiodol-filled trachea.

Surgery is advised in symptomatic patients with radiographic evidence of tracheal and/or esophageal compression. The appropriate vessel is divided in patients with double aortic arch (Fig. 274). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. An anomalous right subclavian artery is divided at its origin from the aorta. Anomalous innominate or carotid arteries cannot be divided; the tracheal compression is relieved by attaching the adventitia of these vessels to the sternum.

### ANOMALOUS ORIGIN OF CORONARY ARTERIES

**Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery.** In this condition the arterial blood supply to the left myocardium is from the pulmonary artery (venous blood at a low perfusion pressure).

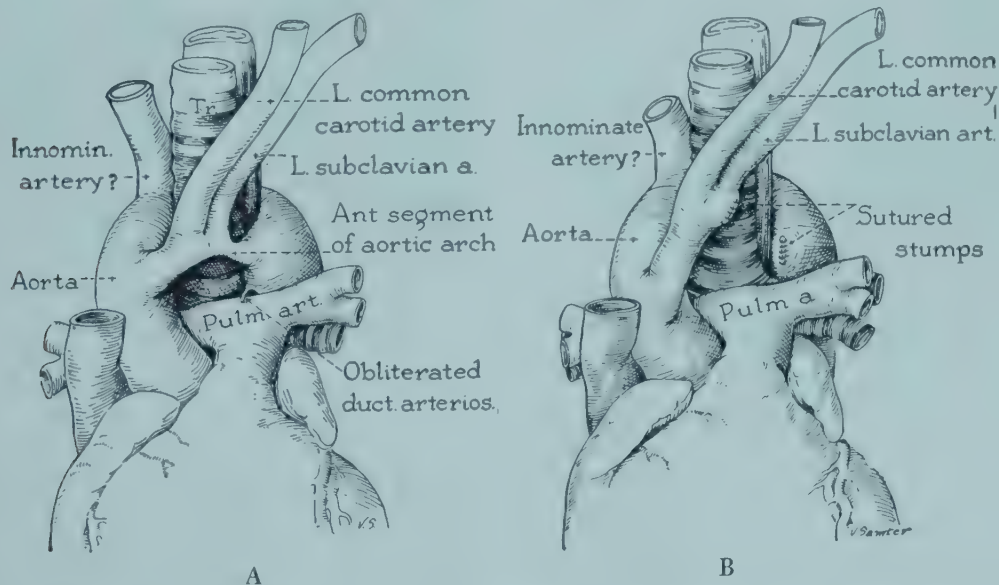


FIG. 274. Double aortic arch. A, Small anterior segment of double aortic arch (most common type). B, Operative procedure for release of vascular ring. (Courtesy of Dr. Willis J. Potts.)

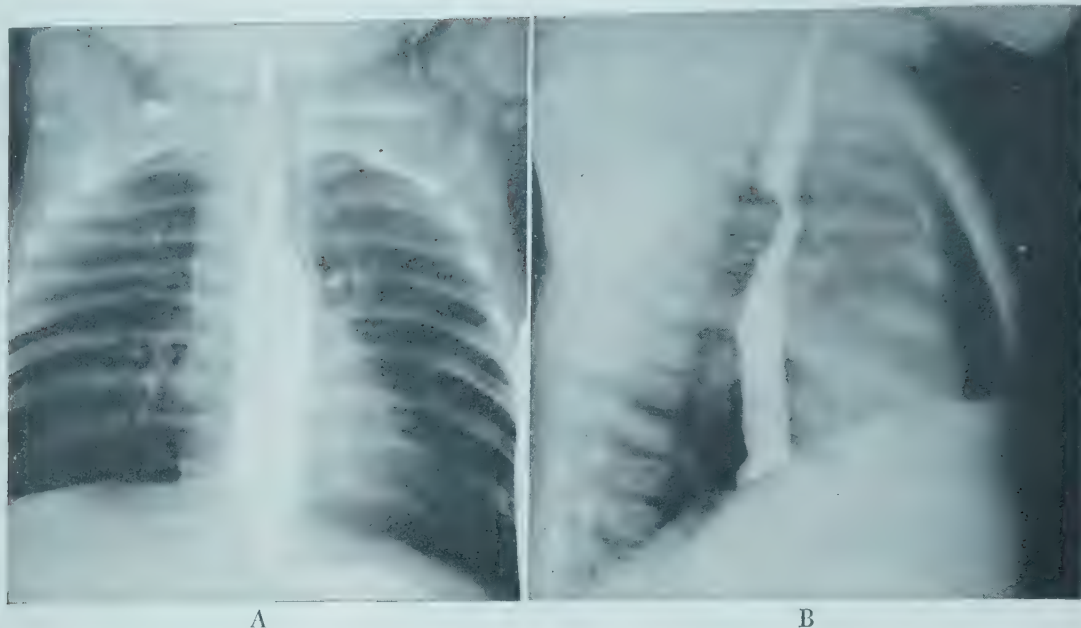


FIG. 275. Double aortic arch in an infant aged 5 months. *A*, Anteroposterior view. The barium-filled esophagus is constricted on both sides. *B*, Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at operation. (Courtesy of Drs. Eugene Saenger, Frederick Silverman and Edward McGrath.)

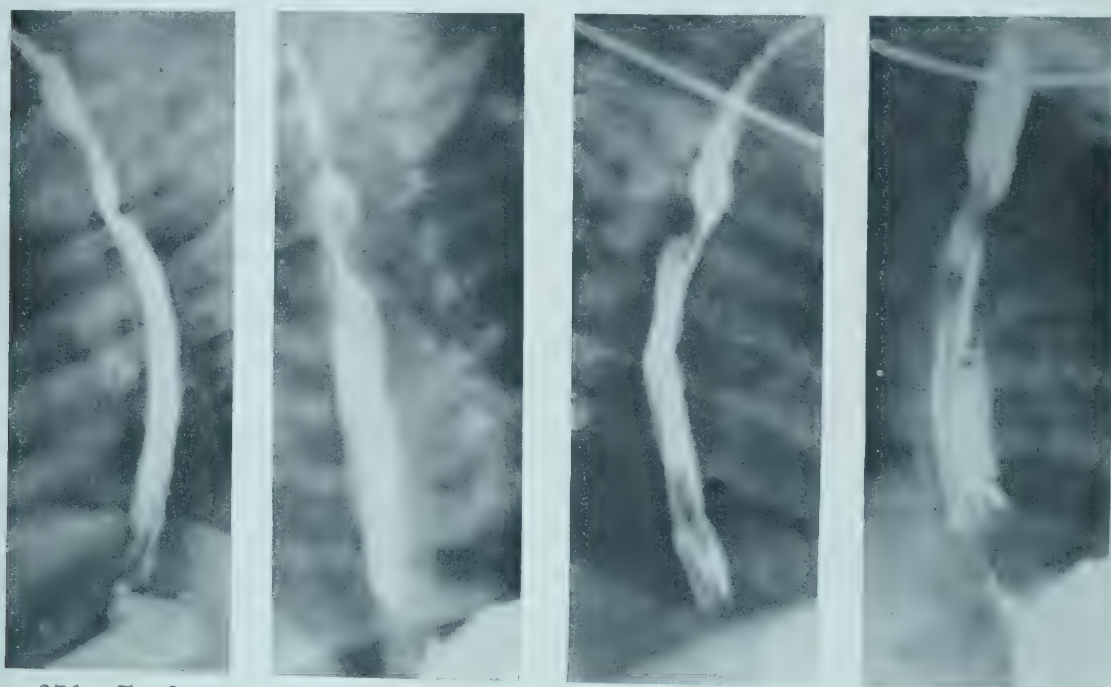


FIG. 276. Esophagram of a child with aberrant origin of the right subclavian artery as a last branch from the arch of the aorta. The positions from left to right are lateral, left anterior oblique, right anterior oblique, anteroposterior. A constant defect is visualized on the posterior aspect of the esophagus.

The right coronary artery becomes enlarged, and collateral channels may result in a reverse flow in the abnormal left coronary artery (Keith, Rowe and Vlad). The left ventricle becomes dilated and somewhat hypertrophied with patchy fibrosis and microscopic deposition of calcium.

In the majority of instances symptoms

occur during the first few years of life, and are those of congestive heart failure, frequently associated with or precipitated by respiratory infections. Irritability and discomfort, sometimes aggravated by feeding could be interpreted as being produced by angina pectoris. Cardiac enlargement is moderate to marked, but murmurs are insignifi-



cant. Roentgen examination confirms the cardiomegaly, but the contour and pulsations are not specific unless there is a complicating ventricular aneurysm. The electrocardiogram resembles the pattern described in anterior myocardial infarction in adults. A QR pattern followed by inverted T waves is seen in standard lead I and aVL. The left ventricular surface leads ( $V_5$  and  $V_6$ ), show deep wide Q waves and may also exhibit elevated S-T segments and inverted T waves. The diagnosis may be established by selective angiocardiology when injection of contrast material into the pulmonary artery demonstrates the origin and distribution of the abnormal left coronary artery. The large right coronary artery may be visualized by retrograde aortography.

In the majority of instances death from heart failure occurs within the first few years of life, although there are some reported cases of survival into adult life. Treatment is symptomatic. Surgical transplantation of the origin of the left coronary artery to the aorta is being investigated.

**Anomalous Origin of Both Coronary Arteries from the Pulmonary Artery** is extremely rare and may be associated with other severe cardiac malformations. The prognosis is usually poor.

**Anomalous Origin of the Right Coronary Artery from the Pulmonary Artery** is also rare, but does not produce signs or symptoms. The prognosis is good, and the condition is found as an incidental pathologic entity.

## PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension is a disease of unknown etiology characterized by hypertension of the lesser circulation and right-sided heart failure. The disease may occur at any age and may be clinically recognizable during childhood and adolescence. The pulmonary hypertension is associated with sclerosis of the pulmonary arteries and arterioles, thickening of the intima, atheromatous deposits and thromboses. Other causes of pulmonary heart disease (chronic cor pulmonale) are absent, and there is no evidence of emphysema, pancreatic fibrosis or kyphoscoliosis. Recurrent pulmonary emboli may produce the same clinical picture, but this disease is rare in childhood.

**Hemodynamics.** The pulmonary hypertension places a mechanical burden on the right ventricle and pulmonary artery with resultant right ventricular hypertension and dilatation

of the pulmonary artery. Sooner or later right-sided heart failure develops, at times with tricuspid insufficiency.

**Clinical Manifestations.** The predominant symptom is increasing dyspnea on effort. Peripheral cyanosis may be present and is associated with cold extremities and a nearly normal arterial oxygen saturation. If right-sided heart failure has supervened, the jugular venous pressure is elevated, and there are hepatomegaly and edema. Jugular venous "a" waves are present and, if functional tricuspid insufficiency has supervened, a conspicuous jugular "c" wave develops with systolic hepatic pulsations. The heart is slightly to moderately enlarged with a right ventricular apical tap. Thrills are absent, and murmurs may be insignificant. A grade 1 systolic murmur may be audible over the pulmonary area, sometimes followed by a blowing diastolic murmur due to pulmonary incompetence. The second heart sound is normally split and accentuated, and presystolic gallop rhythm may be audible down the left sternal border.

*Roentgen studies* reveal a prominent pulmonary artery and right ventricle (Fig. 277). The pulmonary vascularity in the hilar areas may be normal, but the peripheral lung fields are clear. The *electrocardiogram* shows right ventricular hypertrophy with spiked P waves. The diagnosis is confirmed by *cardiac catheterization*, which reveals right ventricular



FIG. 277. Teleroentgenogram in primary pulmonary hypertension, showing moderate cardiac enlargement, pulmonary artery dilatation and relative pulmonary undervascularity in the outer two thirds of the lung fields. This roentgen picture may simulate that found in valvular pulmonic stenosis with normal aortic root.

and pulmonary hypertension with a normal pulmonary "capillary" pressure. The cardiac output is usually low, and the arterial oxygen saturation is nearly normal.

Difficulty may arise in differentiating this condition from isolated pulmonary stenosis. In primary pulmonary hypertension a thrill is absent, murmurs are not significant, and the second sound is normally split. Cardiac catheterization excludes the presence of pulmonary stenosis. If primary pulmonary hypertension is associated with a reversed intratrial shunt through a foramen ovale, the clinical picture may simulate that of the Eisenmenger syndrome.

The disease is progressive, and the results of treatment are disappointing. Some relief may be obtained by the usual measures adopted for congestive cardiac failure.

### MARFAN'S SYNDROME—

#### CARDIOVASCULAR MANIFESTATIONS

The frequent site of involvement in the cardiovascular system in the Marfan syndrome (p. 1243) is the ascending aorta. Aortic dilatation begins at the aortic valve

ring and is usually confined to the ascending aorta. The valve ring is stretched, and the resultant aortic insufficiency may be pronounced. Progressive left ventricular failure occurs with or without angina pectoris. Dissecting aneurysm of the aorta is a common terminal event or may result in the development of aortic valve incompetence. Cardiac symptoms may occur as early as the fifth year of life, but frequently do not appear until adult life.

The pulmonary artery and valve may be involved in a similar way to that of the aorta, resulting in dilatation of the pulmonary artery. This syndrome may explain some cases of *idiopathic pulmonary artery dilatation*. Mitral insufficiency may result from redundant cusps and chordae tendineae. Subacute bacterial endocarditis may be a complication.

The frequency of congenital malformations of the heart in the Marfan syndrome probably has been overstressed. The reported conditions include atrial septal defect, rarely ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus and coarctation of the aorta.

## PRINCIPLES OF TREATMENT IN CONGENITAL HEART DISEASE

The following principles of treatment apply to all patients with congenital heart disease. Owing to rapid advances in the diagnosis and surgical treatment of these anomalies, an attitude of guarded optimism should be adopted. A level of life as nearly normal as possible should be encouraged because untold psychologic trauma is imposed by unnecessary restriction. The parents' attitude toward the child is commonly more relaxed if it is pointed out that sudden death is rare in congenital heart anomalies in contradistinction to some degenerative diseases in adults. Rigorous restriction of physical activities is usually not indicated, since children soon learn their own capacity for exercise. However, if cardiac enlargement is present or there is a history of frank congestive heart failure, competitive sports should be discouraged.

General management includes a well balanced diet, the supplementation of iron and vitamins during the first few years of life and the usual immunization program.

The prevention or prompt treatment of dehydration in cyanotic patients is important so that hemoconcentration and possible

thrombotic episodes will be averted. Infections should be vigorously treated with suitable antibiotics to prevent the onset of subacute bacterial endocarditis or congestive heart failure. The routine use of sulfadiazine, oral penicillin or other antibiotics may be indicated in patients prone to recurrent respiratory infections. Nadas and Rudolph have shown that within limits correction with iron therapy of a "relative hypochromic anemia" in cyanotic patients may improve their exercise tolerance and general well-being. The treatment of congestive heart failure and of paroxysmal dyspneic attacks has been described elsewhere.

**Surgical Treatment.** The standardized surgical therapy of patent ductus arteriosus, coarctation of the aorta and vascular rings has been described elsewhere. The following résumé of open-heart surgery is included because of the widespread successful use of this technique. This complex surgical therapy should not be undertaken until the surgical team has had a successful and wide experience with animals and the physiology of total body perfusion is understood clearly.

**Open-heart surgery.** This technique is used



when surgical treatment of intracardiac defects under direct vision is indicated. The systemic venous return to the heart is diverted to an artificial heart-lung machine, and arterialized blood is returned to the systemic arterial system (*cardiopulmonary bypass*). Thus the major source of blood flow through the heart and lungs is diverted, and the chambers of the "bloodless" heart may be opened widely. The systemic venous return to the heart is picked up by cannulae in the superior and inferior venae cavae usually inserted through the right atrium. The arterialized blood is returned from the heart-lung machine to either the femoral or left subclavian artery. In the former instance the body is perfused in a retrograde direction. With this system of cannulation coronary and bronchial flows are not disturbed, and the heart continues to beat. If it is desired to abolish coronary flow and cardiac contraction during cardiopulmonary bypass, this may be accomplished by the production of *elective cardiac arrest*. This is achieved by cross clamping the ascending aorta, and injecting a "cardioplegic" agent into the aorta so that it enters the coronary circulation.

**Heart-lung machines.** There are a variety of machines to oxygenate the blood, remove an adequate amount of carbon dioxide and pump optimal volumes of arterialized blood back into the patient. These include the following:

**BUBBLE OXYGENATORS.** Oxygen bubbles are allowed to mix directly with the venous blood. The excess gas (mainly oxygen) is coalesced on a polymethylsiloxane surface and removed.

**SURFACE OXYGENATORS.** Venous blood is spread as a thin film on either screens or disks and exposed to oxygen gas.

**MEMBRANE OXYGENATORS.** Membranes permeable to the flow of oxygen and carbon dioxide are placed between the venous blood and the oxygen. Blood is arterialized by the passage of respiratory gases across the membrane.

**The postoperative period.** With successful total body perfusion and direct-vision open-heart surgery, the postoperative course is frequently benign. However, many of these patients may be in a delicate or precarious state. The following complications are listed as a guide to management:

**PLEURAL SPACE COMPLICATIONS.** Pneumothorax and hemothorax are treated along usual lines.

**PULMONARY COMPLICATIONS.** These consist of patchy areas of pulmonary atelectasis with or without edema and hemorrhage. It appears that these complications occur more frequently in patients with pulmonary hypertension and elevated pulmonary resistance. Decompression of the pulmonary vascular tree by cannulation of the left atrium during cardiopulmonary bypass probably decreases the severity of this complication.

**PULMONARY VENTILATION.** Respiratory exchange may be enhanced by the use of tracheotomy and respirators.

**HEMORRHAGE.** Although surgery is conducted in a heparinized state, postoperative bleeding should not be a problem. If it occurs, it may be an expression of inadequate perfusion.

**COMPLETE HEART BLOCK.** This distressing complication is probably produced by surgical trauma to the conduction system during the intracardiac procedure. If the ventricular rate is not adequate, the heart block is treated with isopropylarterenol (Isuprel) intravenously or by the use of a pacemaker. The latter apparatus may be applied externally, but recent reports indicate that better results are obtained by applying the electrical stimulus to wires which have been imbedded in the myocardium. The ultimate prognosis of surgically induced complete heart block is unknown. Spontaneous reversal to sinus rhythm may occur, but death from Stokes-Adams attacks is possible. Digitalis is not contraindicated in the presence of complete heart block.

**CONGESTIVE HEART FAILURE.** This may occur in the immediate postoperative period. Treatment is described elsewhere. We have not used digitalis in all patients preoperatively, but have reserved it for patients who show signs of congestive heart failure.

**ACIDOSIS.** Minor degrees of respiratory acidosis are common and do not require therapy. Severe metabolic acidosis may occur and is usually an indication of inadequate blood flow during cardiopulmonary bypass. It requires treatment (see p. 191).

SAMUEL KAPLAN  
ROBERT A. LYON

## REFERENCES

### General

- Abbott, M. E.: Atlas of Congenital Cardiac Disease. New York, American Heart Association, 1936.  
Keith, J. D., Rowe, R. D., and Vlad, P.: Heart Dis-

ease in Infancy and Childhood. New York, Macmillan Company, 1958.

Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: *Diagnosis of Congenital Heart Disease*. Chicago, Year Book Publishers, Inc., 1955.

Nadas, A. S.: *Pediatric Cardiology*. Philadelphia, W. B. Saunders Company, 1957.

Taussig, H. B.: *Congenital Malformations of the Heart*. New York, Commonwealth Fund, 1947.

Wood, P. H.: *Diseases of the Heart and Circulation*. 2nd ed. Philadelphia, J. B. Lippincott Company, 1956.

#### *Incidence*

MacMahon, B., McKeown, T., and Record, R. G.: The Incidence and Life Expectation of Children with Congenital Heart Disease. *Brit. Heart J.*, 15: 121, 1953.

Ober, W. B., and Moore, T. E., Jr.: Congenital Cardiac Malformations in the Neonatal Period; An Autopsy Study. *New England J. Med.*, 253:271, 1955.

Rauh, L. W.: Incidence of Organic Heart Disease in School Children. *Am. Heart J.*, 18:705, 1939.

Richards, M. R., Merritt, K. K., Samuels, M. H., and Langmann, A. G.: Congenital Malformations of the Cardiovascular System in a Series of 6,053 Infants. *Pediatrics*, 15:12, 1955.

#### *Etiology*

Campbell, M.: Genetic and Environmental Factors in Congenital Heart Disease. *Quart. J. Med.*, 18: 379, 1949.

Warkany, J., Roth, C. B., and Wilson, J. G.: Multiple Congenital Malformations: A Consideration of Etiological Factors. *Pediatrics*, 1:462, 1948.

Wesselhoeft, C.: Rubella (German Measles) and Congenital Deformities. *New England J. Med.*, 240:258, 1949.

Wilson, J. G., and Warkany, J.: Cardiac and Aortic Arch Anomalies in the Offspring of Vitamin A Deficient Rats Correlated with Similar Human Anomalies. *Pediatrics*, 5:708, 1950.

#### *Tetralogy of Fallot*

Brock, R. C.: Congenital Pulmonary Stenosis. *Am. J. Med.*, 12:706, 1952.

Campbell, M., Deuchar, D., and Brock, R. C.: Results of Pulmonary Valvotomy and Infundibular Resection in 100 Cases of Fallot's Tetralogy. *Brit. M. J.*, 2:111, 1954.

Taussig, H. B., and Bauersfeld, S. R.: Follow-up Studies on the First 1,000 Patients Operated on for Pulmonary Stenosis or Atrisia. (Results up to March, 1952.) *Ann. Int. Med.*, 38:1, 1953.

#### *Eisenmenger Syndrome*

Dammann, J. F., Jr., and Ferencz, C.: Clinico-anatomic Correlations; in Lam, C.: *Henry Ford Hospital International Symposium on Cardiovascular Surgery*. Philadelphia, W. B. Saunders Company, 1955.

Edwards, J. E.: Functional Pathology of Congenital Cardiac Disease. *Pediat. Clin. North America*, 1: 13, 1954.

Wood, P.: Pulmonary Hypertension. *Brit. M. Bull.*, 8:348, 1952.

#### *Transposition of the Great Vessels*

Campbell, M., and Suzman, S.: Transposition of the Aorta and Pulmonary Artery. *Circulation*, 4:329, 1951.

Keith, J. D., Neill, C. A., Vlad, P., Rowe, R. D., and Chute, A. L.: Transposition of the Great Vessels. *Circulation*, 7:830, 1953.

#### *Ebstein's Disease*

Mayer, F. E., Nadas, A. S., and Ongley, P. A.: Ebstein's Anomaly: Presentation of Ten Cases. *Circulation*, 16:1057, 1957.

#### *Atrial Septal Defect*

Barber, J. M., Magidson, O., and Wood, P.: Atrial Septal Defect. *Brit. Heart J.*, 12:277, 1950.

Keith, J. D., and Forsyth, C. C.: Auricular Septal Defect in Children. *J. Pediat.*, 38:172, 1951.

Leatham, A., and Gray, I.: Auscultatory and Phonocardiographic Signs of Atrial Septal Defect. *Brit. Heart J.*, 18:193, 1956.

#### *Ventricular Septal Defect*

Blount, S. G., Mueller, H., and McCord, M. C.: Ventricular Septal Defect. *Am. J. Med.*, 18:871, 1955.

Brostoff, P., and Rodbard, S.: Hydrodynamics in Ventricular Septal Defects. *Am. Heart J.*, 51: 325, 1956.

Marquis, R. M.: Ventricular Septal Defect in Early Childhood. *Brit. Heart J.*, 12:265, 1950.

Selzer, A.: Defect of Ventricular Septum. *Arch. Int. Med.*, 84:798, 1949.

#### *Patent Ductus Arteriosus*

Gross, R. E.: The Patent Ductus Arteriosus. Observations on Diagnosis and Therapy in 525 Surgically Treated Cases. *Am. J. Med.*, 12:472, 1952.

Keys, A., and Shapiro, M. J.: Patency of Ductus Arteriosus in Adults. *Am. Heart J.*, 25:158, 1943.

#### *Coarctation of the Aorta*

Crafoord, C., and Nylin, G.: Congenital Coarctation of the Aorta and Its Surgical Treatment. *J. Thoracic Surg.*, 14:347, 1945.

Gross, R. E.: Coarctation of the Aorta. *Circulation*, 7:757, 1953.

Reifenstein, G. H., Levine, S. A., and Gross, R. E.: Coarctation of the Aorta: Review of 104 Autopsied Cases of "Adult Type," 2 Years of Age or Older. *Am. Heart J.*, 33:146, 1947.

#### *Pulmonary Stenosis with Normal Aortic Root*

Abrahams, D. G., and Wood, P. H.: Pulmonary Stenosis with Normal Aortic Root. *Brit. Heart J.*, 13:519, 1951.

Brock, R. C.: Pulmonary Valvulotomy for the Relief of Congenital Pulmonary Stenosis. *Brit. M. J.*, 1: 1121, 1948.

—: Congenital Pulmonary Stenosis. *Am. J. Med.*, 12:706, 1952.

Leatham, A., and Weitzman, D.: Auscultatory and Phonocardiographic Signs of Pulmonary Stenosis. *Brit. Heart J.*, 19:303, 1957.

Swan, H., Virtue, R. W., Blount, S. G., and Kircher, L. T.: Hypothermia in Surgery: Analysis of 100 Clinical Cases. *Ann. Surg.*, 142:382, 1955.



*Anomalous Pulmonary Venous Return*

Edwards, J. E.: Pathologic and Developmental Considerations in Anomalous Pulmonary Venous Return. Proc. Staff Meet., Mayo Clin., 28:441, 1953.

Keith, J. D., Rowe, R. D., and Vlad, P.: Complete Anomalous Pulmonary Venous Drainage. Am. J. Med., 16:23, 1954.

Snellen, H. A., and Albers, F. H.: The Clinical Diagnosis of Anomalous Pulmonary Venous Drainage. Circulation, 6:801, 1952.

*Aortic Stenosis*

Brofman, B. L., and Feil, H.: The Diagnosis of Congenital Subaortic Stenosis: Application of Hemodynamic Principles. Circulation, 6:817, 1952.

Campbell, M., and Kauntze, R.: Congenital Aortic Valvular Stenosis. Brit. Heart J., 15:179, 1953.

*Mitral Stenosis*

Ferencz, C., Johnson, A. L., and Wiglesworth, F. W.: Congenital Mitral Stenosis. Circulation, 9:161, 1954.

*Aortic Arch Anomalies*

Gross, R. E., and Neuhauser, E. B. D.: Compression of the Trachea or Esophagus by Vascular Anomalies: Surgical Therapy in Forty Cases. Pediatrics, 7:69, 1951.

Neuhauser, E. B. D.: The Roentgen Diagnosis of

Double Aortic Arch and Other Anomalies of the Great Vessels. Am. J. Roentgenol., 56:1, 1946.

*Dextrocardia*

Chapman, C. B., and Gibbons, T. B.: New Aids in the Diagnosis of Dextrocardia. Am. Heart J., 39: 507, 1950.

Young, M. D., and Griswold, H. E.: Situs Inversus of the Abdominal Viscera with Levocardia. Report of 8 Cases Submitted to Blalock-Taussig Operation. Circulation, 3:202, 1951.

*Coronary Artery Anomalies*

Hartenstein, H., and Freeman, D. J.: Origin of the Left Coronary Artery from the Pulmonary Artery. Am. J. Dis. Child., 83:774, 1952.

Lyon, R. A., Johansmann, R. J., and Dodd, K.: Anomalous Origin of Left Coronary Artery. Am. J. Dis. Child., 72:675, 1946.

*Primary Pulmonary Hypertension*

Dresdale, D. T., Schultz, M., and Michtom, R. J.: Primary Pulmonary Hypertension. Am. J. Med., 11:686, 1951.

*Principles of Treatment*

Allen, J. G.: Extracorporeal Circulation. Springfield, Ill., Charles C Thomas, 1958.

Rudolph, A. M., Nadas, A. S., and Borges, W. H.: Hematologic Adjustments to Cyanotic Congenital Heart Disease. Pediatrics, 11:454, 1953.

## DISTURBANCES OF RATE AND RHYTHM OF THE HEART

**SINUS ARRHYTHMIA****(RESPIRATORY ARRHYTHMIA)**

This rhythm, characterized by an acceleration of the pulse rate during inspiration and a decrease during expiration, is physiologic in childhood. It is usually associated with cardiac rates under 90 to 100 per minute. It is exaggerated during convalescence from febrile illness and by drugs which increase vagal tone, such as digitalis, and is usually abolished by exercise or atropine. Some children have such great degrees of sinus arrhythmia that the presence of other arrhythmias such as extrasystoles is suspected, and an electrocardiogram is necessary for diagnosis.

**EXTRASYSTOLES****(PREMATURE CONTRACTIONS)**

Extrasystoles are produced by the discharge of an ectopic focus situated anywhere in atrial, nodal or ventricular tissue. They occur less

frequently in children than in adults. In the majority of instances extrasystoles are of no clinical or prognostic significance. Under certain circumstances, however, premature beats may be due to organic heart disease, e.g., in acute rheumatic or diphtheritic carditis. Drugs, especially digitalis and epinephrine, may also produce extrasystoles. Atrial premature contractions may precede atrial fibrillation in rheumatic heart disease with mitral stenosis.

The clinical signs of extrasystoles include the prematurity of the beat followed by a compensatory pause, especially if the ectopic beat arises in the ventricles. In the majority of instances extrasystoles disappear during the tachycardia of exercise. If they remain or become exaggerated during exercise, it suggests that they are associated with organic heart disease. Ectopic beats produce a smaller stroke and pulse volume than normal and, if very premature, may not be audible with a stethoscope or palpable at the radial pulse. Extrasystoles may assume a definite rhythm,

e.g., alternating with normal beats (*pulsus bigeminus*) or occurring after two normal beats (*pulsus trigeminus*). This rhythmicity is frequent in digitalis intoxication. The site of origin of the extrasystoles is determined by the electrocardiogram.

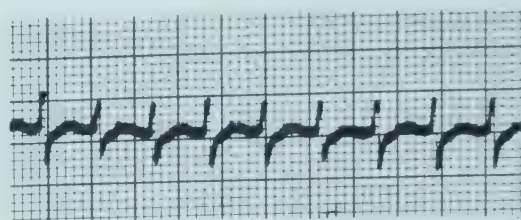
Most patients are unaware of premature contractions. The basis of therapy is convincing reassurance that the arrhythmia is not due to structural heart disease. If extrasystoles are produced by digitalis, the drug should be discontinued or its dose reduced. If relief is sought for palpitations, sedatives, quinidine sulfate or procaine amide may be used.

### PAROXYSMAL TACHYCARDIA

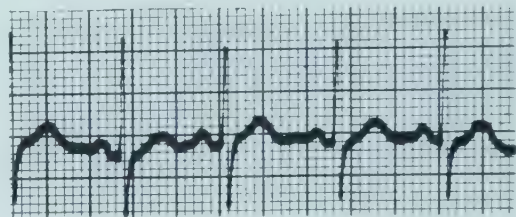
Paroxysmal tachycardia is produced by ectopic beats arising from the same focus in rapid succession. The ectopic focus may be situated anywhere in the atrial, nodal or ventricular tissue. Paroxysmal tachycardia may occur at any age and has been reported in the last month of fetal life. In the majority of instances the ectopic focus is situated in an atrium (paroxysmal atrial tachycardia). Paroxysmal ventricular or nodal tachycardia is rare in infants and children.

In older children attacks of paroxysmal atrial tachycardia are characterized by abrupt onset and cessation. If an attack is not witnessed, its occurrence may be elicited by an accurate history. The attacks may last from a few seconds to several weeks, but usually persist for a few hours and seldom exceed two or three days. The cardiac rate usually exceeds 180 and occasionally may be as rapid as 300 per minute. Sometimes the attack is precipitated by an acute infection. In many instances the patient feels well, and the only complaint is consciousness of the rapid cardiac rate. If the cardiac rate is exceptionally rapid or if the attack is prolonged, precordial discomfort and congestive cardiac failure may supervene.

In young infants the diagnosis may be more obscure. Since the normal cardiac rate at this age is rapid and increases greatly with crying, a persistent tachycardia during quiet periods or sleep suggests the diagnosis. The cardiac rate during paroxysms is frequently in the range of 300 per minute, and signs of congestive cardiac failure rapidly supervene if the attack lasts a few hours or more. The infant is acutely ill, has an ashen and slightly cyanotic color and is restless and irritable. Tachypnea and hepatomegaly are the prominent signs of cardiac failure. Paroxysms may



LEAD I



LEAD I

FIG. 278. Electrocardiogram in paroxysmal atrial tachycardia. Upper tracing taken during paroxysm with heart rate of 215 per minute. Lower tracing, taken during recovery, is within normal limits.

be associated with fever and leukocytosis. The diagnosis is confirmed by the electrocardiogram (Fig. 278), which also identifies the site of the ectopic focus.

**Treatment.** In supraventricular paroxysmal tachycardia (atrial or nodal) simple procedures of vagal stimulation such as pressure over the eyeball or unilateral carotid sinus may abort the attack. Older children may have discovered some maneuver to abolish the paroxysm, such as self-induced vomiting, breath-holding, drinking iced water or the adoption of a particular posture. In infants and many older patients these measures fail, and digitalis should be given in full therapeutic doses if the attack persists for four to eight hours and if congestive cardiac failure has supervened. Sedation is also indicated. In the infrequent instances in which digitalis does not stop the paroxysm, quinidine sulfate or a cholinergic drug such as neostigmine or Mecholyl (acetyl-beta-methylcholine) may be used. Mecholyl may produce side effects of vomiting, sweating, faintness, colic, urgency of micturition and defecation and sometimes cardiac arrest. Atropine sulfate should be available to counteract these side effects. The drugs of choice in paroxysmal ventricular tachycardia are intravenously administered procaine amide or parenteral quinidine sulfate. If attacks occur frequently, digitalis therapy should be maintained, or quinidine sulfate may be continued indefinitely if it is well tolerated.



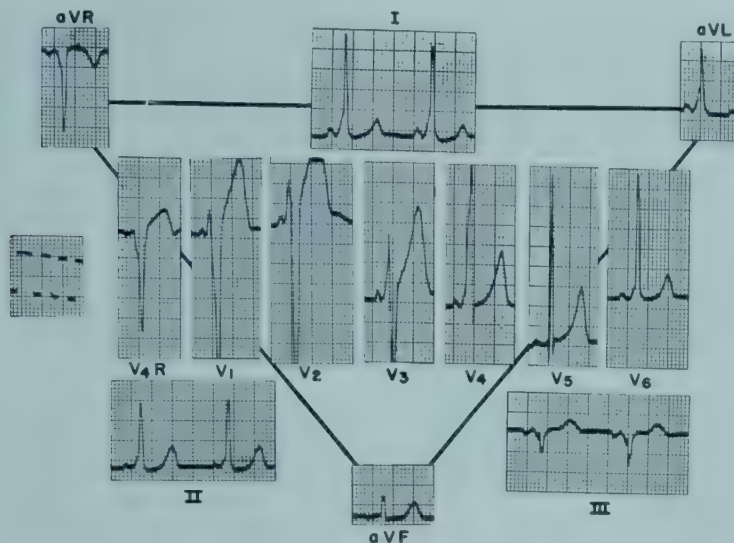


FIG. 279. Electrocardiographic pattern of the Wolff-Parkinson-White syndrome in a 6-year-old boy. The P-R interval is 0.08 second; the duration of the QRS interval, 0.12 second.

In most instances of paroxysmal atrial tachycardia there is no underlying structural cardiac disease. If cardiac failure supervenes during the paroxysms, cardiac function rapidly returns to normal after cessation of the attack. Between attacks some children may exhibit the electrocardiographic signs of the *Wolff-Parkinson-White syndrome*, which is probably due to an anomalous connection by special conducting fibers between the right atrium and the ventricles. Electrocardiography shows a widened QRS complex at the expense of a shortened P-R interval so that the P-S interval as measured from the beginning of the P to the end of the S is normal (Fig. 279). In the majority of instances there is no associated cardiac disease. Paroxysmal atrial tachycardia occurs in about 50 to 60 per cent of patients with the Wolff-Parkinson-White syndrome, and about 5 per cent of patients with paroxysmal tachycardia will exhibit this syndrome between attacks of tachycardia.

## ATRIAL FLUTTER

This arrhythmia is due to rapid and regular but abnormal atrial contractions. Lewis attributed these contractions to a circus movement in the atria; Prinzmetal has suggested that they are due to an irritable focus in the atrial muscle similar to that of paroxysmal atrial tachycardia and atrial extrasystoles. The rate of atrial beats ranges between 250 and 400 per minute. Because the atrioventricular node cannot transmit these rapid impulses, the ventricles respond to every second atrial beat or sometimes to every third or fourth one.

Atrial flutter is not frequent in children, but may sometimes complicate myocarditis of any cause and occasionally acute infectious diseases. The abnormality should be suspected in patients with a regular tachycardia which is not influenced by effort, emotion or posture. Atrial flutter may precipitate congestive cardiac failure. Carotid sinus pressure frequently produces a temporary slowing of the cardiac rate. The diagnosis is confirmed by electrocardiography, which demonstrates the rapid and regular atrial flutter, "f" waves.

*Treatment* is by digitalizing to convert the arrhythmia into atrial fibrillation. Normal sinus rhythm may then be restored when the digitalis is discontinued. If atrial fibrillation persists, quinidine sulfate is used to establish normal rhythm. If atrial flutter continues in spite of this latter treatment, the administration of digitalis is resumed.

## ATRIAL FIBRILLATION

The mechanism of this abnormality is similar to that described under Atrial Flutter except that the atrial excitation is irregular and more rapid (300 to 500 per minute). The arrhythmia occurs most frequently in older children with chronic rheumatic heart disease and mitral stenosis. It is rare in congenital heart disease, but has been reported as a complication of atrial septal defect and patent ductus arteriosus.

The characteristic sign is a grossly irregular cardiac rhythm (Fig. 280) associated with a pulse deficit. Atrial fibrillation may complicate or precipitate congestive cardiac failure.

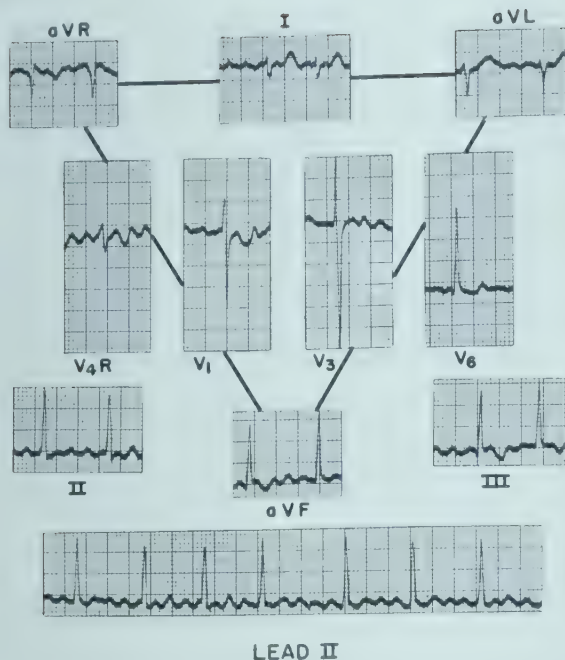


FIG. 280. Electrocardiogram of an 11-year-old girl with rheumatic heart disease and mitral stenosis. The tracing reveals the presence of atrial fibrillation.

All patients should be treated with full doses of digitalis until the cardiac rate returns to normal limits. Normal sinus rhythm may be restored if the patient is treated with quinidine sulfate after digitalization.

### VENTRICULAR FIBRILLATION

This is an irregular ventricular action (Fig. 281) resulting in death unless an effective ventricular beat is restored. Occasionally this arrhythmia occurs during or shortly after cardiac surgery and explains some of the deaths due to intravenous drug therapy. The only effective therapy is cardiac massage and electrical defibrillation.

### BRADYCARDIA

A slow pulse rate may occur during convalescence from acute infections such as rheumatic fever, typhoid fever or infectious hepatitis and in association with lesions of the brain which cause increased intracranial pressure. Older children and young adults who lead active lives frequently have pulse rates of about 60 per minute at rest. Bradycardia of this degree may occur as a family trait. Rates of less than 80 per minute in the first two years of life and less than 60 in older children may be due to heart block.

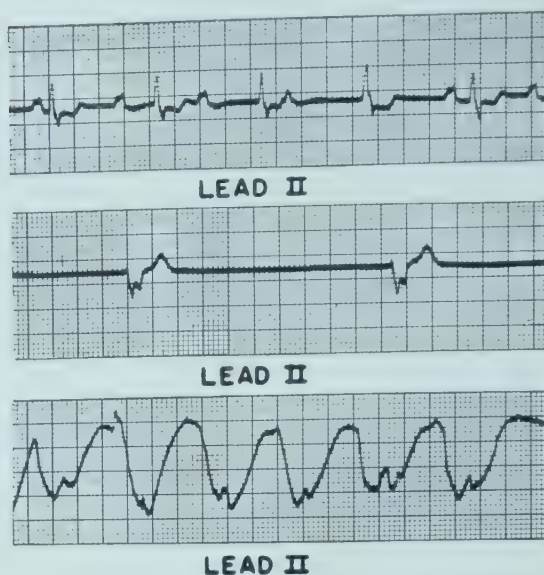


FIG. 281. Electrocardiogram tracings showing various types of arrhythmias. Upper tracing shows the Wenckebach phenomenon. Note progressive prolongation of the P-R interval. Middle tracing shows idioventricular rhythm with a heart rate of 30 per minute. Lower tracing shows ventricular fibrillation.

### HEART BLOCK

The conductive system includes the sino-atrial node (SA node), the atrial muscle, the atrioventricular node (AV node), the bundle of His with its left and right branches, and the Purkinje network. The conductive system may be blocked at any site along this pathway. When the block occurs at the sino-atrial node so that occasional beats are delayed or dropped, it is designated *sino-atrial block*. When the impulse is blocked in its pathway from the sino-atrial node through the atrioventricular node, it is termed *atrioventricular block* (AV block). *Partial atrioventricular block* may have only prolonged P-R interval (*first-degree block*) or may be associated with dropped ventricular beats (*second-degree block*). Second-degree block may occur at regular intervals so that there are two or three atrial beats to one ventricular beat (2:1 or 3:1 partial atrioventricular block). Another type of partial atrioventricular block is a progressive lengthening of the P-R interval from cycle to cycle until a ventricular beat is dropped (*Wenckebach phenomenon*, Fig. 281). When no impulses pass through the atrioventricular node so that the atria and ventricles contract independently of each other, the condition is known as *complete atrioventricular block*. Finally the impulse may be blocked in either the left or right branch of the bundle of His, and the condi-



tion is designated as *left* or *right bundle branch block*.

Complete heart block and first-degree partial block are the common types encountered in children.

### CONGENITAL COMPLETE HEART BLOCK

In children complete block is probably the result of a congenital defect in the main stem of the bundle of His. Atrial or ventricular septal defects may be associated lesions, although it is doubtful whether these defects in themselves cause an interruption of the conductive pathways which produce the block. In the embryo the conduction fibers are developed in the muscular tissue of the heart before the formation of the septa, and it would appear that a common etiologic factor which inhibits the normal development of the bundle of His also affects the cardiac septa. However, the majority of patients with atrial or ventricular septal defects have normal cardiac rhythms, and heart block usually occurs in patients with intact septa.

The condition is commonly asymptomatic, although attacks of syncope may occur. Congenital heart block is suspected if the cardiac rate is less than 80 in infants or less than 60 in older children. On this basis the condition has been occasionally suspected in the fetus several weeks before birth. The peripheral pulse is of the water-hammer type, owing to the large ventricular stroke volume and peripheral vasodilatation, and the systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve. Inconspicuous venous pulsations may occur independently of ventricular contractions. The first cardiac sound has a changing intensity, and isolated atrial contractions may be audible down the left sternal border or at the apex. Taussig has observed that exercise and atropine, which have no effect in increasing the cardiac rate of adults with complete heart block, may produce an acceleration of 10 to 20 beats per minute in the child. Heart block in itself does not produce cardiac enlargement. Left sternal border systolic murmurs are frequent and do not indicate the presence of a ventricular septal defect. Apical mid-diastolic murmurs are not unusual.

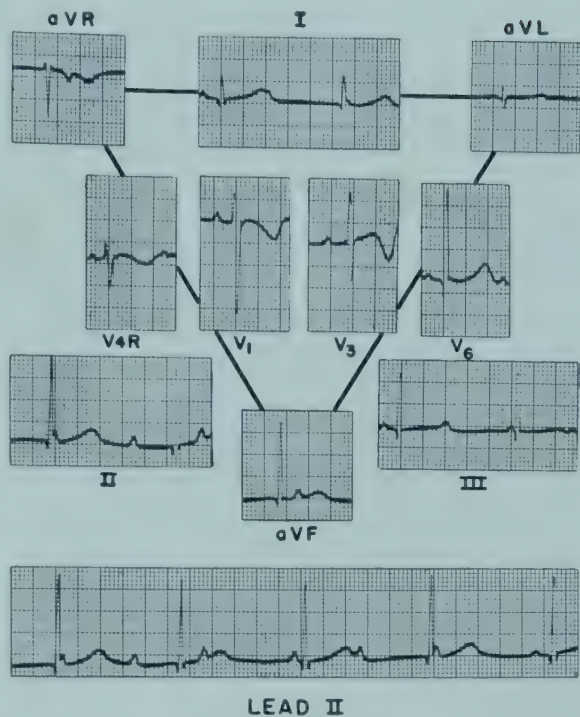


FIG. 282. Electrocardiogram of 5-year-old boy showing complete heart block (see text).

The diagnosis is confirmed by electrocardiograms which reveal that the P waves and QRS complexes have no constant relationship to each other (Fig. 282). The shape and amplitude of the individual waves are generally normal.

The *prognosis* is usually favorable, and a number of patients who have been followed up to the age of thirty to forty years have lived normally active lives except for occasional attacks of syncope. *Treatment* is guided toward encouraging an active and normal life. The following may be used in treatment of the rarely occurring syncopal attacks: ephedrine, isopropylarterenol (Isuprel) or external pacemakers.

SAMUEL KAPLAN  
ROBERT A. LYON

### REFERENCES

- Campbell, M., and Thorne, M. G.: Congenital Heart Block. *Brit. Heart J.*, 18:90, 1956.
- Nadas, A. S., Daeschner, C. W., Roth, A., and Blumenthal, S. L.: Paroxysmal Tachycardia in Infants and Children: Study of 41 Cases. *Pediatrics*, 9:167, 1952.

# DISEASES OF THE ENDOCARDIUM

## ACUTE OR MALIGNANT ENDOCARDITIS

Acute endocarditis is rare during childhood, but has been observed at all ages, including the newborn period, when it may have been acquired during fetal life. The infection may occur suddenly in a previously well child or may develop during the course of some other illness. Occasionally it occurs as a complication of congenital or rheumatic heart disease. The bacteria most frequently found in the lesions are the *Streptococcus* and *Pneumococcus*, but others such as the *Staphylococcus*, *Gonococcus* and *Hemophilus influenzae* may be the infecting organisms. Vegetations of various sizes develop on the endocardium of the valves and cardiac chambers, more frequently on the left side than on the right. They consist of large numbers of bacteria growing in an exudate of fibrin and blood. Ulceration and the formation of a friable granulation tissue occur later, and the destructive process may extend to the muscle layers beneath the endocardium, causing fragmentation of the muscle fibers and hemorrhage. Parts of the vegetations or necrotic tissue may break off at any time and be carried to other regions of the body where they are caught in small blood vessels, obstructing blood flow beyond that point and establishing secondary foci of infection.

**Clinical Manifestations.** The symptoms of acute endocarditis are indefinite at first; high fever, usually remittent, may be the first indication. The cardiac rate is rapid, and the patient becomes prostrated. Septic emboli lodging in various organs may cause symptoms such as abdominal pain, hematuria, diarrhea, or paralysis of parts of the body. Murmurs are either absent or limited to soft systolic ones in the midcardiac or apical area. Blood cultures are usually positive, and the disease must be differentiated from other septicemias not involving the heart.

**Prognosis.** The prognosis is generally grave, and death usually occurs within a few weeks unless treatment is started early in the course of infection.

**Treatment.** Antibiotics selected on the basis of the sensitivity of the infecting organism to them should be prescribed in large doses. Supportive therapy, including the use of blood transfusions and intravenous fluids, is the same as for other acute infections.

## SUBACUTE BACTERIAL ENDOCARDITIS

This disease resembles the acute form in many ways, but its course is more protracted. The infection often develops at the site of congenital or acquired defects of the heart, and the common causative organisms are *Streptococcus viridans*, other types of streptococci, staphylococci and *Escherichia coli*. It rarely occurs in infancy, but has been noted occasionally in children three or four years of age; the incidence increases with advancing age. In a series of 181 patients with congenital heart disease who were over two years of age at the time of death, 16.5 per cent had subacute bacterial endocarditis (Gelfman and Levine). About 5 per cent of patients with rheumatic fever acquire the disease after an average period of ten to fifteen years.

The vegetations are usually smaller than those in the acute types, but resemble them in structure. They may destroy the endocardial lining and underlying muscle and may even perforate valves or septa of the heart. When superimposed upon acquired cardiac disease, the subacute form attacks the left rather than the right side of the heart, so that the mitral and aortic valves are involved more frequently than the pulmonic or tricuspid ones. In congenitally malformed hearts the bacterial invasion begins at the site of the defect, such as the border of a perforated septum, the constricted or stenotic part of the pulmonary artery or aorta, or at the pulmonary terminus of a patent ductus arteriosus.

**Clinical Manifestations.** The symptoms are obscure at first, consisting only in the daily rise in temperature characteristic of any septic condition. Moderate degrees of malaise and prostration tend to occur, and a rapidly developing anemia produces pallor. Anorexia and loss of weight have been early symptoms in some children. After a few days or weeks emboli from the vegetations lodge in various parts of the body and produce symptoms referable to the tissue involved. Among the first embolic signs are the reddish-purple petechiae, which appear in the skin or mucous membranes, and the raised nodules in the soft tissue at the ends of the fingers (Osler's nodes). Linear hemorrhages under the fingernails are characteristic, and in long-



continued infections clubbing of the fingers may develop. Abdominal pain suggests infarction of the spleen or some other abdominal organ; blood in the stool or urine indicates involvement of the intestinal or urinary tract. Enlargement of the spleen from numerous infarctions is a common sign. Hemiplegia and other nervous symptoms denote involvement of the brain or cord and provide a warning of impending death. The high degree of toxicity, which develops late in the disease, may be responsible for the hemorrhagic tendency, some of the nephritic symptoms and the severe prostration and fatigue. Murmurs are those of the underlying congenital or rheumatic lesion. Occasionally a soft systolic murmur at the apex is noted early in the disease and changes to a louder, harsher murmur as the disease progresses.

**Diagnosis.** Anemia and leukocytosis are common, but the most important finding in addition to the characteristic clinical signs is a positive blood culture. A number of samples of blood may have to be examined before the causative organism is isolated. In any child with congenital or acquired heart disease who suddenly has fever, subacute bacterial endocarditis may be developing, and repeated blood cultures should always be obtained. Cultures should be saved at least two weeks before a final negative report is given.

**Prognosis.** The prognosis has changed completely since the advent of antibiotics. Whereas in the past recovery was not to be expected, now most children recover completely. Children seem less likely to have cardiac failure than do adults, and they respond more rapidly to treatment. However, the disease runs such a mild course during its first weeks or even months that the diagnosis may not be suspected until suddenly there develops a fulminating course, resulting in death. If therapy is inadequate, recurrences may take place. A child must be free from evidences of the disease for at least two years before recovery can be said to be permanent.

**Treatment.** Penicillin is effective against most strains of the common infecting organisms. There are, however, notable differences in the relative susceptibility of various bacteria. For this reason it is desirable to know the sensitivity in vitro of the infecting organism. Therapy need not be delayed until the sensitivity of the organism is known, but it is advantageous to have secured the organism before therapy is started, so that sensitivity tests can be made. In rare instances the child may be in such a serious condition and

the diagnosis seem sufficiently obvious that delay in starting therapy is not justified, but blood for culture should be obtained initially. When the sensitivity of the organism is known, sufficient amounts of penicillin should be given to exceed the susceptibility level in vitro for at least part of the time between the individual injections. When the sensitivity of the organism is not known, the dosage must be gauged by the clinical response and by culture of the blood. As a rule daily doses of 2 to 3 million units of penicillin are required. Streptomycin is used in addition to penicillin, especially in infections with *Streptococcus viridans* even if studies in vitro indicate that the organism is not sensitive to streptomycin. There are no accurate means for determining how long therapy should be continued after the child has become fever-free and the blood cultures have become negative. In many instances a two-week course of therapy with penicillin and streptomycin has been curative. In other patients there is some justification for extending therapy for four to eight weeks. From that time on, for at least two years, he should be observed frequently and blood cultures obtained to make certain that he has recovered entirely. Some children whose symptoms do not abate quickly or whose blood cultures remain positive for a long time may need as much as 10 to 15 million units of penicillin per day for four to six weeks. If the causal organism is highly insensitive to penicillin, sensitivity tests in vitro may suggest the antibiotic or combination of antibiotics of choice. In all instances bacteriocidal drugs are preferable.

**Prophylaxis.** All children with rheumatic heart disease and congenital cardiovascular anomalies (especially of the acyanotic group) are exposed to the hazard of subacute bacterial endocarditis. Therefore these patients should be protected with large doses of penicillin for forty-eight hours before and after operations on the ears, nose or throat and dental extractions. Acute infections should be vigorously treated with suitable antibiotics to prevent the onset of subacute bacterial endocarditis.

## RHEUMATIC ENDOCARDITIS

Rheumatic infections (p. 903) are, of course, not limited to the endocardium, but involve other parts of the heart and other organs of the body; only the endocardial changes will be mentioned here.

Rheumatic involvement of the valves and

endocardium is by far the most common type of endocarditis in children. The lesions begin as small verrucae composed of fibrin and blood cells along the borders of the valves. The mitral valve is affected most often, the aortic next most frequently, and the tricuspid and pulmonary valves less commonly. As the infection subsides, the verrucae tend to disappear and leave scar tissue. With each repeated infection more small lesions of this type form near the previous ones, and the mural endocardium and chordae tendineae also become involved.

#### Clinical Patterns of Valvular Disease.

**Mitral insufficiency.** Organic mitral insufficiency which prevents normal closure of the mitral valve is most frequently rheumatic in origin. There is usually some loss of substance of the mitral valve, and the chordae tendineae may be shortened and thickened. There is often associated mitral stenosis due to sclerosis of the base of the mitral ring and cusps.

During ventricular systole, blood regurgitates from the left ventricle to the left atrium. This may result in left atrial enlargement, which is sometimes aneurysmal. Owing to the greater work load and filling pressure of the left ventricle, this chamber may also enlarge. The increased left atrial pressure may be reflected through the pulmonary bed to the right heart, producing enlargement of the right ventricle and atrium, with subsequent congestive cardiac failure.

The pulse, blood pressure and the jugular venous pressure are normal. Cardiac enlargement may be present and depends on the degree of mitral insufficiency and associated myocarditis. An apical systolic thrill may be present. The murmur of mitral insufficiency is an apical blowing systolic one, lasting throughout systole, and may radiate to the axilla or to the left sternal border. The first heart sound is soft or normal. If there is associated mitral stenosis, the murmur of this lesion will be heard in diastole.

Enlargement of the left ventricle and atrium may be determined roentgenographically. On fluoroscopic examination the left atrium may be seen to pulsate paradoxically during ventricular systole, but this sign is not diagnostic of mitral insufficiency. Calcification of the mitral valve is rarely seen in children. The electrocardiogram may demonstrate left ventricular hypertrophy if the lesion is severe.

A frequent problem is evaluation of an apical systolic murmur without other signs in

patients who have had a mild attack of rheumatic fever or a history of recurrent upper respiratory tract infections. Though many of these patients are considered to have organic mitral insufficiency, the diagnosis is often incorrect. In some the murmur is extracardiac, and sometimes an innocent murmur is transmitted to the apex. Many children with murmurs suggestive of mitral insufficiency lose all evidence of cardiac disease after some years. Wilson observed that only 11 per cent of a group of 179 children with mitral insufficiency retained the signs of this lesion over a period of two to sixteen years. Individual patients may require careful follow-up studies for many years before the cause of the murmur becomes apparent. Untold harm may be done if the patient's activities are reduced only on the basis of the presence of a murmur.

During convalescence children with mild cardiac disease often make great improvement, while those with far advanced cardiac disease suffer from the effects of rapid growth and development. If rheumatic infections recur, the valvular condition becomes progressively worse. For prophylactic therapy, see page 910.

**Mitral stenosis.** Congenital mitral stenosis is described on page 876.

Organic mitral stenosis is nearly always rheumatic in origin and results from sclerosis of the mitral ring and the base of the valve leaflets. It may take two years or more for the lesion to become fully established (Bland, Jones and White). Mitral stenosis is often associated with mitral insufficiency.

In established mitral stenosis the left atrium has difficulty in emptying, which results in hypertrophy and increased pressure in this chamber. The increased pressure is reflected through the pulmonary veins into the pulmonary artery to the right side of the heart, resulting in pulmonary and right ventricular hypertension. The right ventricle hypertrophies, and congestive cardiac failure may be the terminal event. Effort dyspnea due to pulmonary engorgement may be present and is slowly progressive until congestive cardiac failure supervenes. Attacks of paroxysmal dyspnea may occur and are due to left atrial failure. Another symptom is recurrent hemoptysis, probably due to ruptured bronchial veins or pulmonary infarction. Patients with mitral stenosis may have a malar cyanotic tinge. The pulse is small and the jugular venous pressure normal unless congestive cardiac failure or tricuspid insuffi-



ciency has supervened. Varying degrees of cardiac enlargement occur, depending on the associated valvular lesions and rheumatic myocarditis. In severe mitral stenosis without mitral insufficiency the apical impulse is tapping, and an apical diastolic thrill may be palpable. The murmur of mitral stenosis is heard at the apex in mid-diastole or late diastole (presystole). It is low-pitched or rumbling and is often best heard with the patient lying on his left side or after exercise. The first sound is slapping, and the pulmonary second sound is accentuated. An opening snap of the mitral valve may be heard down the left sternal border during diastole. Associated functional pulmonary insufficiency may result in a blowing diastolic murmur down the left sternal border (Graham Steell murmur).

Roentgenologic studies reveal varying degrees of cardiac enlargement, depending on the severity of mitral stenosis and rheumatic myocarditis (Fig. 283). The aorta is small and the pulmonary artery segment prominent. The enlarged left atrium may be visualized in the anteroposterior projection as a prominence below the pulmonary artery and by a double shadow overlapping the right atrium. In the right anterior oblique projection the enlarged left atrium displaces the barium-filled esophagus posteriorly. The left main stem bronchus may be elevated by the enlarged left atrium. The lung fields may occasionally show a fine nodularity, probably due to pulmonary hemosiderosis. Calcification of the mitral valve is not frequent in children.

The electrocardiogram may reveal signs of right ventricular hypertrophy or incomplete right bundle branch block. The P waves are notched and widened and occasionally are tall and spiked. The vital capacity is reduced and the arm-to-tongue circulation time prolonged. Cardiac catheterization is seldom indicated in children with mitral stenosis.

Complications of mitral stenosis include atrial fibrillation, subacute bacterial endocarditis, congestive cardiac failure, functional tricuspid insufficiency and systemic emboli from thrombi in the left atrium.

The *course* and *prognosis* are extremely variable. Some patients succumb during adolescence, and others reach old age. It appears that most patients who die during adolescence have persistent active rheumatic carditis.

*Treatment* is directed toward the prevention of further attacks of rheumatic fever, prophylaxis against the onset of subacute bacterial endocarditis and encouragement to

lead as active and normal a life as possible. Although brilliant results have been obtained by the surgical treatment of mitral stenosis in adults, operation is seldom indicated in children. In rare instances mitral valvotomy can be considered if heart failure persists in the absence of demonstrable active rheumatic carditis.

**Aortic insufficiency.** In the majority of instances aortic insufficiency results from rheumatic heart disease, but occasionally is associated with congenital cardiovascular lesions (see Coarctation of the Aorta and Ventricular Septal Defect). In chronic rheumatic aortic insufficiency, sclerosis of the aortic valves results in distortion and retraction of the cusps. The lesion produces hypertrophy of the left ventricle, which may be extreme. Aortic insufficiency which develops during the acute stage of rheumatic fever is more likely to be permanent than mitral valvular stenosis.

Owing to the reflux of blood through the aortic valve during diastole and to associated vasodilatation, the radial pulses are water-hammer in type, and the carotid arteries show bounding Corrigan pulsations. Associated signs include capillary pulsations in the lips or fingernails, an audible systolic shock over the peripheral arteries (pistol shot) and systolic and diastolic murmurs over the femoral arteries if pressure is applied to the artery just distal to the stethoscope (Duroziez's sign). The systolic blood pressure is elevated, the diastolic lowered.

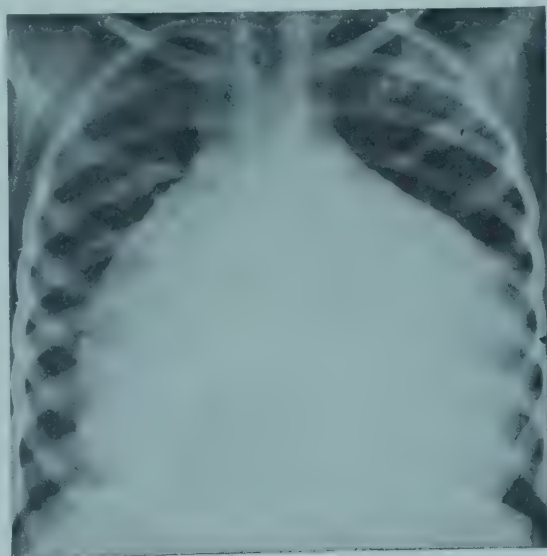


FIG. 283. Teleroentgenogram of a 9-year-old girl with rheumatic mitral stenosis, tricuspid insufficiency and atrial fibrillation. The gross cardiac enlargement is evident. Pericardial effusion was not found at autopsy.

In severe aortic insufficiency the heart is enlarged with a left ventricular apical heave. Thrills are absent unless there is an associated aortic stenosis. The typical murmur is heard over the pulmonary area with radiation down the left sternal border, to the apex and to the aortic area. It occupies the whole of diastole and is blowing. Associated functional mitral stenosis occasionally produces the typical diastolic murmur of mitral stenosis without organic involvement of this valve (Austin Flint murmur).

*Roentgenologic studies* show prominence and exaggerated pulsations of the left ventricle and aorta. The electrocardiogram may be normal, but in severe cases reveals signs of left ventricular hypertrophy.

The *course and prognosis* depend on the degree of aortic insufficiency (as gauged by the peripheral signs), the size of the left ventricle and the presence or exacerbation of rheumatic infection. *Complications* include the development of congestive cardiac failure, usually preceded by left ventricular failure, and subacute bacterial endocarditis.

*Treatment* consists in prophylaxis against the recurrence of acute rheumatic fever and occurrence of subacute bacterial endocarditis as well as encouragement to lead as active and normal a life as possible.

**Aortic stenosis.** Aortic stenosis in children is usually the result of a congenital lesion (p. 875). Rheumatic aortic stenosis is rare in children, although some degree of stenosis may be associated with aortic insufficiency. The signs of pure aortic stenosis include an anacrotic pulse with small pulse pressure, left ventricular enlargement and a systolic murmur and thrill over the aortic area with radiations to the neck, down the left sternal border and to the apex.

**Tricuspid valvular disease.** Tricuspid involvement is rare. *Tricuspid insufficiency* is usually functional, secondary to right ventricular dilatation. The signs produced by tricuspid insufficiency include prominent pulsations of the jugular veins with a "c" wave, systolic pulsations of the liver and a blowing systolic murmur in the fourth and fifth left parasternal spaces. Atrial fibrillation is frequently present.

*Acquired tricuspid stenosis* is also rare and is usually associated with rheumatic mitral stenosis and sometimes with aortic valvular disease. Tricuspid stenosis produces signs of increased jugular venous pressure with prominence of the "a" wave, presystolic hepatic pulsation and sometimes a rumbling diastolic murmur in the fourth and fifth left parasternal spaces.

**Pulmonary valve disease.** Pulmonary insufficiency is rarely due to organic disease and is usually functional, secondary to congenital lesions such as interatrial septal defects or patent ductus arteriosus. Occasionally it complicates severe mitral stenosis (Graham Steell murmur). The murmurs are similar to those of aortic insufficiency, but the peripheral arterial signs are absent in pulmonary insufficiency. Pulmonary stenosis is usually congenital in origin (see p. 866).

SAMUEL KAPLAN  
ROBERT A. LYON

## REFERENCES

### *Acute Endocarditis*

Macaulay, D.: Acute Endocarditis in Infancy and Early Childhood. *Am. J. Dis. Child.*, 88:715, 1954.

### *Subacute Bacterial Endocarditis*

Bloomfield, A. L.: Diagnosis and Prevention of Bacterial Endocarditis. *Circulation*, 8:290, 1953.

Cates, J. E., and Christie, R. V.: Subacute Bacterial Endocarditis. *Quart. J. Med.*, 20:93, 1951.

Friedberg, C. K.: The Use of Drugs in the Treatment of Bacterial Endocarditis. *M. Clin. North America*, 38:385, 1954.

Geraci, J. E., and Martin, W. J.: Antibiotic Therapy of Bacterial Endocarditis. *Circulation*, 8:494, 1953.

Hamburger, M., and Stein, L.: Streptococcus Viridans Subacute Bacterial Endocarditis: Two Week Treatment Schedule with Penicillin. *J.A.M.A.*, 149:542, 1952.

Hunter, T. H.: Bacterial Endocarditis. *Am. Heart J.*, 42:472, 1951.

### *Valvular Disease*

Bland, E. F., and Jones, T. D.: Rheumatic Fever and Rheumatic Heart Disease: A Twenty Year Report on 1000 Patients Followed since Childhood. *Circulation*, 4:836, 1951.



# DISEASES OF THE MYOCARDIUM

## CONDITIONS CAUSING MYOCARDIAL DAMAGE

The status of the myocardium is the factor which influences most the prognosis of cardiac disease. If, in spite of congenital cardiac malformations, acquired valvular disease or arrhythmias, the myocardium is able to provide satisfactory circulation of blood to all tissues, the child will be able to maintain adequate nutrition, growth and normal activities of life. The conditions which may directly affect the myocardium include the following: infections, mesenchymal diseases, endocrine disorders, metabolic and nutritional diseases, neuromuscular diseases, blood diseases, tumors, hypertension and congenital anomalies.

**Bacterial Infections. Diphtheria.** The toxin of diphtheria bacilli may produce peripheral circulatory failure or toxic myocarditis. These complications occur from all types of diphtheria, including the cutaneous form. Peripheral circulatory failure occurs within the first two weeks of the disease and is associated with a rapid thready pulse, cold, pale and clammy skin, and hypotension. In addition to the general therapy for diphtheria (p. 418), these patients are treated with elevation of the foot of the bed and intravenous pressor amines.

Toxic myocarditis occurs during the second and third weeks of the disease. It is characterized by the development of arrhythmia in the form of partial or complete heart block, bundle branch block or extrasystoles. Congestive cardiac failure occurs later and is associated with cardiac enlargement and gallop rhythm. In addition to the arrhythmia, the electrocardiogram shows S-T segment depression and T wave inversion in most leads. The immediate prognosis is grave (about 50 per cent mortality). In the patients that survive, peripheral neuritis is common, but the ultimate prognosis is good. Treatment (see also p. 419) consists in enforcing strict bed rest until all signs of myocarditis have disappeared. Digitalis is reserved for patients with frank congestive heart failure.

**Typhoid fever.** Toxic myocarditis may be inferred if there is electrocardiographic evidence of T wave inversion in most leads. However, this sign may be transient and by itself is of no clinical significance. Cardiac failure is rare, and peripheral circulatory

failure is less common now that specific therapy for typhoid fever is available.

**Acute glomerulonephritis** (p. 1035). Myocardial involvement is considered in patients who have congestive cardiac failure, cardiac enlargement or electrocardiographic abnormalities. Cardiac failure is evidenced by dyspnea and pulmonary congestion, which are soon followed by increased venous pressure and hepatomegaly. Frequently it is difficult to determine whether cardiac failure contributes to edema in acute nephritis. Frank pulmonary edema is not common. Tachycardia, cardiac enlargement, gallop rhythm and a nonspecific apical systolic murmur may be found. Hypertension is usual but not invariable. The electrocardiogram is usually normal, and only a small number of patients show nonspecific T wave inversion or prolonged electrical systole.

In addition to antihypertensive drugs, digitalization is indicated when signs of cardiac failure appear. The response is good, and digitalis may be discontinued after a week or two.

**Other bacterial infections.** Circulatory involvement in bacterial infections is manifest as peripheral circulatory collapse or toxic myocarditis. The incidence of toxic myocarditis is difficult to gauge because it frequently depends on minor pathologic evidence such as cloudy swelling or fatty degeneration. Toxic myocarditis as indicated by tachycardia, gallop rhythm and cardiac enlargement may complicate pneumonia, bacterial endocarditis and septicemia. The prognosis depends on the response of the primary infection to specific antibiotics.

**Viral Infections.** Myocarditis complicating such viral infections as measles, chickenpox and mumps is exceedingly rare. It is difficult to gauge the incidence of myocarditis in *poliomyelitis*; hypertension is not uncommon, but cardiac failure is rare. Terminal pulmonary edema may occur. Nonspecific electrocardiographic abnormalities occur in less than 15 per cent of patients. Recently severe myocarditis has been identified with *Coxsackie B virus* (p. 529).

**Parasitic and Fungal Infections.** Lesions in the myocardium have been described in association with *histoplasmosis*, *coccidioidomycosis*, *toxoplasmosis* and *trichiniasis*. In these conditions the cardiac lesion is usually inci-

dental and seldom produces clinical signs of myocarditis. *Actinomyces* may involve the pericardium and myocardium by direct contiguity as for example from a pulmonary abscess. *Hydatid* cysts of the pericardium may be found on routine roentgenograms of the chest and usually produce symptoms only when they rupture. *Schistosomiasis* may produce pulmonary hypertension and cor pulmonale. *Cruz trypanosomiasis* (Chagas' disease) seldom occurs in the North American continent. The South American literature indicates that this infection may produce acute or subacute myocarditis and sudden death.

**Mesenchymal Diseases.** *Rheumatic carditis* is described on pages 890 and 907.

The cardiovascular manifestations of rheumatoid arthritis, *disseminated lupus erythematosus*, *periarteritis nodosa*, *dermatomyositis* and *scleroderma* are described elsewhere. In *rheumatoid arthritis* pericarditis is not uncommon. In patients with rheumatoid arthritis and mitral or aortic valve disease the latter may be due to coincidental or past rheumatic carditis.

**Endocrine Disorders.** *Hyperthyroidism* produces tachycardia, vasodilatation, wide pulse pressure, cardiac enlargement and rarely atrial fibrillation. *Cretinism* seldom produces gross cardiac involvement, but the electrocardiogram discloses a slower than normal cardiac rate, low voltage of all complexes, but especially the P and T waves, left axis deviation and prolonged electrical systole. Serial tracings indicate improvement of these signs with adequate thyroid therapy and a return to a normal tracing within about one month.

**Metabolic and Nutritional Diseases.** Among vitamin deficiency diseases, *beriberi* (p. 365) causes the most conspicuous cardiac damage. However, in patients with malnutrition the deficiencies are often multiple, including an unbalanced high carbohydrate, low protein diet, and it is difficult to separate the cardiac lesion of one nutritional disease from that of another.

**Neuromuscular Diseases.** In the original description of *Friedreich's ataxia* (p. 1097), heart disease was noted in five of the six cases. In the majority of instances, however, there are few cardiac symptoms, the most common evidence of cardiac involvement being an abnormal electrocardiogram with T wave inversion in the left ventricular surface leads. Arrhythmias may also occur and consist of atrial tachycardia or fibrillation or

extrasystoles. Cardiac failure has been reported.

In *progressive muscular dystrophy* (p. 1271), 50 per cent of children have post-mortem evidence of myocardial involvement similar to that of the striated muscle. Cardiac symptoms, however, are not common in these children, but the electrocardiogram is frequently abnormal and may reveal tachycardia, abnormalities of the P wave, short P-R interval and abnormal Q and T waves. Minimal evidence of right or left ventricular hypertrophy may also occur, and some patients have congestive heart failure.

**Blood Diseases.** In infants and children anemia is the most common blood disease associated with cardiac involvement, as, for example, in leukemia, hemolytic anemias, severe iron deficiency and hemorrhage. Although cardiac output increases when the hemoglobin is below about 7 gm. per 100 ml., cardiac enlargement with or without congestive heart failure occurs only with an extreme reduction in hemoglobin to about 3 or 4 gm. In these patients the heart rate is rapid, the pulse pressure is widened, the venous pressure is increased, and the heart is enlarged. An apical or left sternal border systolic murmur is usual, gallop rhythm is common, and diastolic murmurs in the same areas occur in a few patients. The electrocardiographic changes are such nonspecific ones as depressed S-T segments and flat T waves.

Treatment is directed toward the cause of the anemia. If blood transfusions are indicated in the presence of cardiomegaly or cardiac failure, packed cells are preferred. We have found it useful to measure the venous pressure during the transfusion. This can be accomplished easily by measuring the pressure in the vein being used for the transfusion.

**Tumors of the Heart.** See page 1350.

**Carcinoid** of the small intestine with metastases is associated with a secretion of large amounts of serotonin (5-hydroxytryptamine). In these patients pulmonary and tricuspid valve disease may occur and is associated with patchy areas of reddish-blue cyanosis, attacks of flushing, diarrhea and bronchial asthma.

**Hypertension.** In the majority of instances the etiology of hypertension in children can be clearly ascertained. Renal disease is the most common cause. Coarctation of the aorta has been described elsewhere. Hypertension may be found in patients with poliomyelitis.



lead poisoning, encephalitis and brain tumor. Endocrine disturbances, which may be associated with hypertension, include steroid therapy, pheochromocytoma, congenital adrenal hyperplasia and Cushing's syndrome.

*Essential hypertension* is rare in children. The diagnosis is based on the exclusion of the abnormalities described above.

## CONGENITAL ANOMALIES

### ENDOCARDIAL SCLEROSIS

This condition has been described under a variety of terms, which include fetal endocarditis, endocardial fibrosis, prenatal fibroelastosis and elastic tissue hyperplasia. The term "endocardial sclerosis" is used in this text because it describes the gross appearance of the heart at autopsy and makes no commitment regarding the age at which the disease might originate or its cause.

No single etiologic cause has been established. There is insufficient evidence that the process is the result of inflammation or infection before or after the birth of the child. Other theories of etiology include abnormalities of development of the endocardium or a deficient blood supply to the endocardium and its trabeculae. The disease may occur in siblings.

*Pathologically*, the disease is characterized by a white, opaque fibroelastic thickening of the endocardium, especially of the left side of the heart, which frequently obscures the trabeculation of the inner surfaces of the cardiac chamber. The lesion may spread to involve the valves, especially the aortic and mitral ones. There may be coexisting congenital cardiovascular lesions, which include coarctation of the aorta, patent ductus arteriosus, aortic atresia and premature closure of the foramen ovale. Microscopically, the lesion consists of a fibroelastic thickening of the endocardium which follows the course of the trabecular sinusoids and may result in subendocardial degeneration or necrosis of muscle with vacuolation of muscle fibers. The involved valve leaflets show a myxomatous proliferation with an increase in collagenous elements.

The *clinical picture* is variable, the majority of patients falling into one of the following groups:

1. Young infants, usually less than six months of age, who apparently have been in good health until the sudden onset of congestive cardiac failure; this is frequently pre-

cipitated by a respiratory infection. Death occurs at this early age.

2. Infants with similar symptoms, but of milder degree and with periods of remission. At some time during the first two years of life they may manifest some dyspnea, refusal of feedings, failure to gain weight adequately and recurrent pulmonary infections. There are repeated episodes of congestive cardiac failure, finally ending in death.

3. A miscellaneous group includes patients in whom valvular lesions or associated congenital cardiovascular defects are predominant.

The majority of patients fall into groups 1 and 2. During episodes of congestive cardiac failure the infant is acutely ill with dyspnea, cough and anorexia. Cyanosis is infrequent, but is sometimes found in the terminal phase or as a sign of associated congenital cardiovascular defects. The jugular venous pressure is elevated, the liver greatly enlarged, and edema of the extremities, sacral area or face may be present. Rales and rhonchi in the lung fields are due to intercurrent pulmonary infection and congestion. The heart is moderately or greatly enlarged with a normal or left ventricular apical impulse. Thrills are not common, and murmurs are insignificant. About 25 per cent of patients have a grade I or II blowing systolic murmur down the left sternal border.

Roentgenograms confirm the cardiac enlargement, but the cardiac silhouette is of a nondistinctive contour (Fig. 284). There may be signs of intercurrent pulmonary infection. The electrocardiogram is usually abnormal, but not pathognomonic (Fig. 285).

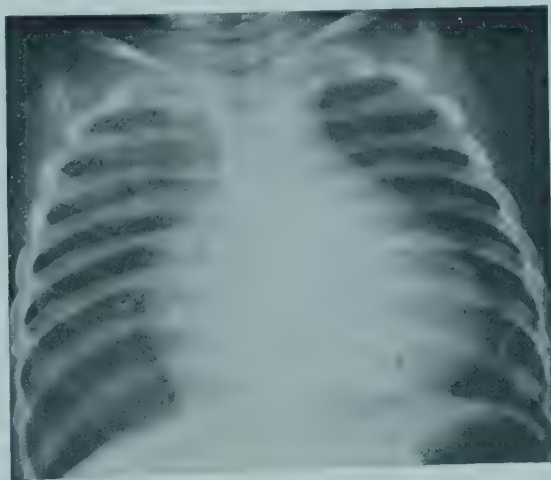


FIG. 284. Teleroentgenogram of a 7-month-old girl with endocardial sclerosis. The enlarged heart is of an undistinctive contour.

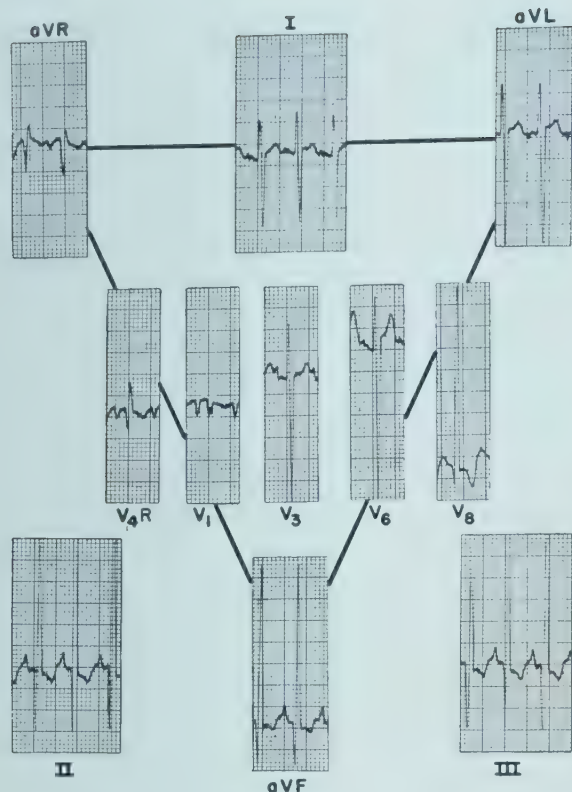


FIG. 285. Electrocardiogram of 3-month-old girl with endocardial sclerosis. Note the abnormal T waves in leads II, aVF and  $V_8$  and the deep Q and tall R waves in aVF and  $V_8$ .

In the majority of cases tall R waves and inversion of the T waves over the left ventricular surface indicate dominance of the left ventricle. These signs are associated with inversion of the T waves in the standard leads and sometimes with a deep S in the right precordial leads. These electrocardiographic changes may also be seen in gargoyism, glycogen storage disease of the heart, aberrant origin of the left coronary artery from the pulmonary artery and medial necrosis or calcinosis of the coronary artery.

More than 90 per cent of patients succumb during the first two years of life; occasional patients survive to adult life. In rare instances symptoms may appear for the first time at five or six years of age.

*Treatment* is directed toward alleviation of congestive cardiac failure and prevention of intercurrent infections.

## OTHER MYOCARDIAL DISEASES

Glycogen storage disease (pp. 268 and 1095) produces myocardial degeneration characterized by deposition of glycogen in the muscle fibers. The hepatic forms of glycogen disease usually do not involve the heart.

Simple hypertrophy of the cardiac muscle has been described in which there is no inflammatory reaction or any extrinsic contributory factors. Damon and Moore have reported an increase in the number and size of muscle fibers, but no changes in the number of nuclei were observed. McMahon, however, has noted mitotic figures in the cardiac muscle fibers of such patients. Some of these cases appear to have a familial basis.

In gargoyism (see p. 1238) the pathologic

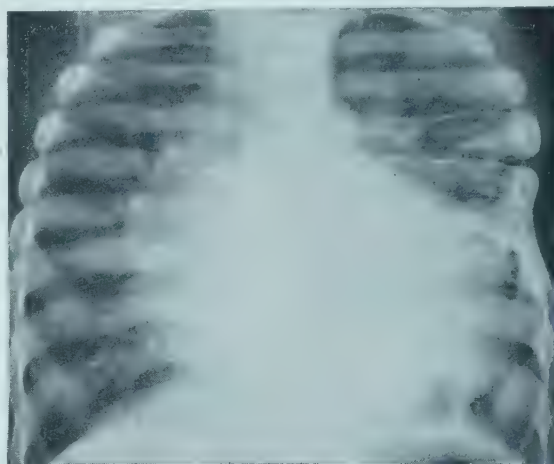


FIG. 286. Teleroentgenogram in gargoyism. The enlarged heart shadow is of an undistinctive contour. The ribs are broadened and the intercostal spaces narrowed.

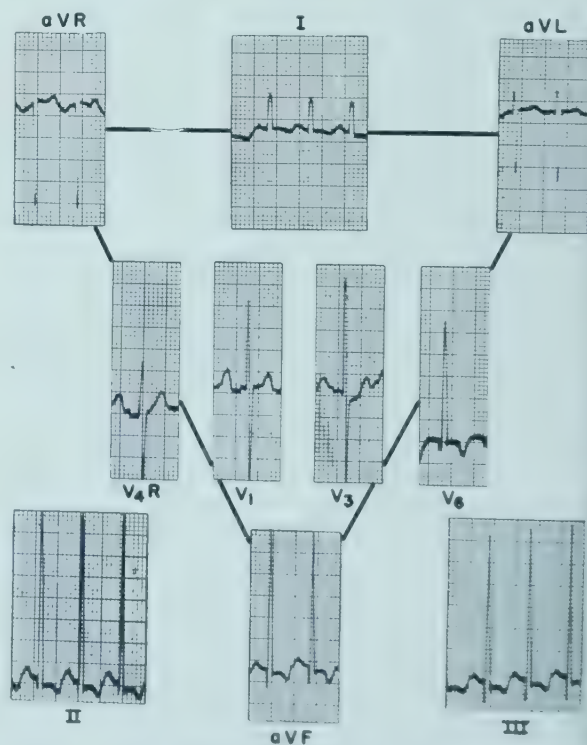


FIG. 287. Electrocardiogram in gargoyism. Note the abnormal T waves in leads I, II, aVF and  $V_6$ . Compare with Figure 285.



lesion in the heart and great vessels is the same as that of the connective tissue found elsewhere in the body. The most pronounced lesions are found in the valves and coronary arteries, but abnormalities in the pericardium and aorta are not uncommon. Significant left ventricular hypertrophy may be present. Many of these patients die of congestive cardiac failure during the second decade. The heart may be moderately enlarged, but murmurs are not diagnostic (Figs. 286, 287).

Calcinosis of the coronary arteries is a rare disease of infancy. Familial incidence has been recorded. The coronary arteries are tortuous and calcareous, and the ventricles, especially the left, are hypertrophied. Other blood vessels may be similarly involved. The onset of cardiac failure is sudden; death usually occurs in infancy.

### TREATMENT OF CARDIAC FAILURE

The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiovascular anomaly which is amenable to surgery, medical treatment is indicated prior to the surgical procedure and is continued in the immediate postoperative period. For some diseases, such as hyperthyroidism, hypothyroidism, anemia and beriberi, specific therapeutic measures are available, but in the majority of instances only general procedures are adaptable.

*Bed rest* in a comfortable position is essential. Some patients prefer to lie flat, but for most of them breathing is easier in a semi-reclining position. Initially sedatives or analgesics may be necessary to produce complete relaxation; the most frequently used drugs are morphine, codeine and the barbiturates.

A low *sodium diet* is efficacious in the treatment of cardiac edema and paroxysmal cardiac dyspnea. The oral intake of sodium should be reduced to 0.5 gm. daily; the diet may be made more palatable with a salt substitute. Powdered milk with a low sodium content (Lonalac) is available for infants.

*Oxygen* administered by any method which is effective and comfortable for the patient will help to relieve dyspnea and cyanosis.

*Mercurial diuretics* are the most effective agents for the treatment of cardiac edema and pulmonary congestion due to cardiac failure. Mercaptomerin sodium (Mercuhydrin and Thiomerin) (p. 220) is the most frequently used mercurial, but it should be used cautiously if there is associated nephritis and hematuria. The dose of mercurial diuretics

varies according to the age of the patient and the severity of cardiac failure. In infants 0.25 ml. may be given intramuscularly daily or on alternate days in the early stage of treatment. In older children the dose is 0.5 to 1 ml. The easiest method of gauging the efficacy of the drug is by comparison of daily body weights. When a constant level is reached, it should be maintained. When the acute stage of cardiac failure is over, the injection of a mercurial diuretic is necessary in a few patients once or twice weekly. Mercurials act by increasing sodium excretion; a decrease in venous pressure parallels the diuresis. In adults the action of mercurial diuretics is supplemented with orally administered ammonium chloride, but this is seldom necessary in children. Other diuretics used in conjunction with mercurials include the xanthine derivatives, theobromine and theophylline. Chlorothiazide (Diuril) and acetazolamide (Diamox) are other diuretics which can be used orally (pp. 214, 216). If ascites or pleural effusions produce discomfort, fluid should be removed by paracentesis.

Digitalis should be used in all forms of cardiac failure. The most satisfactory response is obtained in failure due to rheumatic carditis, paroxysmal tachycardia and myocardial diseases. In general, it may be said that patients with primary left ventricular failure respond better than those with primary right-sided failure. Patients with congestive cardiac failure due to cyanotic congenital cardiovascular disease respond poorly to digitalis.

Many preparations of digitalis are available, but familiarity with only a few is necessary. The preparations include those of the whole leaf and purified digitalis glycosides. The ones most frequently used are digitoxin and Digoxin for slow digitalization and maintenance, and lanatoside C (Cedilanid) for rapid digitalization. The dose of digitalis (p. 215) and the rapidity of administration depend on the weight of the patient, the severity of congestive cardiac failure, the type of preparation, and subsequently on the response of the patient.

The average adequate digitalizing dose of *digitoxin* (oral or intramuscular) for children varies from 0.02 to 0.04 mg. per kilogram of body weight, but infants require 0.04 to 0.06 mg. per kilogram. Owing to the wide variations of these dosage schedules, it may be preferable to calculate the digitalizing dose of digitoxin in all age groups on the basis of 0.75 mg. per square meter of body surface (see Nomogram, p. 209). The daily main-

tenance dose of digitoxin is one tenth of the digitalizing dose. The full digitalizing dose is given in divided doses within twelve, twenty-four or forty-eight hours, depending on the severity of congestive failure. If digitalization is required within twelve hours, half of the digitalizing dose may be given immediately and the remaining half in divided doses over twelve hours. The total dose may be more evenly distributed if twenty-four or forty-eight hours are taken for digitalization. Because the size of the effective dose of digitoxin varies greatly in different patients, the dose may need to be modified after part or all of the calculated digitalizing dose has been given. The optimal effect of digitoxin occurs four to eight hours after administration, and its excretion is slow (about ten to fourteen days).

*Digoxin* is more rapidly absorbed and excreted than digitoxin. The optimal effect of Digoxin occurs four hours after administration, and it is excreted within forty-eight to seventy-two hours. The oral digitalizing dose of Digoxin is 0.08 to 0.16 mg. per kilogram of body weight in patients under the age of two years and 0.04 to 0.08 mg. per kilogram in patients over the age of two years. The oral digitalizing dose in all age groups may be calculated on the basis of surface area with a dose of 1.50 mg. per square meter (see Nomogram, p. 209). The digitalizing dose may be given in three or four divided doses over a period of twelve to twenty-four hours, depending on the urgency of therapy. In extremely ill patients one quarter to one half of the digitalizing dose may be given intravenously. The remainder of the digitalizing dose and the daily maintenance dose are given orally. The average daily maintenance dose is 25 per cent of the digitalizing dose.

Lanatoside C (*Cedilanid*) is a glycoside used for rapid intravenous digitalization; it should be reserved for emergency situations. It begins to act within three to fifteen minutes after administration, and optimal effects are achieved in about one hour; it is excreted within twenty-four to thirty-six hours. The digitalizing dose is 0.75 mg. per square meter of surface area (see Nomogram, p. 209). Cautious redigitalization with Digoxin or digitoxin is started about twenty-four to thirty-six hours later.

It cannot be overemphasized that there is a great variation in individual patients to digitalis preparations and that the foregoing dosage schedules are only a guide to therapy for a given patient. The digitalizing dose is effective if the cardiac rate is reduced, the venous pressure and liver size are decreased, dyspnea is relieved and diuresis is instituted. Electrocardiographic evidences of digitalis effect include shortening of electrical systole, depression of the S-T segment with T wave inversion and lengthening of the P-R interval. In many patients the difference between an adequate and toxic dose of digitalis is small. The signs of digitalis toxicity include anorexia, nausea, vomiting, diarrhea, visual symptoms, dizziness, headache and arrhythmias. The arrhythmias consist of atrial and ventricular extrasystoles, paroxysmal atrial tachycardia with block, atrial flutter or fibrillation, bundle branch block, ventricular tachycardia and intra-atrial block. If signs of digitalis toxicity occur, the drug should be discontinued, and potassium chloride may be given orally or by intravenous drip, if the arrhythmia warrants therapy.

The convalescent care of children (p. 231) who have suffered from congestive cardiac failure is important. As the child improves, greater freedom of activity may be permitted, and schoolwork may be resumed. For many months after recovery, rest periods throughout the day and ten to twelve hours' rest at night should be advised.

SAMUEL KAPLAN  
ROBERT A. LYON

#### REFERENCES

- Blumberg, R. W., and Lyon, R. A.: Endocardial Sclerosis. *Am. J. Dis. Child.*, 84:291, 1952.
- Craig, J. M.: Congenital Endocardial Sclerosis. *Bull. Internat. A. M. Mus.*, No. 30:15, 1949.
- di Sant'Agnese, P. A., Andersen, D. H., Mason, H. H., and Bauman, W. A.: Glycogen Storage Disease of the Heart. *Pediatrics*, 6:402, 607, 1950.
- Gore, I., and Saphir, O.: Myocarditis: A Classification of 1402 Cases. *Am. Heart J.*, 34:827, 1947.
- Nadas, A. S., Rudolph, A. M., and Reinhold, J. D. L.: The Use of Digitalis in Infants and Children. *New England J. Med.*, 248:98, 1953.
- Saphir, O., Wile, S. A., and Reingold, I. M.: Myocarditis in Children. *Am. J. Dis. Child.*, 67:294, 1944.



## DISEASES OF THE PERICARDIUM

Congenital malformations of the pericardium are rare. They consist chiefly of defects of the parietal pericardium and are of little clinical significance.

Pericardial cysts are usually asymptomatic and discovered on roentgenograms of the chest. The cardiopericardial shadow is increased and distorted, depending on the location and size of the cyst. The electrocardiogram is normal. The cysts, which are usually benign, may be removed surgically.

### PERICARDITIS

**Etiology.** The most common causes of pericarditis in children are acute rheumatic fever and bacterial pathogens. Other causes include acute idiopathic or viral pericarditis, rheumatoid arthritis, uremia, tuberculosis, lupus erythematosus, constrictive pericarditis, trauma and postoperative pericarditis.

**Hemodynamics.** The effects on the circulation depend largely on the presence or absence of significant amounts of pericardial fluid, the speed of accumulation of the fluid and the myocardial efficiency. Thus a small amount of fluid in the pericardium with a normal myocardium is compatible with normal cardiovascular dynamics. On the other hand, the rapid accumulation of large amounts of fluid in the pericardium with a normal myocardium may result in cardiac compression or *cardiac tamponade*, as in hemorrhage into the pericardium or in septic pericarditis. Smaller amounts of pericardial fluid with a diseased myocardium may also result in cardiac tamponade as in acute rheumatic fever. Cardiac compression also occurs in long-standing chronic constrictive pericarditis.

The basic physiologic abnormality in cardiac compression is inadequate diastolic filling of the ventricles (Fig. 288), which results in increased pressure in both atria and in the venous systems. The stroke volume is small and more or less fixed. Cardiac output is maintained by tachycardia, and reflex vasoconstriction maintains the blood pressure.

**Clinical Manifestations.** Pain may or may not be present and varies in its intensity, location and distribution. Only the lower third of the pericardium, the area supplied by the phrenic nerve, is sensitive to painful stimuli. Therefore the pain may be referred

to the neck or shoulder. The pain may be precordial and pleural when it is aggravated by inspiration and coughing, and may be referred to the back. Or it may be precordial, constant and uninfluenced by respiration, but aggravated by rotating the trunk or by swallowing (McGuire, Kotte and Helm). The pain is either sharp or a dull, oppressive, poorly localized ache.

The venous pressure varies with the intrapericardial pressure. If the latter is raised, the venous pressure is elevated, especially during inspiration. Hepatomegaly, ascites and edema may also be present. The pulse is normal and small in volume or paradoxical; it depends on the degree of cardiac compression. A small rapid pulse is found in patients with a tense pericardium and a low cardiac output. *Pulsus paradoxus* indicates that the pulse becomes smaller or disappears during inspiration; this sign may be confirmed by measuring the blood pressure during the phases of respiration. In the presence of cardiac compression the precordium is quiet to palpation. A large amount of fluid may be detected by percussion, shifting dullness and by recognizing that the apical impulse is well within the border of cardiac dullness. The heart sounds may be normal or distant. A pericardial friction rub may be audible even in the presence of large amounts of fluid. The rub is heard anywhere over the heart, but is frequently situated over the lower left sternal border. It is superficial, of varying intensity and does not have any definite relationship to the heart sounds.

Pericardial effusion may result in pressure on the left main stem bronchus with collapse of the left lung resulting in percussion dullness and bronchial breathing at the left base (*Ewart's sign*). Similar signs may occur from secondary pleural effusion.

The findings on *roentgen examination* vary according to the amount of pericardial fluid. In dry pericarditis there are no abnormal findings. If the accumulation is large, the cardiopericardial shadow is enlarged, the normal contours are obscured, and the amplitude of cardiac pulsation is decreased. Other non-diagnostic signs include changes in the shape of the cardiac silhouette with changes in posture, divergent vascular shadows at the base, an acute right cardiophrenic angle and rapid changes in the size of the cardioperi-

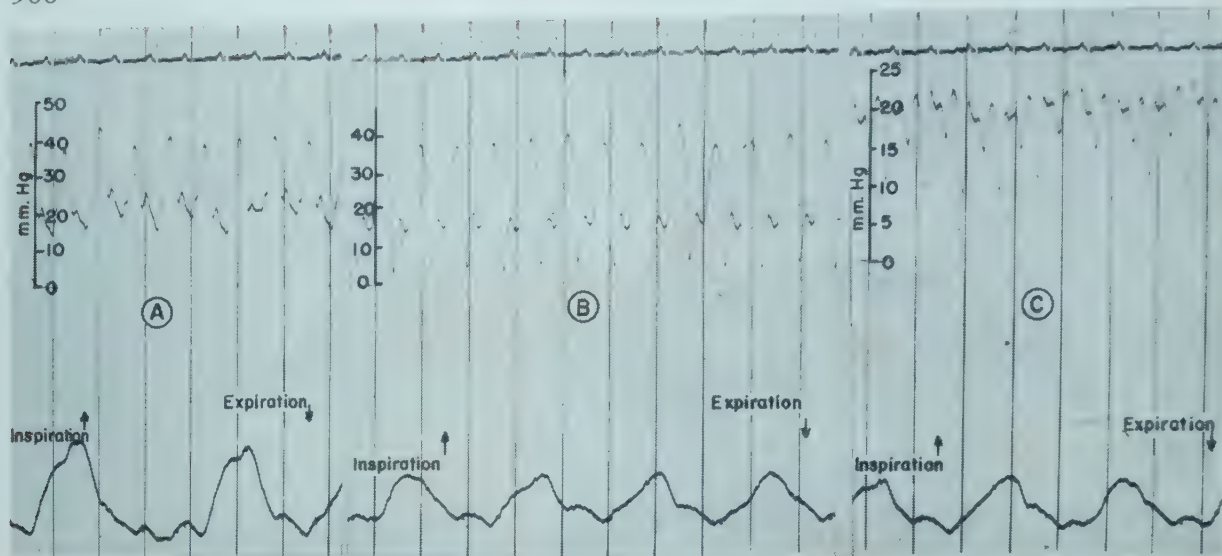


FIG. 288. Hemodynamics in a patient with cardiac compression. The upper tracing is the electrocardiogram, and the lower is the record of respiration. The middle tracing shows the intracardiac pressures. A, Pulmonary artery; B, right ventricle; C, right atrium. Note the diastolic dip in the right ventricular curve and the high right atrial pressure (see text).

cardial shadow. The radiologic findings are not pathognomonic and may be simulated closely by acute cardiac dilatation. Pericardial calcification due to chronic constrictive pericarditis is rare in children.

The *electrocardiogram* is abnormal in many instances. The abnormalities are widespread and involve most of the leads. In the acute phase the S-T segment is elevated, and the QRS voltage may be low. As healing progresses the S-T segment becomes isoelectric or depressed, and the T waves are flattened, diphasic or inverted. The graph returns to normal when the pericarditis heals, although T wave inversion may persist for many months after clinical recovery. This electrocardiographic pattern may be transient and localized, and may be recognized only with serial tracings.

In the presence of cardiac compression *cardiac catheterization* reveals an increased pulmonary "capillary" and right atrial pressure. The pulmonary artery and right ventricular pressures are normal or moderately elevated, and there is a conspicuous dip in early diastole in the right ventricular pressure curve (Fig. 288). If the catheter is coiled in the right atrium, the width of the pericardial shadow can be detected. The diagnosis may be confirmed also by angiocardigraphy, which delineates the cardiac chambers and separates that part of the cardiac silhouette which is produced by pericardial effusion.

*Cardiac tamponade*, whatever the etiology, is a medical emergency. If the cardiac output is not maintained during cardiac compression,

the patient goes into shock. The intrapericardial pressure must be reduced immediately, usually by pericardiocentesis.

**Rheumatic Pericarditis.** Rheumatic pericarditis is usually fibrinous or serofibrinous, and a large accumulation of fluid is unusual. Its diagnosis proves the presence of active rheumatic carditis. These patients are usually acutely ill with fever, dyspnea and pericardial pain. The heart is frequently enlarged, and a pericardial friction rub is common. The electrocardiographic changes are as described above. Treatment is directed towards the rheumatic illness as a whole, the relief of pain and pericardiocentesis in the rare cases with cardiac tamponade. Rheumatic pericarditis, per se, does not produce serious after-effects and does not lead to constrictive pericarditis. Children with rheumatic pericarditis usually have more serious underlying carditis and therefore a poorer long-term prognosis.

The differential diagnosis of rheumatic pericardial effusion from acute cardiac dilatation may be difficult. In some patients it may be necessary to resort to pericardiocentesis to establish the presence or absence of significant amounts of pericardial fluid. The essential difference between dry rheumatic pericarditis and other forms of dry pericarditis such as acute benign pericarditis is the presence in the former of significant systolic and/or diastolic murmurs as well as other stigmata of acute rheumatic fever.

**Septic Pericarditis.** Septic pericarditis is produced by a variety of organisms, including



pneumococci, streptococci and staphylococci. Foci of infection, usually pneumonia, are frequently present at other sites. The purulent exudate in the pericardium is of varying consistency, and coagulated masses of fibrin and pus are common.

The patients are acutely ill with fever, pericardial pain and tachypnea. The heart is enlarged, murmurs are insignificant, and a friction rub may or may not be present. The electrocardiographic and radiologic pictures are as described above. The diagnosis is confirmed by pericardiocentesis. In some patients this procedure may yield only small amounts of pus, owing to the consistency of the exudate and the multiple loculations. Surgical drainage is usually necessary and should be instituted early. This therapy with the use of appropriate antibiotics gives excellent results, and the long-term prognosis appears to be good.

**Acute Benign Pericarditis (Idiopathic, Nonspecific or Viral).** This disease frequently follows an upper respiratory tract infection with an average latent period of twelve days (McGuire, Kotte and Helm). The onset is usually acute with fever, and pericardial pain and a friction rub are common. Varying amounts of straw-colored pericardial fluid develop, but cardiac compression is rare. The electrocardiogram usually shows the typical pattern of pericarditis.

Although the disease is benign without any after-effects, recurrences, sometimes multiple, have been noted in up to 20 per cent of patients. Symptomatic treatment is all that is usually necessary. Corticosteroid therapy may be considered in the severe forms of the disease or in patients with multiple recurrences.

**Pericarditis in Rheumatoid Arthritis.** Pericarditis may occur at any stage of rheumatoid arthritis and may precede the typical joint manifestations. Pericardial effusion is rare and a pericardial friction rub common. Steroid therapy is indicated in the severe forms of the disease.

**Pericarditis in Uremia.** In the terminal stages of uremia a pericardial friction rub may be heard. The pericarditis seldom produces symptoms, and the electrocardiographic changes are minimal.

**Tuberculous Pericarditis.** Tuberculous pericarditis is usually secondary to a lesion in the hilar nodes or in the lung. Pericardial effusion is common and is later followed by a fibrotic reaction which may result in constrictive pericarditis. The onset may be in-



FIG. 289. Purulent pericarditis due to type 29 *Pneumococcus* in an infant aged 12 months.

sidious and be associated with cough, dyspnea, fever, weight loss and night sweats. The diagnosis depends on signs of tuberculosis elsewhere in the body and recovery of the organism from the sputum, gastric washings or the pericardial fluid. Treatment is that of the tuberculous infection (p. 464).

**Chronic Constrictive Pericarditis.** This disease is rare in children. In the majority of instances the etiology is unknown, or the disease may follow tuberculosis and possibly septic pericarditis. The hemodynamics and clinical picture are those of chronic cardiac compression and must be distinguished from chronic congestive heart failure. Atrial fibrillation may occur. If the constriction is severe, pericardiectomy is advised.

**Postoperative Pericarditis.** Postoperative pericarditis may follow any direct surgical procedure in the heart. Friction rubs are common during the first two weeks after surgery. In some patients signs of pericarditis without significant effusion recur some weeks after surgery and may be repeated over a period of about three to four months. The prognosis is good, and treatment is symptomatic.

SAMUEL KAPLAN  
ROBERT A. LYON

#### REFERENCES

- Carmichael, D. B., Sprague, H. B., Wyman, S. M., and Bland, E. F.: Acute Nonspecific Pericarditis. *Circulation*, 3:321, 1951.
- Friedman, S., Ash, R., Harris, T. N., and Lee, H. F.: Acute Benign Pericarditis in Childhood: Comparisons with Rheumatic Pericarditis, and Thera-

peutic Effects of ACTH and Cortisone. *Pediatrics*, 9:551, 1952.  
 McGuire, J., Kotte, J. H., and Helm, R. A.: Acute Pericarditis. *Circulation*, 9:425, 1954.

Scott, R. W., and Garvin, C. F.: Tumors of the Heart and Pericardium. *Am. Heart J.*, 17:431, 1939.

## DISEASES OF THE BLOOD VESSELS

*Congenital anomalies* involving the structure, origin or position of blood vessels may occur in any part of the body, but rarely do they cause any circulatory disturbance unless the aorta and its primary thoracic branches, the pulmonary artery or coronary arteries, are involved (See *Congenital Heart Disease and Diseases of the Myocardium*). *Fetal blood vessels*, especially the umbilical vein and hypogastric arteries, may be the site of infection in the neonatal period. *Hemangiomas* are described on page 1358. *Dilatation of veins* (varices) rarely occurs in childhood as a congenital malformation, but may result from obstructive lesions such as tumors, thromboses and hepatic cirrhosis.

### ANEURYSMS AND FISTULAS

Aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus and Marfan's syndrome and in intracranial vessels (p. 1080). They may also occur secondary to an infected embolus, infection contiguous to a blood vessel, trauma, congenital abnormalities of structure, especially of the medial coat, and arteritis, e.g., periarteritis nodosa.

*Arteriovenous fistulas* may be limited to small cavernous hemangiomas or may be extensive. In a group of forty-four children observed by Ward and Horton, congenital arteriovenous fistulas involved the vessels of the lower extremity in twenty-five instances, the upper extremity in nine instances, the brain in four, the face, scalp and neck in four, and produced hemihypertrophy in two instances. *Trauma* accounts for a large number of arteriovenous fistulas.

The *clinical manifestations* of arteriovenous fistulas appear to depend primarily on the size of the shunt across the fistula and the associated vasodilatation. Discoloration of the skin, prominence of the superficial vessels and local edema may occur at the site of the fistula or involve a whole extremity. Prominent arterial pulsations and a continuous machinery bruit may be heard over the site of the lesion, especially in the traumatic types.

The venous pressure is elevated in an affected extremity, the temperature of the skin may be higher at the site of the lesion, and the venous oxygen saturation distal to the fistula is higher than that of venous blood taken from a similar site on the unaffected side. In extensive fistulas there is left ventricular hypertrophy and dilatation, a widened pulse pressure and congestive heart failure. Arteriograms with the injection of contrast material into an artery proximal to the fistula confirm the diagnosis. Symptomatic arteriovenous fistulas should be eradicated surgically.

### FROSTBITE

Frostbite may occur in the face or extremities from prolonged exposure to cold. The skin first becomes red and then pale or rarely cyanotic, as the arterioles remain in a spastic condition in an effort to preserve the body heat. During thawing, hyperemia occurs, and blisters may form on the skin. Gangrene may occur if early relief is not obtained.

The *treatment* consists in application of mild heat and gentle massage, but vigorous rubbing should be avoided to prevent irritation of the skin. Overheating the affected tissue before the blood supply is re-established may lead to edema and gangrene.

### EMBOLISM

Emboli, consisting of bacteria and fibrinous material, usually arise from mural thrombi or vegetations in the heart or large blood vessels, as for example in subacute bacterial endocarditis. Other rarer causes of emboli include fat (secondary to trauma) and foreign material, such as air, introduced accidentally into the vascular system during therapeutic procedures. In patients with atrial or ventricular septal defects, emboli arising in the systemic venous system may pass across the defect and enter the systemic arterial system (*paradoxical embolus*).

When emboli lodge in an artery, the blood flow through the vessel is compromised. If the collateral circulation to the involved area is inadequate, necrosis or gangrene supervenes. However, if the collateral circula-



tion is adequate, the emboli may be silent; thus an embolus to the arteries of the forearm may not give rise to any symptoms and is detected only when the radial or ulnar pulse disappears.

The symptoms and signs produced by arterial emboli depend on their location; e.g., an embolus to the middle cerebral artery may result in hemiparesis; an embolus to the femoral artery may result in ischemia with or without gangrene in the lower extremity. If the emboli are infected, an abscess forms locally.

*Treatment* of arterial embolism consists in eradication of the source of embolism, as for example treatment of subacute bacterial endocarditis and therapy to increase the collateral circulation to the affected area. Surgical therapy such as embolectomy, sympathectomy and amputation may be indicated in specific instances.

Pulmonary embolism is not as frequent in children as in adults. Thrombosis of the calf veins with secondary pulmonary embolism is rare in children. However, pulmonary emboli may arise secondary to subacute bacterial endocarditis in patients with a left-to-right shunt. Occasionally pulmonary embolism is seen in older children with chronic rheumatic heart disease and atrial fibrillation. Multiple small pulmonary emboli have been described elsewhere (see Primary Pulmonary Hypertension, p. 879).

## THROMBOSIS

The common cause of *arterial thrombosis* in

children is polycythemia secondary to severe cyanotic congenital heart disease. A frequent site for such thrombi is in the brain, but they may occur anywhere in the body. They may be precipitated by dehydration.

*Venous thrombosis* may occur in veins used for prolonged intravenous therapy or in an area surrounding an infective process. The inflammation in the vein (*phlebitis*) is usually local, and the thrombi seldom give rise to emboli.

Venous thrombosis may also occur in patients with severe cyanotic congenital heart disease and polycythemia. A common site for these thrombi is in the venous sinuses of the brain, and they too may be precipitated by dehydration.

Any severe illness associated with intense dehydration may be complicated by venous thrombosis. This complication is more frequent in infants with diarrhea or septicemia. The common site for thrombosis is in the sagittal sinus of the brain and in the renal vein with extension into the inferior vena cava. (See Vascular Disorders of the Central Nervous System, p. 1080, and Hemorrhagic Infarction of the Kidney, p. 1053.)

SAMUEL KAPLAN  
ROBERT A. LYON

## REFERENCES

- Editorial: Frostbite. J.A.M.A., 148:940, 1951.
- Gross, R. E.: Arterial Embolism and Thrombosis in Infancy. Am. J. Dis. Child., 70:61, 1945.
- Ward, C. E., and Horton, B. T.: Congenital Arteriovenous Fistulas in Children. J. Pediat., 16:746, 1940.

## RHEUMATIC FEVER

Rheumatic fever is one of the leading causes of chronic illness, invalidism and death in children. Although the onset usually is during childhood, the effects are projected into adult life. During World War II 100,000 young men were ineligible for military service because of rheumatic heart disease, and an additional 40,000 had an initial attack or a recurrence of the disease.

The mortality rate due to rheumatic heart disease appears to be declining from both the initial attack and from recurrences. Whether this apparent decline is due to changes in the natural history of the disease, to the improvement in the economic condition of urban populations or to more effective control of streptococcal upper respiratory tract

infections is not known. If the prophylactic procedures for decreasing the incidence of initial attacks and recurrences recommended by the American Heart Association come into general use, the morbidity and mortality caused by rheumatic fever may be still further reduced.

In 1888 Cheadle pointed out that polyarthritis, chorea and heart disease formed part of the same clinical syndrome. Rheumatic fever is now recognized as a general systemic disease characterized by frequent recurrences or exacerbations. It may occur at any age, but usually begins in childhood. The symptoms and course are extremely variable, and the diagnosis is often difficult. Three major clinical manifestations, however,

are pathognomonic: migratory polyarthritis, Sydenham's chorea and carditis. Subcutaneous nodules, although they occur frequently in the course of rheumatic infection and are a characteristic manifestation, are also found in rheumatoid arthritis.

**Etiology.** Both initial and subsequent attacks of rheumatic fever follow scarlet fever or upper respiratory tract infections due to group A beta hemolytic streptococci. Attacks of rheumatic fever also occasionally follow streptococcal skin infections. However, unless the presence of streptococci in the pharynx of such patients is excluded by throat cultures, it seems possible that the skin lesions may have been preceded or accompanied by an inapparent streptococcal upper respiratory tract infection. The common cold, influenza and the contagious diseases of childhood, with the exception of scarlet fever, do not precipitate rheumatic attacks. Further evidence that infection with group A hemolytic streptococci bears a specific relation to the development of rheumatic fever has been obtained by prophylactic administration of sulfonamides or penicillin. If streptococcal pharyngitis is prevented by this means, rheumatic subjects escape rheumatic recurrences. At present, however, it is not known whether streptococci act in conjunction with some other agent or are the sole cause of rheumatic fever, and, if so, by what mechanism they produce the disease.

The development of relapses in rheumatic patients after streptococcal infections usually follows a characteristic pattern. The attack of streptococcal pharyngitis may be extremely mild or moderately severe and has been designated by Coburn as phase I. In most instances the symptoms of the respiratory infection subside quickly and are followed by a latent or nonsymptomatic period (phase II), usually lasting one to three weeks, which in turn is followed by the onset of acute rheumatic fever (phase III).

After outbreaks of pharyngitis or scarlet fever, often caused by a capsulated strain of a single type of group A hemolytic streptococci, the percentage of rheumatic children who have rheumatic sequels varies greatly. A child who escapes a rheumatic recurrence after one streptococcal infection may subsequently have a recurrence after another infection. The upper respiratory tract infection may be caused by any of the forty or more specific types. The regular occurrence of a latent period (phase II) and the inability to demonstrate streptococci in the affected tis-

ues or in the blood during an acute attack (phase III) suggests that hypersensitivity to these microorganisms or their products may be the cause of rheumatic fever. The similarity of the symptoms of serum sickness, namely, polyarthritis, skin manifestations, leukocytosis and fever, to those of rheumatic fever lends support to this view. Further studies may show that the characteristic lesions of rheumatic fever are due to enzymatic action on connective tissue either by streptococcal enzymes themselves or by the catalytic effect of some streptococcal derivative on enzymes already present in the body. Another possibility is that the streptococcal pharyngitis facilitates invasion by an unknown filtrable agent. So far, attempts to demonstrate a virus have been unsuccessful, as have attempts to transmit rheumatic fever to animals.

**Epidemiology.** The incidence of rheumatic fever in the United States is not accurately known, because it is not a reportable disease in most communities and, in its milder forms, is frequently overlooked. It is estimated that about 1,000,000 people in the United States have rheumatic fever.

**Climate.** Rheumatic fever is most prevalent in the temperate zones, although it is more common in subtropical and tropical climates than was formerly supposed. The incidence of rheumatic heart disease in adults who have lived all their lives in the South apparently is almost as high as in the North, suggesting that the onset in southern latitudes may be more insidious. Climate appears to be a more important factor than racial susceptibility; whereas rheumatic fever is relatively uncommon in Puerto Rico and southern Italy, Puerto Rican and Italian children often contract the disease shortly after their arrival in the northern part of the United States.

**Season.** There is a definite seasonal incidence of rheumatic fever which varies in different localities. On the west coast of the United States the peak is usually reached in January and February, along the Eastern seaboard in March and April and in England, in November. In general, the seasonal variation in rheumatic fever follows the curve and incidence of streptococcal diseases.

**Race.** There are no data which permit valid conclusions as to differences in racial susceptibility.

**Sex.** Although it is frequently stated that rheumatic fever is more common among girls than boys, available data do not show a distinct difference in this respect.



**Age at onset.** Rheumatic fever is rare in children under three years of age. The age of greatest incidence is between five and fifteen years. First attacks occur most commonly from six to eight years of age.

**Socio-economic factors.** Rheumatic fever is usually considered to be a disease of the poor, since it is relatively uncommon among children from wealthy or middle class homes. It is also essentially an urban disease. Attempts to relate the high incidence to nutritional factors have so far failed. The prevalence of rheumatic fever among Army and Navy recruits during World War II suggests that infection through close contact of susceptible persons rather than a deficient diet may explain the high incidence of this disease.

**Familial incidence.** Rheumatic fever frequently occurs in more than one member of a family. Studies have shown that a higher percentage of children born of rheumatic parents contracted the disease than of those born of nonrheumatic parents and that the incidence was higher in relatives of rheumatic children who lived in separate households than among relatives of a control group of nonrheumatic children. Further work indicates that the risk of contracting the disease in a rheumatic family is greatly increased by association with another member of the family suffering from an acute attack. These data suggest that the tendency to acquire rheumatic fever may be inherited, but that contact with the etiologic agent is necessary.

**Pathology.** The characteristic lesions of rheumatic fever are found in the connective tissue of the heart, in the arteries and in the subcutaneous tissue. Collagenous structures become edematous, often resulting in the formation of a granuloma. This granuloma, observed by Aschoff in 1904 and known as the Aschoff body, constitutes the pathognomonic histologic lesion of rheumatic fever. Typical Aschoff bodies are usually most numerous in the interventricular septum and in the wall of the left ventricle, but they are also often demonstrable in the left auricular appendage obtained by biopsy during commissurotomy. The cellular reactions in the valves and in the subcutaneous tissue (subcutaneous nodules) resemble those found in the myocardium.

Depending on the location of the lesions, exudative and proliferative or predominantly exudative manifestations develop. Effusions into the joint cavities, the pleura or the pericardium are examples of the primarily exuda-

tive type of response; the lesions in the myocardium, the valves and the subcutaneous tissues are both exudative and proliferative. Transient rheumatic effusions are absorbed without causing permanent injury, but proliferative reactions often follow repeated or long-standing exudates, leading to formation of extensive adhesions, especially in the pericardium.

Large pericardial effusions are relatively uncommon, but evidence of pericarditis is found in most children dying of acute carditis. Both the parietal and the visceral layers are affected. The serous surfaces are red and roughened, and fibrin is deposited. The pericardial fluid may be slightly increased and is sometimes turbid, but never purulent. Cicatrization causes localized thickening of the epicardial surface, and in severe cases the epicardial and parietal layers may become adherent.

MacCallum described a characteristic rheumatic lesion in the endocardium of the left atrium which is often visible grossly as a thickened, opaque and roughened patch. Acute valvular lesions appear as warty vegetations or verrucae along the line of closure. Microscopically, the verrucae consist of hyaline masses. Inflammatory cells are present in the entire valve leaflet and in the chordae tendineae. The formation of scars, as the lesions heal, results in thickening of the leaflet and shortening of the chordae tendineae. Valvular sclerosis develops slowly, usually requiring months or years. Valvular deformities in most instances are due to repeated insults.

Functional impairment of the heart is the result of damage to one or more of its component structures: the myocardium, the endocardium, including the valves, or the pericardium. The extent of the damage determines the degree of impairment.

Since patients with active chorea rarely die, few pathologic studies of the central nervous system in this disease have been made. The findings reported are not consistent, and no characteristic lesions have been described.

**Clinical Pattern.** The latent (incubation) period (see p. 904) usually varies from one to three weeks. The clinical course of rheumatic fever varies greatly. The onset may be acute or insidious, the initial attack at times not being recognized. It is not uncommon to discover unsuspected cases of rheumatic heart disease in routine examinations of children. Either no history of previous rheumatic

attacks is obtained, or there is only a history of equivocal symptoms such as "growing pains," fatigability, nosebleeds, pallor, attacks of abdominal pain or frequent colds.

In the majority of instances, however, typical attacks of any of the three major rheumatic manifestations, polyarthritis, chorea and carditis, tend to recur at varying intervals of time. Most attacks are monocyclic, lasting one to three months. In some children, however, the signs of rheumatic activity continue much longer with intermittent exacerbations. A polycyclic attack of this kind should be differentiated from a true recurrence. A recurrence is a new attack following a streptococcal upper respiratory tract infection in a rheumatic subject in whom there has been no clinical or laboratory evidence of rheumatic activity for at least three months. Recurrences are most common during the first and second years after the initial attack. If a child after apparent recovery from an initial attack remains free of rheumatic manifestations for five years, the prognosis is usually good. Except in the case of chorea, careful questioning will usually reveal a history of a respiratory infection or an attack of scarlet fever preceding the initial attack or the subsequent relapses. The tendency to rheumatic recurrences is greatest during childhood and declines after puberty.

In children less than six years of age carditis is often the presenting symptom, whereas in older children polyarthritis and chorea are more common. Signs of carditis in most instances appear only during subsequent attacks.

**Major Rheumatic Manifestations. Arthritis.** Usually the larger joints (ankles, knees, hips, wrists, elbows, shoulders) are involved, often in succession. Rarely, only one joint is affected. The duration of involvement of each joint is variable and may last only a day or two. The joint is usually swollen and tender to touch and may be hot and red. Active and passive motion is painful. Occasionally the small joints of the fingers and toes are involved. In contrast to rheumatoid arthritis, permanent deformities are never caused by rheumatic polyarthritis. The temperature is usually elevated to 101° or 102° F., a moderate leukocytosis is present, and the erythrocyte sedimentation rate is increased.

Patients with polyarthritis may have cardiac involvement even if definite clinical evidence of carditis is lacking. It is therefore advisable to secure several electrocardiograms during the course of polyarthritis. The most

frequent finding is a prolongation of the conduction time. Only increases of at least 0.04 second in tracings with comparable rates are significant. Usually the P-R interval returns to its previous length, but sometimes it remains permanently prolonged. Other indications of myocardial involvement are inversion of the T waves in any two of the three standard leads, and various types of arrhythmias. Such changes are transitory, but provide objective evidence of carditis. In some instances, a comparison of teleroentgenograms taken at the beginning of the attack and after recovery may show a transient increase in the size of the heart.

**Chorea (Sydenham's chorea, St. Vitus' dance).** Chorea is a disorder of the central nervous system characterized by emotional instability, purposeless movements and muscular weakness. The attacks are recurrent and often prolonged, but eventually recovery is complete. Chorea occurs most commonly between the ages of seven and fourteen years, with the peak incidence at eight years. It is rare after puberty and never occurs after the age of twenty years.

The onset is almost always gradual. The mother states that the child, previously well controlled, has become increasingly nervous. He tends to drop things and stumbles frequently. Often the school teacher reports grimacing and writing difficulties. Speech becomes indistinct, and characteristic purposeless movements of the arms and the legs develop. The movements are increased by effort, excitement and fatigue, but cease when the patient is asleep. Muscular weakness is frequent, so that the child is unable to walk, talk or even sit up. Often the movements are so violent that the patient has to be placed in a padded crib to prevent injury. Infrequently only one side of the body is involved. Symptoms of chorea do not occur concurrently with active arthritis.

The relation of chorea to rheumatic fever has been questioned, chiefly because evidence of general infection is lacking and the incidence of associated carditis is low. Choreic patients are usually afebrile, and the cerebrospinal fluid shows no abnormalities. The C-reactive protein is negative, and the leukocyte count, sedimentation rate and the antistreptolysin-O titer in many instances are normal. It has been suggested that the absence of serologic evidence of a preceding streptococcal infection may be due to a long latent period between the attack of pharyngitis and the appearance of chorea.



Certain clinical tests may aid in establishing the diagnosis of chorea. In mild cases the choreiform movements are exaggerated after periods of direct questioning or enforced quiet. Dysfunction of speech may be elicited by having the child count rapidly to ten and then back to one; for the first few numbers he may speak clearly, and then suddenly the speech becomes thick, or he hesitates or is unable to utter a sound for several seconds. When he talks, there may be a clucking sound, due to the sudden contraction of the tongue to the floor of the mouth. There is only slight resistance to passive movements. The hand grasp is frequently weak and may consist of spasmodic contractions followed by rapid relaxation. Fibrillary twitchings in the muscles may also be detected while the hand is held. There may be a broad grin one moment, followed suddenly by a "poker-face" or even a tearful expression. When the tongue is protruded, it is impossible to hold it quietly, and its undulating, jerky movements have been described as a bag of worms. The child may bite the tongue to keep it protruded, or may jerk it back rapidly. If he is asked to extend his arms with outstretched fingers in front of him, he soon hyperextends his wrists and his fingers; or if he is asked to raise his arms above his head, he soon turns his arms so that the backs of the hands oppose. With deep breathing the diaphragm may be drawn upward so that the abdominal wall is drawn inward. The response to the patellar reflex is often "hung-up."

**Carditis** (see p. 890). Carditis is the most serious manifestation, since it often leads to permanent disability or death. In most cases of acute carditis the temperature is elevated and may be as high as 104° F. Leukocytosis is present. The hemoglobin often falls rapidly, and pallor is striking. The pulse is of poor quality, and tachycardia is out of proportion to the fever. The respiratory rate is increased. Weakness, prostration, orthopnea, cyanosis and precordial pain are frequent symptoms in severe cases. Evidence of cardiac decompensation may develop. Cardiac dilatation occurs in most cases and is probably due to the weakening of the muscle fibers as a result of the inflammatory reaction. The apical impulse becomes wavy, and the heart sounds are muffled. Owing to exaggeration of the third heart sound, gallop rhythm is frequent. Often the muscular quality of the first heart sound is diminished, resulting in a "tick-tock" rhythm. New murmurs arise,

or the quality of murmurs previously present may change and assume a musical or "seagull" quality. Prolongation of the conduction time and arrhythmias resulting from dropped beats to 2:1 or complete heart block occur occasionally. (See page 886 for other electrocardiographic changes.) Atrial fibrillation is uncommon in children and develops only in patients with long-standing heart disease.

**Pericarditis** (see p. 899). Precordial pain usually indicates pericarditis; a friction rub, a leathery or scratchy to-and-fro sound, is pathognomonic. It may be heard over the entire precordium or only in limited areas. Most pericardial effusions are not massive, but occasionally are sufficiently extensive to cause respiratory embarrassment. In most instances the symptoms subside without paracentesis. The differentiation of cardiac dilatation and pericardial effusion is difficult by physical examination and by roentgenography. In pericardial effusion the apical impulse may disappear, the heart sounds are distant, but the quality of the pulse remains fair. The cardiac silhouette on the roentgenogram is usually more rounded with an effusion than with dilatation.

**Subcutaneous nodules.** Nodules are one of the most characteristic manifestations of rheumatic fever and are not observed in any other disease except rheumatoid arthritis. They are found on the extensor tendons of the hands and feet, on the elbows (Fig. 290), at the margin of the patella, on the scalp, over the scapula and over the spinous processes of the vertebrae. They vary from 0.2 to 2 cm. in diameter. They are often more readily felt than seen and can easily be



FIG. 290. Rheumatic nodules at the elbow in a Negro girl 10 years of age. She had polyarthritis and endocarditis; later, pericarditis developed. She died 3 weeks after the picture was taken.



FIG. 291. Annular erythema on the chest and abdomen of a boy 8 years of age, who also had rheumatic carditis.

overlooked unless a careful search is made. They tend to be distributed symmetrically. They lie in the deep connective tissue, and the skin is freely movable over them. Nodules are never painful. They are most numerous in children with severe rheumatic infections and with extensive cardiac involvement.

**Symptoms Frequently Associated with Rheumatic Fever, but not Pathognomonic.** *Muscle and joint pains.* Children frequently complain of vague muscle and joint pains commonly known as "growing pains." In most instances they are confined to the lower extremities, and it is important to exclude orthopedic defects. Such pains which occur only at night are rarely rheumatic, nor are most other muscle and joint pains, but periodic examinations are indicated.

*Abdominal pain.* Abdominal pains occur frequently during the course of acute rheumatic attacks and may simulate appendicitis. Pain of rheumatic origin is often localized in the epigastrium, and muscular rigidity is absent. In some instances, however, acute appendicitis cannot be excluded, and laparotomy is indicated. There are usually no abnormal findings, although occasionally the mesenteric lymph nodes are enlarged and congested and petechial hemorrhages are found in the mesentery. If there are other definite signs of rheumatic fever and if the

patient is under close observation, operation can usually be delayed temporarily and often becomes unnecessary.

*Epistaxis.* Nosebleeds are common in rheumatic children and are often an early manifestation. They may be of such severity that transfusion becomes necessary. Usually no lesion of the nasal mucosa is found. Hemorrhagic manifestations such as epistaxis, purpura and occasionally hematuria in rheumatic subjects are not associated with thrombocytopenia. The nature of the underlying vascular lesions is not known.

*Skin manifestations.* Various types of erythema occur, usually erythema marginatum (erythema annulare) (Fig. 291), less often erythema multiforme. The lesions come and go for months or years. Whether rashes of this kind, unless accompanied by other evidence, should be considered a sign of rheumatic activity is controversial. Purpuric eruptions (nonthrombocytopenic) are relatively uncommon.

Erythema nodosum occurs occasionally as it does in a variety of other conditions, including tuberculosis and coccidioidomycosis.

*Low grade fever.* In some instances there may be no abnormal manifestations other than a low grade fever during the late afternoon. If other cause for the fever is not established, the possibility of rheumatic fever must be kept in mind. An erythrocyte sedimentation rate is indicated in all such instances and should be repeated at intervals of three to four weeks. When there are equivocal cardiac changes, the diagnosis of rheumatic fever becomes more probable.

*Pneumonic consolidation and pleurisy.* Occasionally so-called rheumatic pneumonia or pleurisy develops during the course of acute carditis. Signs of consolidation appear first in one part of the lung and then in another, and may occur in the absence of congestive failure.

There is doubt whether the pulmonary involvement represents a rheumatic infection of the lung itself, or is the result of generalized vascular changes involving the lungs as well as other organs. Since Aschoff bodies are never found in the lung, the latter theory seems more likely. According to Epstein and Greenspan, the pathologic findings can be explained on the basis of increased capillary permeability, and consist in alveolitis resulting from diapedesis of erythrocytes and transudation of sero-albuminous material.

*General symptoms.* Since rheumatic fever is a generalized disease it often produces such



general symptoms as pallor, fatigue, anorexia and loss of weight. In such instances, when a definite diagnosis cannot be established, the patient should be examined at frequent intervals, especially after upper respiratory tract infections.

**Differential Diagnosis.** Rheumatic polyarthritis may be confused with *rheumatoid arthritis* in its early stages. The chronicity of the latter disease, however, soon becomes apparent. The response of rheumatic polyarthritis to salicylates is so rapid and striking that administration of these drugs may be used as a therapeutic test to differentiate the two. In *septic arthritis* usually only one joint is involved and the patient has more toxic symptoms. The fluid aspirated from a rheumatic joint is clear or only slightly turbid, whereas that obtained in pyogenic infections is frankly purulent except in the earliest stage, when the presence of bacteria is a distinguishing factor.

*Syphilitic hydrarthrosis* can be distinguished from rheumatic polyarthritis by its chronicity, the presence of other physical signs of syphilis and serologic tests. Joint pains may occur in *acute leukemia*, which can be identified by blood studies. The generalized hyperesthesia common in the early stages of *anterior poliomyelitis* may suggest rheumatic fever. Poliomyelitis is rare in the early spring months, when rheumatic fever is prevalent, and nuchal rigidity is common and the pain is not localized in the joints. The rarity of rheumatic fever in the first two or three years of life should be borne in mind in the differentiation of *acute* or *chronic arthritic symptoms in infants*.

Cardiac enlargement and dilatation of the mitral ring, which occur frequently in severe *anemias*, often suggest mitral insufficiency of rheumatic origin. This is particularly true of Negro patients with sickle cell anemia.

Any disease which causes symptoms of *low grade infection*, such as tuberculosis, undulant fever and sinusitis, can simulate rheumatic fever and must be excluded. In all cases of unexplained fever, patients should be examined during the febrile episode and again several weeks later.

At the onset of *chorea* there may be some difficulty in differentiating the grimacing of chorea from habit spasm. In the latter condition the same movements are repeated, whereas the facial twitchings in chorea are variable. *Athetoid movements* are slower, usually limited to the extremities, most often to the hands. In *encephalitis, tuberculous menin-*

*gitis* and *brain tumor* the choreiform movements are, as a rule, more or less stereotyped, and the history and other physical signs help in the differentiation. *Maladjustments* at home or elsewhere may produce nervous manifestations and instability. Emotional instability is not uncommon in *mentally retarded children*. *Hyperthyroidism* must also be considered when nervousness is the most prominent symptom. The peculiar and purposeless movements of the arms and legs in chorea are characteristic, however, and the diagnosis usually offers no difficulty. It should be recognized that a child in close contact with a case of active chorea may imitate choreiform movements without having the disease.

**Evaluation of Clinical Status.** When a diagnosis of rheumatic fever is established, it is important to decide whether the rheumatic process is active or quiescent.

**Clinical appraisal.** Salicylate therapy may and often does mask the symptoms of rheumatic fever; therefore it should have been discontinued for at least fourteen days before it is concluded that there is no fever or joint involvement. Low grade fever is often an indication of continued rheumatic activity. Rectal temperatures should be taken in the morning and at bedtime, and the child should have been at rest for at least a half-hour, since exercise or excitement may elevate the temperature normally. The presence of subcutaneous nodules indicates active rheumatic infection. Whether recurring erythematous rashes by themselves have the same significance seems doubtful. Since the pulse rate of children is often labile and likely to be accelerated by emotional factors, the presence of tachycardia should be determined during sleep. Persistent tachycardia in the absence of fever is evidence of active cardiac involvement. Extension of endocardial involvement from the mitral to the aortic valve is also indicative of rheumatic activity.

The child should be kept in bed until the pulse rate is normal, and the C-reactive protein is negative and the erythrocyte sedimentation rate decreasing. If the rheumatic process has become quiescent, the heart sounds should have improved in quality, and any abnormalities of cardiac rhythm should have disappeared. If cardiac enlargement has been present, a decrease in size may be demonstrable roentgenographically. There should also be a satisfactory response to exercise, and the child must show an ability to sustain growth and development before the disease is considered to be inactive.

**Laboratory appraisal.** At present there is no specific laboratory test for rheumatic fever. However, two nonspecific tests, the erythrocyte sedimentation rate (ESR) and the C-reactive protein determination, are useful in patients with equivocal symptoms and in evaluating activity of the established disease.

**ERYTHROCYTE SEDIMENTATION RATE.** In patients with rheumatic polyarthrititis or carditis unaccompanied by congestive failure the ESR is almost always elevated. During congestive failure the ESR often becomes normal, but usually rises as soon as compensation returns. Since the ESR is normal in uncomplicated chorea, the finding of an elevated rate in a choreic patient often indicates cardiac involvement.

The erythrocyte sedimentation rate frequently remains elevated after the subsidence of all clinical symptoms, indicating that the rheumatic process is still active at a subclinical level. Patients should be kept in bed until the ESR becomes normal or at least shows a tendency to decrease.

In children with vague complaints of joint pains, frequent epistaxes, pallor, fatigue, bouts of abdominal pain, erythematous rashes or low grade fever, an elevated ESR suggests the possibility of rheumatic fever.

**C-REACTIVE PROTEIN.** The C-reactive protein is not normally present in blood and frequently appears in the serums of patients who are acutely ill with a variety of diseases, including rheumatic fever. As the patient improves, this protein disappears. In contrast to the ESR, which depends upon a number of factors (fibrinogen, globulin and number of red blood cells) and is affected by stimuli other than those of rheumatic activity, the C-reactive protein is a single substance detectable by a highly specific precipitin reaction. During congestive failure of active rheumatic carditis, the ESR is frequently normal, whereas the test for the C-reactive protein is usually positive.

*Leukocytosis* per se is a less reliable indication of a subclinical rheumatic infection than is the sedimentation rate. The rheumatic process should not, however, be considered quiescent when the white blood cell count is consistently above 10,000 per cubic millimeter, especially when there is a definite shift to the left of the polymorphonuclear cells. Persistence of anemia is also evidence that the infection is still active.

The *P-R interval*, which frequently becomes prolonged during the course of an acute

attack, usually returns to its previous length as the patient improves. In some patients, however, it becomes fixed and remains permanently prolonged, probably as the result of scarring of the conduction system. A prolonged P-R interval, therefore, does not always indicate rheumatic activity.

**Prognosis.** Though some children who have no preceding history of rheumatic disease are found to have rheumatic carditis, in most instances serious cardiac damage is the result of repeated severe rheumatic attacks. The prognosis for children who contract rheumatic fever before they are six years of age is usually graver than for those who have their first attack at a later age. This difference is related principally to the frequency with which carditis is the principal or sole manifestation in the initial attack in the younger age group and the frequency with which there is residual cardiac damage. Young children are also more susceptible to streptococcal upper respiratory tract infections and are thus more apt to have recurrences unless adequate prophylaxis is maintained.

The outlook for children in whom the rheumatic manifestations are mild with little or no evidence of cardiac involvement is good, whereas the prognosis of patients with persistent cardiac enlargement indicative of a chronic infection of the myocardium is poor. Children usually die as a result of further rheumatic infection rather than as a result of mechanical failure, and at autopsy fresh as well as old lesions are found. Even with fairly marked valvular deformities the heart is able to function more or less adequately, provided the cardiac muscle is in good condition.

There are no permanent changes in the joints after rheumatic polyarthrititis or in the central nervous system after chorea.

**Prevention.** It is now generally accepted that the initial and recurrent attacks of rheumatic fever can be prevented by the control of streptococcal upper respiratory tract infections.

**Initial attacks.** It is estimated that 1 to 3 per cent of untreated cases of pharyngitis due to group A streptococci are followed by rheumatic fever. The incidence of rheumatic sequels can be greatly reduced by treatment which eliminates streptococci from the upper respiratory tract. Penicillin is the drug of choice, and therapeutic levels must be maintained for ten to fourteen days. One intramuscular injection of 600,000 units of pro-



caine penicillin G combined with 600,000 units of benzathine penicillin G will give adequate levels for fourteen days. Oral administration of penicillin has the disadvantage that patients tend to discontinue the medication as soon as they feel well and hence do not receive treatment for an adequate length of time. Broad-spectrum antibiotics should be used only in patients known to be hypersensitive to penicillin and must also be continued for at least ten days.

Every patient with scarlet fever should be treated as outlined above. In the absence of a scarlatinal rash the clinical diagnosis of streptococcal pharyngitis is often difficult. The following signs and symptoms are sufficient to warrant treatment: fever of  $101^{\circ}$  to  $104^{\circ}$  F., pain on swallowing, an inflamed throat often with exudate, tender swollen cervical nodes, and leukocytosis of more than 12,000 per cubic millimeter.

**Recurrent rheumatic fever.** In known rheumatic subjects the incidence of recurrent rheumatic fever may be as high as 50 per cent after streptococcal pharyngitis. With each recurrence the danger of permanent cardiac damage increases. Since the symptoms of the streptococcal infection may be so mild as to escape attention, rheumatic subjects should receive continuous prophylactic therapy. At present three methods are available: (1) intramuscular injection of 1,200,000 units of benzathine penicillin once a month; (2) oral administration of penicillin, 200,000 units twice a day, preferably thirty minutes before breakfast and supper; (3) sulfadiazine, 0.5 gm. for children weighing less than 60 pounds, and 1.0 gm. for those weighing more than 60 pounds, once daily. The method selected depends on the patient and his family. Oral medication often fails because the patient forgets to take the medicine regularly. Hypersensitivity reactions to penicillin in children are uncommon, but may occur. Sulfadiazine occasionally causes toxic reactions during the first two months of administration which necessitate discontinuance of the drug. Urticaria and abdominal pain accompanied by fever may occur during the second to third week. Agranulocytosis sometimes develops, usually during the third to the eighth week, and therefore leukocyte counts should be obtained once a week during this period. If no untoward reactions occur during the first two months, sulfadiazine is well tolerated and has the advantage that a single daily dose taken at any time provides adequate levels.

**Prophylaxis against bacterial endocarditis.** Transient bacteremia, most commonly due to alpha streptococci (*Streptococcus viridans*), occurs frequently after dental extractions or tonsillectomy. These organisms may lodge on valves damaged by rheumatic fever. Routine prophylactic measures are not adequate protection. Rheumatic children should receive 200,000 units of oral penicillin four times a day for a total of five days; two days before, on the day of and two days after operation. In addition to the oral medication, on the day of the operative procedure 600,000 units of aqueous and 600,000 of procaine penicillin should be given intramuscularly approximately one hour before operation.

**Treatment.** No specific therapy which will terminate the activity of the rheumatic process is available. In any given case, irrespective of whether the clinical manifestations are mild or severe, it is impossible to predict how long rheumatic activity will persist or how much permanent cardiac disease may develop. Suppressive therapy is all that is available until the attack has run its course. Penicillin is of no value in alleviating the manifestations of rheumatic fever; however, since rheumatic activity may be prolonged by the presence of group A streptococci, it is advisable to give all patients with acute rheumatic fever or chorea an intensive course of penicillin for two weeks to eliminate these organisms from the body. The prophylactic regimen should then be instituted.

The response of rheumatic polyarthritis to salicylates is dramatic. The fever decreases, and the pain and swelling of the joints often subside within twenty-four to forty-eight hours. The erythrocyte sedimentation rate usually decreases, and the C-reactive protein disappears. The effect on the arthritic manifestations is so rapid and striking that salicylates are often given as a therapeutic test to differentiate other arthritides from those of rheumatic origin.

The effect of salicylates on carditis, on the other hand, is equivocal. Although they tend to improve the general condition and the temperature is reduced, the pulse rate usually remains elevated, the size of the heart does not decrease, and signs of congestive failure, when present, persist. Pericarditis, like polyarthritis, is an exudative reaction and often appears to respond to salicylate therapy. The duration of pericarditis is extremely variable, however, and symptoms often subside without treatment.

A standard dosage schedule for salicylate therapy has not been established. Intravenous administration has no advantages over the oral route. Either acetylsalicylic acid (aspirin) or sodium salicylate may be used, though most children prefer aspirin. A dose of 120 mg. (2 grains) per kilogram of body weight per day in four to six divided doses for the first forty-eight hours is commonly used. If the symptoms are alleviated, the dose may be reduced by one third, then by one half if improvement continues, and finally gradually discontinued. The duration of the attack cannot be predicted. The C-reactive protein should be negative and the erythrocyte sedimentation rate should have been decreasing for at least three weeks before therapy is discontinued. If a "rebound" of clinical symptoms occurs, therapy should be reinstituted. If the rebound is limited to laboratory observations, the deviations usually disappear without further treatment.

*Toxic reactions* characterized by tinnitus, nausea, vomiting and headache are frequent with large doses of salicylates, which may also cause hyperpnea by stimulation of the respiratory center. Salicylates also interfere with prothrombin synthesis, so that purpuric manifestations, ecchymoses and even hemorrhage may occur.

Children tend to tolerate salicylates better than do adults, but the tolerance of different children varies greatly. The simultaneous administration of sodium bicarbonate decreases the absorption of salicylates, thus decreasing the serum level, and has the same effect as lowering the dose.

Aminopyrine or phenylbutazone (Butazolidin) may be used in patients who cannot tolerate salicylate. Aminopyrine has a tendency to cause agranulocytosis; therefore weekly leukocyte counts should be obtained. Phenylbutazone is chemically closely related to aminopyrine, but is supposed to have a less deleterious effect on leukocyte formation.

*Corticosteroid therapy.* Similar results are obtained with ACTH, cortisone and prednisone. Since ACTH must be given parenterally, it is rarely used. Prednisone has less tendency to cause sodium retention than cortisone and is preferable.

The effect of corticoid therapy on clinical symptoms in acute rheumatic arthritis is similar to that with salicylates. The abnormal laboratory findings tend to disappear somewhat more quickly, however.

In acute rheumatic carditis the immediate effect is often striking. Fever, "toxicity" and

anorexia appear to be controlled more quickly than with salicylates. In many instances congestive failure disappears, provided the intake of salt is limited. Since the prognosis for patients with carditis severe enough to cause decompensation is almost always poor, the presence of this complication is a definite indication for corticoid therapy. Tachycardia usually persists even though the temperature becomes normal, the quality of the heart sounds improves, and a gallop rhythm, if present, disappears. In the absence of pericardial effusion the heart size usually does not decrease rapidly, and organic murmurs tend to persist.

When rheumatic activity cannot be controlled with salicylates, a good response is often obtained with a corticoid. Relapses or rebounds are frequently observed following premature withdrawal of hormone therapy, suggesting that, as with salicylates, these agents suppress but do not terminate the rheumatic process. However, the fact that congestive failure is often controlled by them suggests that the inflammatory reaction in the myocardium may be rapidly decreased. In contrast to the effect of corticoid therapy in acute rheumatic carditis, the response of patients with long-standing chronic myocarditis has been disappointing.

Corticosteroid dosage\* depends on the

\* Provided treatment is begun within two to three weeks of the onset, the following regimen may be used for the average patient with rheumatic carditis. To minimize rebound phenomena after termination of hormone therapy, some physicians prescribe aspirin during the period of gradual decrease of the dose of the corticosteroid. After cessation of therapy the child should be observed for three to four weeks for rebound phenomena.

1st week: prednisone, 60 mg./24 hours

2nd week: prednisone, 50 mg./24 hours

3rd week: prednisone, 40 mg./24 hours, and aspirin, 100 mg./kg./24 hours

4th week: prednisone, 30 mg./24 hours, and aspirin, 100 mg./kg./24 hours

5th week: prednisone, 20 mg./24 hours, and aspirin, 100 mg./kg./24 hours

6th week: prednisone, 10 mg./24 hours, and aspirin, 100 mg./kg./24 hours

7th week: omit prednisone; aspirin, 100 mg./kg./24 hours

8th and 9th weeks: aspirin, 70 mg./kg./24 hours

10th week: aspirin, 30 mg./kg./24 hours

Dosage schedules vary in different clinics. One plan provides about 2 mg. per kilogram per day of prednisone for the initial dose; another, 40 mg. a day for children under five years of age and 60 mg. for those over five years. In some clinics the termination of the tapering-off period varies from the eighth to the twelfth week.



severity of the symptoms, irrespective of age or weight. With adequate dosage of cortisone or prednisone for a few days, one may expect disappearance of fever and the C-reactive protein reaction and a decrease in the sedimentation rate.

Since steroid therapy masks symptoms of all kinds, children receiving such medication must be watched closely for serious complications and intercurrent infections. A careful history of the patient and the family in regard to tuberculosis, diabetes, hypertension, psychosis and ulcers helps to keep the physician alert for untoward effects. If the patient has a positive tuberculin reaction, isoniazid should be given. Steroid therapy should be postponed or discontinued in patients who have been exposed to or have such viral diseases as chickenpox, measles or poliomyelitis. Several deaths due to chickenpox have been reported in children receiving steroid therapy. The patient's blood pressure should be taken daily and the steroid discontinued if the diastolic pressure rises to 100 mm. or above. Frequent urinary examinations for glycosuria should be obtained. Intercurrent bacterial infections such as furuncles or pneumonia often occur. It is advisable to secure a roentgenogram of the chest at frequent intervals to rule out the latter possibility. These patients remain afebrile in spite of severe infections. The leukocyte count is usually elevated during steroid therapy and therefore in itself does not indicate an inflammatory process. Even with prednisone it has been found advisable to restrict the salt intake moderately and to add 1 to 2 gm. of potassium chloride to the diet daily.

Cushing's syndrome (moon face, acne, hirsutism, increased pigmentation, striae and abnormal fat distribution, including fat deposited in the liver) is a usual side effect which subsides when therapy is discontinued.

**Treatment of chorea.** At present there is no really effective treatment for chorea. Corticosteroids have not proved of definite value. Ketogenic diets have been tried, but no adequate data of a beneficial effect are available. Patients with chorea should be kept in bed in a room by themselves and should be cared for by sympathetic attendants. Both physical and mental rest are necessary. Padded sideboards for the bed are required for the most severe cases to avoid injuries. When choreiform movements are intense, the child should be fed by an attendant; adequate dietary intake should always be maintained. Various methods of treating chorea

have been tried, but since it is a self-limited disease (four to ten weeks), drastic measures are usually not necessary. The movements can in most instances be controlled by sedatives such as phenobarbital, Dilantin or tranquilizers. Opiates should be avoided. The child's progress can be followed by noting the improvement in handwriting.

**General measures.** Morphine is the most effective drug in controlling precordial pain and should be used in severe cases. If the patient is restless and apprehensive, a sedative such as phenobarbital should be given.

As long as the rheumatic process is active there is the possibility of progressive cardiac damage. Bed rest, therefore, is essential and may be necessary for a long time. As the patient improves, the inflammatory reaction in the myocardium subsides, and the heart tends to decrease in size. By reducing the work of the heart as much as possible, healing is promoted with the formation of a minimum of scar tissue.

Rheumatic patients often feel well, and it is difficult to keep them in bed. It is important to explain to the child that his illness is temporary and that rest is essential for recovery. Elementary education and occupational therapy must be provided. Prolonged bed rest can often be given more satisfactorily in institutions for convalescent care (see p. 231) than at home. It is generally considered desirable to keep rheumatic patients in bed until all laboratory as well as clinical evidence of rheumatic activity has disappeared. However, the child's personality must be taken into consideration. Prolonged confinement in bed makes some children irritable, and they are more active in bed than they would be otherwise. In such instances it is often better to permit a limited amount of activity in spite of abnormal laboratory findings. The diet must be adequate in all respects; though maintenance of nutrition is often a problem, overnutrition is not infrequent, especially among girls during the convalescent phase.

ANN G. KUTTNER

#### REFERENCES

- Anderson, H. C., and McCarty, M.: Determination of C-Reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever. *Am. J. Med.*, 8:445, 1950.
- Denny, F. W., Wannamaker, L. W., Brink, W. R., Rammelkamp, C. H., and Custer, E. A.: Prevention of Rheumatic Fever. Treatment of the Preceding Streptococcal Infection. *J.A.M.A.*, 143: 151, 1950.

- Good, R. A., Vernier, R. L., and Smith, R. T.: Serious Untoward Reactions to Therapy with Cortisone and Adrenocorticotropin in Pediatric Practice. *Pediatrics*, 19:1, 1957.
- Hench, P. S., Slocumb, C. H., Polley, H. F., and Kendall, E. C.: Effect of Cortisone and Pituitary Adrenocorticotrophic Hormone (ACTH) on Rheumatic Diseases. *J.A.M.A.*, 144:1327, 1950.
- Jones, T. D., and Bland, E. F.: Rheumatic Fever and Heart Disease: Completing 10 Year Observation on 1,000 Patients. *Tr. A. Am. Physicians*, 57:265, 1942.
- Kuttner, A. G.: Tissue Culture Studies of Auricular Appendages Obtained at Mitral Commissurotomy. *Proc. Soc. Exper. Biol. & Med.*, 98:392, 1958.
- Kuttner, A. G., and Meyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide. *J. Clin. Investigation*, 22:77, 1943.
- Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects. Printed for the American Heart Association by the Metropolitan Life Insurance Co., New York, 1943.
- Rantz, L. A.: The Prevention of Rheumatic Fever. Springfield, Ill., Charles C Thomas, 1952.
- Stollerman, G. H., and Rusoff, J. H.: Prophylaxis against Group A Streptococcal Infections in Rheumatic Fever Patients. Use of New Repository Penicillin Preparation. *J.A.M.A.*, 150:1571, 1952.
- Taranta, A., and Stollerman, G. H.: The Relationship of Sydenham's Chorea to Infection with Group A Streptococci. *Am. J. Med.*, 20:170, 1956.
- The Treatment of Acute Rheumatic Fever in Children. A cooperative clinical trial of ACTH, Cortisone and Aspirin. *Circulation*, 11:343, 1955.
- Ziegler, S. R., and Kuttner, A. G.: Reappearance of Abnormal Laboratory Findings in Rheumatic Patients Following Withdrawal of ACTH or Cortisone. *Am. J. M. Sc.*, 222:516, 1951.



# Diseases of Mesenchymal Tissues

## (SO-CALLED COLLAGEN DISEASES)

This section contains descriptions of several diseases, grouped together because of similarities in symptomatology and pathology. Although such grouping has a certain logic and many advantages, it may be misleading. The etiology and pathogenesis of these illnesses are unknown. What is today considered a single disease may in actuality represent a variety of distinct entities, which may subsequently be differentiated as more critical techniques are available.

The diseases described here are (1) rheumatoid arthritis, (2) the Schönlein-Henoch syndrome, (3) dermatomyositis, (4) systemic lupus erythematosus, (5) periarteritis nodosa, (6) scleroderma, (7) morphea.

Generally, certain other diseases—rheumatic fever, acute glomerulonephritis, the nephrotic syndrome and chronic nephritis—are also considered to belong within this group; they are discussed in other sections. The clinical manifestations of some of these diseases are summarized in Table 101. The similarities which have in part led to their being grouped together are apparent. Differences, however, also exist, and each disease has characteristic manifestations which are rarely found in other members of the group.

### RHEUMATOID ARTHRITIS

#### (STILL'S DISEASE)

Juvenile rheumatoid arthritis is a protean systemic disease with an extraordinarily broad spectrum of manifestations. Even the forms of joint involvement by which the disease is characterized vary widely.

**Etiology.** The etiology is unknown. The onset is not generally associated with a preceding infection, and attempts to isolate causative infectious agents from blood, joint fluid or other potentially infected areas have failed. On the basis of pathologic similarities to various experimental diseases in animals, the illness has been classified by some as a

hypersensitivity response and by others as a direct infection with as yet unknown infectious agents, such as pleuropneumonia-like organisms, L-forms or protoplasts. A variety of factors influence the expression of the disease: (1) *Heredity*—There is a relatively high familial incidence of rheumatic diseases. (2) *Environment*—The incidence is presumably higher in temperate climates and in the spring months. (3) *Constitution*—The disease is more frequent in females under the age of six years. (4) *Psyche*—Psychologic stresses appear to be linked to the onset and to exacerbations. Thus it appears that the disease may be the response to an unrecognized exogenous stimulus (or stimuli), made manifest by the interaction of a variety of secondary factors.

**Epidemiology.** The incidence is not known, but the disease is not rare. Some estimates indicate that about an equal number of new cases of juvenile rheumatoid arthritis, juvenile diabetes and the nephrotic syndrome occur each year. The disease occurs almost twice as often in females as in males, even in the preschool age groups. The age at onset is rarely under one year; the median is about five years, and the mode, two to three years.

**Pathology.** The earliest noted pathologic change in the joints is periarticular swelling with edema; there is little synovial reaction or increase in the amount of joint fluid. Thereafter proliferation of the synovium and joint capsule occurs, and projections of thickened synovial membrane form villi which protrude into the joint cavity. At this stage there is an increase in joint fluid. Microscopically, there is edema, vascularization of the connective tissue and infiltration with lymphocytes. Later, as the synovial reaction spreads to the joint space, the articular cartilage undergoes change with ulceration and sometimes actual destruction. Change in the weight-bearing articular surface occurs late

Table 101. Symptomatology of Some of the Mesenchymal Diseases

<i>Symptoms and Findings</i>	<i>Rheumatic Fever</i>	<i>Rheumatoid Arthritis</i>	<i>Schönlein- Henoch's Purpura</i>	<i>Dermato- myositis</i>	<i>Systemic Lupus Erythematosus</i>	<i>Periarteritis Nodosa</i>
Constitutional	⊕	+	+	+	+	+
Skin { general facial	⊕ 0	⊕ 0	⊕ 0	⊕ ⊕	⊕ ⊕	⊕ 0
Arthritis	⊕	⊕	+	±	+	+
Polyserositis	+	+	±	±	⊕	+
Cardiac involvement	⊕	+	0	±	+	+
Pulmonary	+	+	0	0	+	+
Muscles	0	+	0	□	+	⊖
Nodules	⊕	⊕	0	0	⊕	+
Vasomotor	±	+	±	+	+	±
Splenomegaly and lymphadenopathy	0	+	±	0	+	+
Gastrointestinal	0	0	⊕	+	0	+
Renal	0	0	+	0	⊕	⊕
Hypertension	0	0	+	0	+	⊕
Purpura	0	0	⊕	0	+	+
Peripheral nerves	0	+	0	0	0	⊕
Chorea	⊕	0	0	0	±	0
Ocular	0	⊕	0	0	±	0
Mucous membrane	0	0	0	±	⊕	0
WBC	↑	↑ or ↓	↑ or N	N or ↑	⊖	•
Elevated ESR, etc.	+	+	+	+	+	+
Eosinophilia	0	±	±	±	0	⊕

⊕ = Characteristic when present; + = Frequently found; ± = Rare or sometimes present; 0 = Seldom if ever found; N = normal; ↑ = elevated; ↓ = depressed.

Adapted from Bauer and Clark: Recent Progress in Hormone Research. The Proceedings of the Laurentian Hormone Conference, 1953, Vol. VIII.

in the disease. The synovial tissue may then entirely fill the joint space, leading to fibrous ankylosis. Bony invasion and fusion may then occur.

**Clinical Manifestations.** The onset may be sudden and fulminating with the classic pattern of spiking fever, adenopathy, splenomegaly, anemia and arthralgia, or the systemic manifestations may precede the arthralgia by a considerable time. In other instances the onset may be insidious, with

almost imperceptible development of joint stiffness, swelling, pain and eventual limitation of motion which may at times be localized for months or years to a single joint. The degree of systemic involvement, of which Still's triad (splenomegaly, lymphadenopathy and arthralgia) and less often hepatomegaly are a part, is usually greater, the younger the patient, occurring in 10 to 20 per cent of cases; 30 to 50 per cent of affected children have involvement of only one





FIG. 292. Characteristic posture of a child with rheumatoid arthritis, showing the anxious appearance and guarding of joints.

joint for a time, usually of the knee or ankle, but eventually almost all manifest polyarthritis.

Particularly in young children, pain and stiffness of the joints may be manifest initially without observable changes. Acutely ill children sit in bed with a characteristic posture (Fig. 292), appearing anxious and worried. They guard their joints against movement and desire to be left alone. The early changes in the joints are periarticular swelling and synovial thickening. Spindling or fusiform changes of the fingers as a result of this swelling (Fig. 293) are observed in over half of the children, even in infants with pudgy hands. There is limitation of motion, usually owing to pain; the joints may be warm, but not tender, and redness is not marked. Roentgenographically, the joint space may be widened, suggesting an increase in fluid; however, aspiration at this time is usually unsuccessful. Later the accumulation of fluid may increase. Destruction of the joints may follow with resultant deformity and sometimes with bony ankylosis. In some instances repeated episodes of severe arthritis occur without destruction, and sometimes without residual limitation of motion of the joints. Generally the symptoms of arthritis first become obvious in the joints of the lower

extremities. By the time, however, the child is usually brought to the physician, joint involvement of the upper extremities, characteristically symmetric in distribution and including the small joints, is present. Apparently any joint may be involved. Changes occur frequently in the spine, particularly obvious in the cervical vertebrae and in the temporomandibular joints, which may lead to micrognathia. Involvement of the sternoclavicular joints and costochondral junctions may mimic pleurisy; that of the chondral articulations of the larynx may result in hoarseness. During the acute phases of the disease major joint changes are obvious, but during quiescent phases involvement may be noted only by stiffness or limitation of motion. Morning stiffness or "gelling" is as frequent in children as in adults. Limitation of motion may lead to flexion contractures which more frequently cause residual deformity than does destruction of articular tissues.

Fever is the most striking systemic manifestation. In the acute phase the temperature may show wide diurnal fluctuations ( $99^{\circ}$  to  $107^{\circ}$  F.) or remain continuously elevated for prolonged periods. Sudden drops to subnormal levels may be precipitated by overvigorous antipyretic therapy, producing a shocklike state. In some instances there is only a low grade fever. Children, especially the younger ones, often have a characteristic evanescent rash (Fig. 294), usually at the height of the fever, consisting of small, dis-



FIG. 293. The spindling or fusiform swelling of the fingers in rheumatoid arthritis.

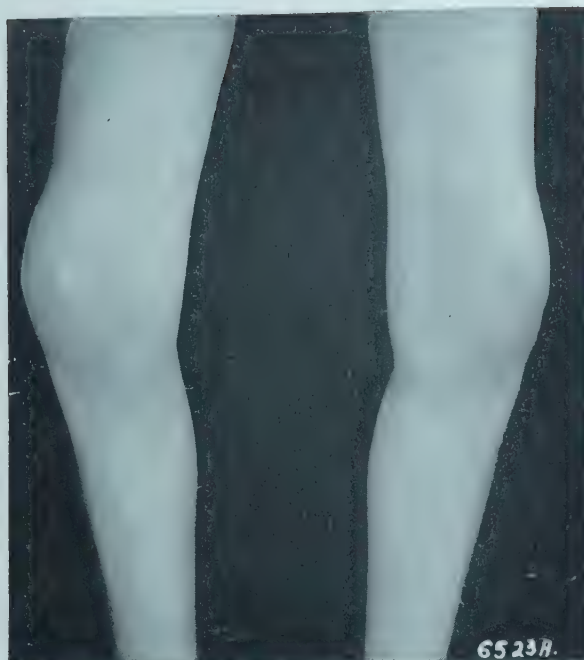


FIG. 294. The skin rash of rheumatoid arthritis.

crete, salmon-pink macules with pale centers. They may coalesce and become blotchy. The rash is found mainly on the trunk, is labile and can be increased by trauma or heat.

There are a variety of other systemic manifestations. Carditis is not infrequent, being reported in 10 per cent or more of cases; the lesions include pericarditis, frank myocarditis with electrocardiographic changes, consisting in P-R and Q-T prolongation and distortion of S-T segments, and cardiac enlargement with failure. Although murmurs are heard frequently during acute episodes, they are probably functional or hemic in origin; valvular deformities are conspicuously absent. The sudden appearance of anemia in addition to carditis is particularly serious. The cause of the anemia is unknown; there are aspects of increased blood destruction and of decreased regeneration. Such manifestations of polyserositis as pleuritis, hepatitis and abdominal pain suggestive of peritoneal involvement have been described. On rare occasions there are scattered pulmonary lesions which persist for a long time. Ocular changes, including iridocyclitis, may lead to blindness.

Tendons and muscles are involved by the disease process, atrophy usually becoming manifest late in the disease. Pigment changes of the skin, including vitiligo, occur over the involved joints. Superficial capillaries and venules become prominent. There may be changes suggesting vasomotor instability, and the skin appears pale and waxy. The hands and feet are likely to be cold; though at other

times the palms and soles appear red and moist ("liver palms"). Subcutaneous nodules may appear especially along the ulna and spine and over the occiput. The terminal complication of amyloidosis is no longer common.

**Diagnosis.** There are few early diagnostic radiologic changes. Swelling can be seen, and, as fluid accumulates, the joint spaces may be widened. The articular surfaces show marginal irregularities, and the bones become rarified, with a ground-glass appearance. Finally, if fusion takes place, the joint space becomes narrow and obliterated. Osseous maturation is advanced in the involved joints, which may lead to premature epiphyseal closure with resultant shortening and deformity.

There are no specific laboratory data. During the active phase the sedimentation rate is elevated, and acute phase reactants such as C-reactive protein appear in the serum. Anemia is frequently present, and the white blood cell count is usually elevated, although on occasion there is leukopenia. Febrile albuminuria is common. Serologic tests are not of much assistance. The antistreptolysin-O titer is seldom elevated; L.E. tests are negative; in adults serum factors which agglutinate sensitized sheep red cells, and gamma globulin-coated latex or bentonite particles have been described, but they are rarely found in children. Other evidences of protein reactions to stress are manifest by increases in serum globulins with reversal of the A/G ratio, by positive flocculation tests and by elevation of the serum complement.

In its florid and typical form this disease presents little difficulty in diagnosis. Early in the disease, when there are arthritis, fever and carditis, differentiation from rheumatic fever may be difficult. Evidence of a preceding streptococcal infection, either by history or by laboratory tests, may aid in differentiation. Often, however, the diagnosis depends upon the course of the disease.

Other causes of arthritis must be excluded. Among these are leukemia, pyogenic and tuberculous arthritis, rat-bite fever, and other collagen diseases, especially systemic lupus erythematosus. Arthritis indistinguishable from the usual rheumatoid disease is seen in patients with ulcerative colitis, regional enteritis, Whipple's disease, psoriasis and congenital agammaglobulinemia. Villous synovitis and allergic intermittent arthritis are probably related syndromes.

**Course and Prognosis.** The course is char-



acterized by recurrent exacerbations and remissions; generally each exacerbation is slightly less severe than the preceding one. The systemic manifestations of the disease become less marked, and the arthritic changes predominate. Gradually the disease appears to burn itself out over a period of two to ten years, becoming quiescent usually before puberty. Exacerbations in adult life have been reported.

During the acute phase cardiac failure and "toxicity" may threaten life. Once these hazards are passed, the immediate prognosis for life is good. The eventual prognosis will depend upon the residual deformity. Intercurrent infections, which were a major cause of death, can be controlled by the appropriate use of antibiotics. In rare instances the illness progresses uncontrollably to severe crippling or death many years after the onset. With adequate care more than three fourths of the children surviving the acute phase should be able to lead functionally adequate lives; over half of them will have complete functional recovery.

**Treatment.** Management of these children and their families constitutes one of the most severe tests of a physician's ability to treat the "whole child." The unpredictable exacerbations of the disease are discouraging and make evaluation of therapy difficult. There is a natural tendency to "shop" for medical help and to try "fad" cures. The eventual failure of any therapy to produce dramatic results may lead the family to "give up," allowing unnecessary crippling deformity to occur.

Adequate care demands a carefully planned long-term program. The parents and the child should come to know what to expect of the disease. The physical and emotional development of the child should be consistently followed and interpreted to the family. Optimal therapy may require at times some or all of the following: an orthopedist, a physical therapist, an ophthalmologist, an orthodontist, a psychiatrist, an occupational therapist, and aid from the child's school teacher. Their recommendations, however, should be channeled and coordinated through one person, the child's physician. This "team" approach is costly, and financial aid may be needed. The wide range of facilities required is usually found only in hospitals or group practice. However, these children need the individualized treatment, reassurance and restrained optimism which are best provided by the family physician. The schism represented by these requirements presents one of the

problems of therapy of chronic disease and has no easy solution.

The aims of therapy are to maintain motion in affected joints, to prevent deformity and to ensure as far as possible the normal growth and development of the child physically, mentally and emotionally. The first is best achieved by physiotherapy with active and passive exercises. Rest in bed does not seem to be beneficial except during acute febrile episodes, and may be harmful in predisposing to contractures. Weight bearing does not seem to increase the amount of joint damage. The activity of an ambulatory child often constitutes an adequate physiotherapy program. The child usually limits the activity of the most severely involved joints because of pain, while continuing to use, and so exercise, the rest of the body. In addition to this general activity, the patient and parents should be taught exercises designed to increase or maintain the range of motion in the most severely affected joints and to increase muscular strength.

No specific therapy is known. Although corticosteroids initially suppress symptoms to a remarkable degree, they do not induce a permanent remission. On discontinuance of therapy symptoms recur, often more severely than before. The therapeutic dose usually suppresses growth, and with prolonged therapy there is often a need to increase the dose; some patients become so addicted to therapy with corticosteroids that they cannot be weaned. Thus therapy with corticosteroids is indicated only when the disease is so severe that it threatens life, or when a short course of therapy might achieve an otherwise unobtainable goal, such as increased motion of joints to attain ambulation. Expected therapeutic gains should always be weighed carefully against the disadvantages.

Usually the initial dose required is about 4 to 5 mg. per kilogram per day (100 mg. per square meter) for cortisone and 1 mg. per kilogram per day (25 mg. per square meter) for prednisone. As soon as it is apparent that the corticosteroids are suppressing symptoms the dose should be gradually decreased until a minimum suppressive dose is reached. When the desired result is achieved, steroid therapy should be discontinued. On withdrawal, even if gradual, there is almost always a rebound of symptoms, which can sometimes be controlled by salicylates. Rebounds may, however, simply have to be weathered out. Occasionally the rebound is so severe that therapy with corticosteroids must be reinstituted. Under

such circumstances steroids may be required for years.

Salicylates are the most satisfactory suppressive medication; in doses adequate to maintain blood levels of 25 mg. per 100 ml. they will reduce fever and alleviate pain and stiffness. From the long-term point of view they are as effective as the corticosteroids and have fewer and less severe side effects. To maintain adequate blood levels initially, about 100 mg. per kilogram of aspirin divided into four or six doses are needed daily. There is considerable individual variation, however, in the levels obtained and in the therapeutic or toxic response. If blood levels are checked and the patient's reactions, particularly for toxicity, are observed, the medication can be given for years. Side effects other than toxicity from excessive levels are rare. An enteric-coated medication can be used for the night dose to ensure an adequate blood level for the following morning.

Other therapeutic agents which have been used include gold, phenylbutazone, chloroquine and nitrogen mustards. None at present offers sufficient advantages to warrant the dangers of their toxicity, except as it is used in a carefully controlled clinical study.

The comfort achieved by adequate salicylate medication usually allows full participation in a program of physiotherapy. With encouragement from parent and physician most children can lead active lives, attend school, and compete with their peers in most activities except those of strenuous and competitive sports. The use of hot morning baths often tends to reduce the stiffness from night "gelling" and helps to get the child ready for school. The parents become a pivotal point for therapy, and they often develop individualistic methods to help their child in everyday tasks. In accepting responsibility they adjust to the situation more adequately. Only rarely do parents become overwhelmed, but even in such instances patient reassurance will usually enable them to utilize their own potentialities.

### ANAPHYLACTOID PURPURA

(SCHÖNLEIN-HENOCH SYNDROME, ANAPHYLACTOID OR ALLERGIC NON-THROMBOPENIC PURPURA)

The term "Schönlein-Henoch syndrome" includes Schönlein's purpura (purpura with arthralgia), Henoch's purpura (purpura with visceral manifestations) and anaphylactoid or allergic nonthrombocytopenic purpura. The

word "syndrome" is preferred because the illness is a polymorphic systemic disease. The skin lesion, which is not always purpuric, is the most obvious but probably the least important sign; the visceral lesions are less easily recognized, but far more serious.

The primary manifestations are due to angitis. There are no changes in the clotting mechanism or in the blood or blood-forming organs which might lead to spontaneous bleeding.

**Etiology.** The etiology is unknown. In rare instances the onset or exacerbations of the disease may be linked to contact with some specific substance, in which case allergy seems to play a distinct role. Family history of allergy in these patients is not significantly increased. About one third of the cases follow closely an upper respiratory tract infection. *Beta hemolytic streptococci* can be cultured from the throats of about half of these, but a remarkable rise in antistreptolysin-O titer is unusual. Attempts to identify causative agents have otherwise been unsuccessful. Pleuropneumonia-like organisms have been found in blood cultures, but their presence is difficult to interpret.

Osler called attention to the similarity between this syndrome and serum sickness. Lesions resembling those of this disease have been produced in animals by injection of antibodies to the endothelial lining of their arteries. Although pathologic similarity cannot be equated with identity, it seems possible that this disease, like systemic lupus erythematosus, represents one type of hypersensitivity response (perhaps auto-immune) to a variety of antigenic stimuli.

**Epidemiology.** The incidence is not known, but this disease is not rare. There has been an apparent increase in recent years. Males are attacked twice as often as females. It affects all races; the recorded incidence may be lower in Negroes, owing to the difficulty in recognizing the rash. The age of onset is rarely less than one year; it is most common between three and seven years. The median and mean age of onset is five years.

**Pathology.** There is a paucity of pathologic data relating to this disease. Skin biopsies show the primary reaction to be an acute inflammatory exudate containing polymorphonuclear and round cells around the small vessels of the corium; eosinophils may be present, and the number of erythrocytes varies with the degree of purpura. Capillaries are generally involved, although changes in precapillary arterioles and necro-



tizing arteriolitis have been described. The pathologic difference between this disease and periarteritis nodosa is only one of degree. In the latter, medium-sized arteries are affected. Adjacent to the vascular changes, there is edema and swelling of the collagen fibrils. The early changes in the kidney as revealed by renal biopsy are characterized by endothelial proliferation and focal fibrinoid occlusion of the glomerular capillaries, resembling those of early systemic lupus erythematosus. Later the lesions are said to resemble those of subacute nephritis.

**Clinical Manifestations.** There is usually a progression of symptoms similar to the sequence in serum sickness. In some instances about a week or two following an infection, in others without a preceding infection, arthralgia and/or abdominal pain appear. This is followed within hours to a day or two by a skin rash. Sometimes all occur simultaneously; less frequently the rash precedes the visceral manifestations. There is generally some malaise and, in about half of the cases, a low grade fever. Rarely the onset is fulminating.

The skin changes are variable; classically, the lesion begins as an urticarial wheal. With varying rapidity a small pink or red punctum appears within the center of the wheal. Initially it blanches on pressure, but as it spreads and a variety of other maculopapular erythematous lesions appear, the ability to blanch is lost. Thereafter the lesions may become petechial or purpuric. The purpuric areas progress in the usual manner of ecchymoses, changing from red to purple, becoming rusty and eventually fading (Fig. 295).

The skin lesions appear in crops, but at any one time there may be a variety of different lesions. In some patients the lesions will be only petechial, and in others they never become hemorrhagic. All the various skin changes of erythema multiforme have been described, and angioneurotic edema involving the eyelids, lips, joint areas and the backs of the hands and feet is often an associated finding. The urticarial lesions are not usually pruritic.

In more than three quarters of instances there are symptoms referable to the gastrointestinal tract. The most common complaint is colicky abdominal pain, often associated with vomiting. Blood, either chemically or grossly demonstrable, is found in the stool of about half the cases. The sudden onset of acute abdominal pain and vomiting, with or

without melena, occasionally leads to laparotomy. It is unusual to find anything more than edema, peritoneal exudate, enlarged mesenteric nodes, and petechiae; infrequently there is intussusception with gangrene of the intestine.

Involvement of the joints, usually of the knees or ankles, is the predominant complaint in about two thirds of cases. There may be mild pain or swelling, or both. Motion may be limited, but rarely to the extent that it may be in rheumatic fever. When swelling is present, it usually consists of periarticular edema; synovial thickening is uncommon. The swollen joints may be warm, but they are not red or tender. The fluid within involved joints is serous and not bloody. The joint changes are evanescent and do not leave residual deformity.

Renal involvement is the most serious manifestation and occurs in about half of the cases at some time during the course of the disease. On occasion there is only albuminuria, but most often there is also gross or microscopic hematuria, with casts and other cellular elements. Generally these changes become apparent within the first two weeks of the disease, but they have been first noted after the skin and joint manifestations had become quiescent. About half of the children with renal involvement also have azotemia or hypertension, or both. The hypertension can be severe enough to cause encephalopathy and convulsions, as may be intracerebral angiitis, which also occurs; it may be impossible to differentiate the two conditions clinically. Chronic nephritis may be a residual (see Prognosis).

**Diagnosis.** *Laboratory examinations* are not diagnostic, but may aid in management. Unless blood loss has been great, there is no anemia. The sedimentation rate is elevated, and acute phase reactants (C-reactive protein) are present in the serum. The white blood cell count is increased in over half of the cases, and eosinophilia occurs occasionally. Platelet counts, bleeding time, clotting time and clot retraction are within normal limits. The tourniquet test is usually negative, although the trauma of the tourniquet may induce the local appearance of purpuric skin lesions several hours later. With renal manifestations of the disease, albuminuria or hematuria, or both, may occur. In children with gastrointestinal bleeding the stools may be bloody or found to contain blood chemically. Serologic tests do not assist in diagnosis; the antistreptolysin-O titer is rarely

elevated, and the L.E. and rheumatoid serum factors are not found. The serum complement titer may be elevated, distinguishing this disease from acute glomerulonephritis, in which the complement titer is low.

The urticarial lesions of this disease and the characteristic polymorphic nature of the erythematous eruptions when they appear usually allow easy differentiation from the hemorrhagic diatheses and from septicemia. In addition, the patient with septicemia usually appears more acutely ill. Differentiation from some of the other collagen diseases is more difficult. The clinical manifestations of periarteritis nodosa are related to the involvement of larger arteries; peripheral neurologic changes often occur, and cardiac manifestations are more common. However, the distinctions are simply a matter of degree, and at times no distinction can be made. It is also probable that the erythema multiforme group of diseases represents a variant of the same process. It has been suggested that the Schönlein-Henoch syndrome may occur without skin lesions, when the diagnosis must be based on the visceral and/or joint changes.

**Course and Prognosis.** The course is extremely variable. The average duration of symptoms is about six weeks; the illness has been known to smoulder for as long as one to two years, however. In rare instances there may be apparent exacerbations and remissions. More often the disease is mild, lasting only a few days and being manifest merely by transient joint changes and a few purpuric spots.

During the acute phase of the disease death may occur from gastrointestinal involvement, renal changes, hypertension or intracranial bleeding. The mortality rate in the acute phase is not known; it is probably less than 2 per cent. If death occurs later, it is usually from renal complications. The approximate incidence of such deaths is unknown. Renal insufficiency may not become manifest for several years after subsidence of the initial phase of the illness. It is variously estimated that 5 to 25 per cent of children with renal involvement have persistence of abnormal urinary findings for years and that some of them have loss of renal function as measured by the glomerular filtration rate. The majority have no residuals.

**Treatment.** There is no specific therapy. In the rare instances in which a specific allergen can be proved the patient should be kept from contact with it. When the disease seems to follow closely a bacterial infection,

as, for example, a streptococcal one, the infection should be treated vigorously to eliminate the organism. Eradication of foci of infection such as carious teeth or sinusitis does not seem to affect the course of the disease. The influence of bed rest or limitation of activity on the course and prognosis is not known, but during the acute phase, conservative management with limitation of activity is indicated.

In the acute phase the patient's life may be endangered by hemorrhage secondary to the vascular lesion. Intestinal obstruction may necessitate operation. The associated hypertension and hypertensive encephalopathy respond to hypotensive agents (see p. 1040). Close attention should be paid to the fluid requirements of patients with severe gastrointestinal and renal involvement.

Corticosteroids may give symptomatic relief and modify the hemorrhagic manifestations; they do not appear, however, to influence the course of the illness. With discontinuation of short-term steroid therapy symptoms again become apparent in almost all instances. The use of steroids does not appear to benefit the renal lesions, and there is experimental and clinical evidence to suggest that under some circumstances they may have an adverse effect. Thus the use of adrenal steroids still must be considered to be on an experimental basis; dosages are not established, but are probably similar to those recommended for rheumatoid arthritis.

Relapses are infrequent, but if one should occur, search for an offending allergen should be reinstituted. In children with residual renal damage the usual program for chronic renal disease should be followed.

## DERMATOMYOSITIS

Dermatomyositis involves many systems, but is characterized primarily by nonsuppurative inflammation of striated muscle, with which cutaneous lesions are usually associated. In the rare instances when only muscle is involved, the disease may be termed polymyositis. Pathologic changes are generally found in many organs. Owing to the characteristic perivascular lesions in involved areas, the disease is generally classified as one of the mesenchymal diseases.

**Etiology and Incidence.** The etiology is unknown; there is no convincing evidence that infection plays any role. In adults there is a frequent association with carcinoma; no such relationship is found in children. Mus-



culoskeletal changes produced experimentally by dietary deficiencies in animals have no counterpart in the manifestations of dermatomyositis in humans. Owing to the similarity of the tissue changes to other mesenchymal diseases, the illness is postulated to be a form of hypersensitivity reaction.

Dermatomyositis is not common. In children it occurs less frequently than rheumatoid arthritis, but more frequently than systemic lupus erythematosus. It is seen most often in the five- to twelve-year age group. Girls are affected more often than boys (3:2). It has occurred in twins. There is no racial predilection.

**Pathology.** Tissue obtained by biopsy is not necessarily diagnostic, but may provide supportive evidence. The pathologic lesions occur at the junction of skin and muscle and are irregularly distributed. In the muscle bundles there are vacuolization, centralization of nuclei, degeneration, infiltration between bundles, and perivascular changes. The vascular lesions usually involve small muscular arterioles. There is perivascular cuffing with round cells and medial proliferation. Granular deposits suggesting platelet thrombi sometimes occur.

**Clinical Manifestations.** The onset is insidious. The initial evidence is usually weakness or easy fatigability. This is generally apparent first in the legs, although involvement of the shoulder girdle may exist earlier. Weakness is frequently associated with stiffness of the muscles. The gait becomes awkward, and the muscles sore and painful. The degree of weakness may vary from slight to extreme. All the muscles of the body may be affected. Involvement of those of respiration and deglutition is of particular importance; when severe, this may lead to respiratory difficulty, aspiration, and death. Affected skeletal muscles feel inelastic, brawny or indurated. The skin, subcutaneous tissues and muscles are thickened and may be tender. Edema, which pits poorly, is sometimes present.

The characteristic skin lesion consists of a slight erythema, induration and occasionally scaling over the malar areas and the bridge of the nose in a butterfly distribution. It is rarely as severe as the similarly located rash of systemic lupus erythematosus. Perhaps of more diagnostic significance is a peculiar violaceous or faintly erythematous discoloration on the upper eyelids (Fig. 297), which is usually present in dermatomyositis and occurs rarely in other diseases. It may oc-

asionally be associated with periorbital edema. Other skin areas are also involved with a variety of lesions. The skin over involved extremities appears tight, glossy or scaly. In long-standing disease atrophy occurs, and the skin becomes tightly bound to underlying tissues. The fingers may become tapered. Over the extensor surfaces of the joints, particularly the knuckles, the skin becomes erythematous, atrophic and scaly (Fig. 299). Fine blood vessels become prominently visible (*poikiloderma vasculare atrophicans*), and these areas later have pigmentary changes. Late in the disease deposits of calcium may occur in the subcutaneous tissues, muscle and fascia (*calcinosis universalis*). These may be manifested by stony-hard plaques or small nodules, which sometimes break down and are extruded in semi-solid or solid form.

Low grade fever is most often present, and other evidences of systemic involvement, such as mucous membrane lesions, lymphadenopathy, hepatosplenomegaly, renal, gastrointestinal and cardiac changes, have been reported, but are far less common.

The sedimentation rate may be elevated. The destruction of muscle is responsible for increased urinary excretion of creatine and for elevation of the serum transaminase level. Serologic studies have not shown L.E. cells or rheumatoid factors. The antistreptolysin-O titer is not elevated. The serum complement is sometimes higher than normal. On rare occasions the urine will contain albumin. With gastrointestinal involvement there may be gross or occult blood in the stool. Roentgenograms will reveal calcium deposits if *calcinosis* exists. Electromyograms demonstrate fibrillary changes.

**Diagnosis.** In its typical form dermatomyositis presents little diagnostic difficulty. In the differential diagnosis of this disease various neuromuscular disorders such as poliomyelitis, and illnesses having predominantly muscular lesions, such as trichinosis, should be considered. The skin lesion on the face may be mistaken for *systemic lupus erythematosus*, which can be established by demonstration of the L.E. cell phenomenon and by involvement of other organs, such as the kidneys. *Scleroderma* can be distinguished from dermatomyositis by its characteristic dermal pattern with "hide-binding." At times the onset of dermatomyositis is so insidious that a period of observation is needed before the diagnosis can be established.

**Course and Prognosis.** The case fatality rate is approximately 40 per cent. Death is



FIG. 295.

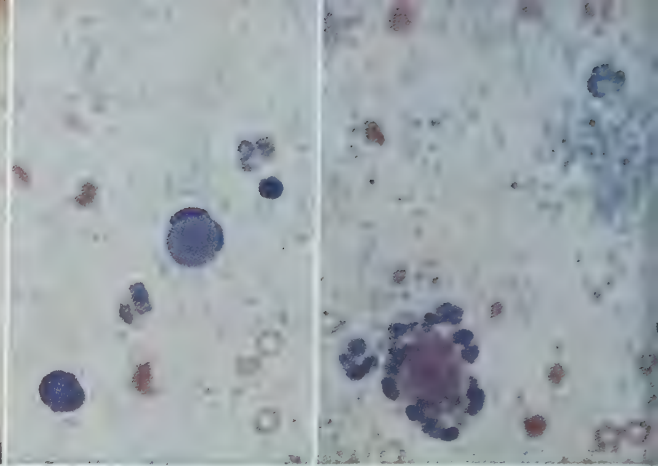


FIG. 296.



FIG. 297.



FIG. 298.



FIG. 299.



FIG. 300.

FIG. 295. Usual appearance of the rash in anaphylactoid purpura.

FIG. 296. An I.F. cell and "rosette" from incubated peripheral blood of a child with systemic lupus erythematosus.

FIG. 297. The facial rash of dermatomyositis. Note the faint erythema over the bridge of the nose and malar areas, and the heliotrope discoloration of the upper eyelids.

FIG. 298. The butterfly rash of systemic lupus erythematosus.

FIG. 299. The skin changes over the knuckles in dermatomyositis.

FIG. 300. The punctate skin lesions and changes of the nail beds in systemic lupus erythematosus. (The child also has remnants of nail polish on the fingernails.)



generally related in some manner to palato-respiratory involvement. Recovery is limited only by the residual deformity. The disease slowly becomes inactive, usually over a period of one to three years. Exacerbations are uncommon after such a period. Of those who survive, a few will have severe contractures with crippling deformities; more than half of them will have few residuals and will be able to lead an active, normal life.

**Treatment.** Functional recovery depends upon prevention of contractures and correction of deformities. There is no substitute for vigorous physiotherapy, carefully planned and supervised to make it acceptable to parents and patient. Such physiotherapy should be instituted in spite of active disease. Orthopedic assistance should be sought early. Absolute bed rest or immobilization in any form is contraindicated, since it predisposes to contractures. Early ambulation, aided by symptomatic therapy, is the optimal form of treatment.

Corticosteroids aid in such therapy by providing symptomatic relief. In some cases this is striking and allows earlier physiotherapy and ambulation than would otherwise be possible. Symptomatic relief may be accompanied by a return of muscle power. Initially the corticosteroids should be given in high doses (cortisone, 4 to 5 mg. per kilogram per day or 100 mg. per square meter per day; prednisone, 1 mg. per kilogram per day or 20 mg. per square meter per day in two or three divided doses). As soon as it is apparent that symptoms are being suppressed (usually seven to ten days) the dose should be gradually decreased over a period of weeks, watching carefully for rebound phenomena, until the minimum suppressive dose is reached. Usually this level (1 to 2 mg. per kilogram per day or less than 37 mg. per square meter per day of cortisone; 0.3 to 0.4 mg. per kilogram per day or 7.5 mg. per square meter per day of prednisone) allows prolonged therapy without the occurrence of serious cushingoid side effects or suppression of growth.

The administration of corticosteroids must be viewed with certain reservations. They do not seem to alter the mortality from this disease. Prior to their use death was usually from palatorespiratory involvement; now it is more often from gastrointestinal crisis and hemorrhage. It is suspected that administration of corticosteroids may accentuate some of the pathologic changes found naturally in this disease.

## SYSTEMIC LUPUS ERYTHEMATOSUS

(LUPUS ERYTHEMATOSUS DISSEMINATUS)

Systemic lupus erythematosus in children is a rare condition which, if untreated, seems to be almost uniformly progressive and fatal. In adults chronic and subacute variants of the disorder are seen; these are infrequent in children. The disease represents the prototype of mesenchymal diseases. In it the involvement of multiple systems is most readily apparent, and for this reason it is of considerable interest to the clinician, the pathologist and the immunologist. The affected person exhibits an extraordinary propensity to form abnormal antibodies, including ones against his own tissues. Auto-immune antibodies are responsible for the development of hemolytic anemia and for the formation of the L.E. cell phenomenon. They may also be involved in the formation of the hematoxylin body which is characteristic of this disease, and perhaps in all the many varied pathologic changes that occur. Such evidence has led to the postulate that this illness is an auto-immune hypersensitivity reaction; that these patients create antibodies against their own tissues and in so doing destroy themselves. Why an organism should fail to recognize its own tissue components as "self" and treat them as foreign substances, forming antibodies to them, is an immunologic paradox of considerable biologic interest.

The mechanism by which the presumed immunologic defect is precipitated is unknown. In a few instances exposure to known heterologous antigens seems to be linked to the onset of the disease. Children as young as two years have been affected, but the usual age at onset is beyond eight years. Girls are affected much more frequently than boys (9:1). The disease has been described in siblings, and there may be a familial predisposition. All races are attacked.

**Pathology.** Changes occur in all mesenchymal tissues. The proliferative and degenerative changes of collagen and the formation of fibrinoid are characteristic. Changes in small arteries and arterioles occur throughout the body. In the spleen these are associated with perivascular fibrosis and proliferation, which forms concentric rings. In the kidneys the basement membranes of the glomerular capillaries become thickened and deeply eosinophilic. Extreme changes of this kind appear like wire loops. Accumulations of

material containing desoxyribose nucleic acid (DNA) in so-called hematoxylin bodies are found.

**Clinical Manifestations.** The onset is usually difficult to determine. Premonitory symptoms, such as intermittent fever, vague arthralgia or episodes of thrombocytopenic purpura, are frequent. These may predate the florid appearance of the disease by many months. In a few patients the disease appears suddenly, systemic symptoms of fever, malaise and anorexia occurring simultaneously with the pathognomonic butterfly rash.

The butterfly rash (Fig. 298) is a striking finding. It appears in more than three fourths of affected children. Usually it is markedly erythematous, covering the malar areas and most often spreading over the bridge of the nose. The rash may be photosensitive. Although involvement of the lower eyelids is common, the upper lids are usually spared. Periorbital edema, in the absence of generalized edema, is uncommon. The rash may spread to involve the entire face, the scalp, neck, chest and upper arms in a patchy manner. The lesions may become bullous and secondarily infected.

Other skin rashes are also found. Minute erythematous puncta that appear on the palms, soles and finger tips are particularly distinctive (Fig. 300). Such spots are apparently secondary to vascular changes and may be petechial. Further infarction may lead to actual loss of tissue from the involved areas. Splinter hemorrhages and capillary tortuosity are seen in the nail beds. The punctate lesions on the mucous membranes of the mouth probably result from an identical pathologic process. Purpura, sometimes associated with thrombocytopenia, appears on dependent or traumatized areas.

Of the many evidences of systemic involvement, fever is the most common. Almost every patient is febrile at one time or another during the course of the disease. Generally there are irregular, moderate to high spikes of fever associated with malaise, anorexia and debility.

Arthralgia is another frequent finding. The affected joints may be red, warm and swollen. When such findings precede other symptoms, this illness may be confused with rheumatic fever or rheumatoid arthritis. Usually large joints are involved, but stiffness of the hands is seen. Polyserositis with pleurisy, pericarditis and peritoneal reactions are characteristic of the disease.

Hepatomegaly, splenomegaly and generalized lymphadenopathy are present in about half of affected children. About two thirds of them have some form of cardiac involvement, as evidenced by variable murmurs, friction rubs and electrocardiographic changes. Verrucous endocarditis (Libman-Sacks syndrome) is found frequently at postmortem examination.

More than three fourths of these patients have clinical evidence of renal involvement, generally manifest by hematuria, albuminuria and cylindruria. Hypertension and azotemia may be present. Once renal disease has become apparent, it characteristically progresses relentlessly, with progressive loss of renal function. Renal or cardiac involvement or intercurrent infection is usually the cause of death. In a few patients urinary abnormalities have disappeared, and renal function appears to have been unimpaired. Whether such remissions are permanent is at present unknown.

**Laboratory Data.** The demonstration of the L.E. cell phenomenon described by Hargraves is the most useful laboratory test. When the serum of the patient is mixed with white cells and a source of nucleic acid (e.g., white cell nuclei), the particles of nucleic acid are coated with gamma globulins from the serum and are phagocytized by the polymorphonucleocytes. The ingested particles form large cytoplasmic inclusion bodies, forcing the cell nucleus to the periphery (Fig. 296). Antibodies to other tissue components have been described, but this one is the most easily demonstrable. The serum factor responsible for the L.E. cell phenomenon can be found in almost all patients with the disease. It is probably relatively specific, being found rarely in any other illness.

Anemia, often partially hemolytic, occurs, as do thrombocytopenia and leukopenia. The sedimentation rate is usually elevated, and there are acute phase reactants in the serum. The proteins generally show a remarkable increase in gamma globulins. Flocculation tests are usually positive, and some of the patients have falsely positive serologic tests for syphilis. There may be difficulties in typing and cross matching blood, owing to the presence of antibodies to heterologous erythrocytes. Auto-agglutination of the patient's own red cells occurs. The serum complement titer is depressed. The urine contains erythrocytes, albumin and casts. Chemical evidence of renal insufficiency, such as elevation of the



blood urea nitrogen or abnormal concentrations of serum electrolytes, may appear terminally.

**Course and Prognosis.** Evaluation of the course and prognosis and of efficacy of therapy has been complicated by an increased frequency of recognition. In children the mortality, even with treatment, appears to be extremely high; more than half die within one to two years of diagnosis. Although permanent remissions must be uncommon, current experiences with steroid therapy suggest that they may occur.

**Treatment.** The symptoms can generally be suppressed by administration of cortisone or prednisone. Whether these hormones alter the prognosis or affect the basic processes responsible for the disease is unknown. The continuous suppression of symptoms by their use is the only available therapy, and the high mortality of untreated cases justifies their long-term use. Initial doses are similar to those used in rheumatoid arthritis (p. 919). The dose should then be adjusted to the least amount giving consistent suppression of symptoms; the dose may have to be altered as the severity of the disease changes. Administration should probably be continued for years. Severe clinical rebounds generally occur if the corticosteroid is withdrawn within a shorter time. On such a regimen the patient can often lead an active ambulatory life; however, as a rule the renal lesion tends to progress. The widespread angiitis may predispose to the untoward usual side effects of the corticosteroids, and salt retention, edema and hypertension must be carefully watched for. Recently it has appeared that some antimalarial compounds, such as chloroquine, may also suppress symptoms. These drugs can be given as adjuncts to steroid therapy.

## PERIARTERITIS NODOSA

### (POLYARTERITIS)

One of the common denominators of the mesenchymal diseases is angiitis. Involvement of *small vessels*, characteristic of the Schönlein-Henoch syndrome, is common also in systemic lupus erythematosus and dermatomyositis. When *great vessels*, such as the aorta, are affected, the resultant illness has been described as "pulseless disease" or Takayasu's syndrome. When *medium-sized* or *small arteries* throughout the body are involved, resulting in actual destruction, aneurysmal dilatation and proliferation of the

vessel wall, the disease is termed periarteritis nodosa. The diagnosis is based on pathologic changes, and the disease is defined in these terms.

The *etiology* of periarteritis nodosa, a rare disease in childhood, is unknown. Experimental studies suggest that the lesions are a form of hypersensitivity response; they have been described as a sequel to serum sickness and to sulfonamide reactions. The disease affects all races and all ages. It is more frequent beyond the age of six years, but has been described in infants. Adult males are affected four times as often as adult females. This sex differentiation is not apparent in childhood.

The *symptomatology* of the disease is explicable by the pathologic changes. Signs of systemic illness such as fever, anorexia, lethargy, weakness and weight loss are usually present. Vague fleeting pains in the extremities are common. Severe sudden pain may result from occlusion of mesenteric or coronary arteries. Skin eruptions of unusual form are seen; they are generally macular or urticarial, but may be hemorrhagic. Peripheral nerves adjacent to involved arteries are affected, giving rise to the usual findings of peripheral neuritis. In some patients the aneurysmal dilatations along peripheral vessel walls are palpable, simulating subcutaneous nodules. Infarction of large masses of tissue may occur; involvement of cerebral vessels may result in convulsions or coma, as may also hypertension, due to vascular changes per se, or secondary to renal involvement.

Albuminuria and, less often, hematuria occur. Anemia and leukocytosis, which may be marked, are common. In many instances there is also a striking eosinophilia. Terminally there are likely to be the findings of renal insufficiency. Electrocardiographic changes may indicate carditis.

Periarteritis nodosa is readily confused with many other mesenchymal diseases. The *diagnosis* is based primarily on the finding of histologic changes in involved tissues, which may not be specific, but the type of blood vessel involved and the tissue response do provide a basis for differentiation. Further, the uniformity of symptomatology in many patients with these pathologic changes suggests that a separate categorization is justified. The diagnosis can be made only through a high index of suspicion, which may be confirmed by biopsy.

The *prognosis* appears to be poor. The

diagnosis is made most frequently at autopsy, but some patients have survived. There is no specific therapy. The value of therapy with corticosteroids is in doubt.

## SCLERODERMA

### (HIDEBOUND DISEASE)

Scleroderma is a rare progressive, generalized, chronic inflammation, usually perivascular, of the skin and subcutaneous tissues and at times of the adjacent muscle; the viscera may also be involved. Little is known about its manifestations in children. The inflammatory changes lead eventually to fibrosis of the involved areas, and the skin becomes firmly adherent ("hidebound") to the underlying tissues. The affected areas feel cool, smooth, waxy or wooden; contractures develop and interfere with motion. Affection of the fingers and toes, known as *sclerodactylia*, results in Raynaud-like symptoms. Changes in the face give an immobile masklike appearance and may interfere with deglutition.

The etiology and pathogenesis are obscure. In addition to the involvement of the skin, there are visceral changes. Those in the esophagus lead to gastric reflux and aspiration pneumonitis. The latter, in conjunction with the primary pulmonary fibrosis, may seriously impair respiratory function. Cardiac involvement may result in progressive congestive failure, or renal dysfunction may be the terminal event.

The course and prognosis in children are poorly defined. Generally the disease is chronic rather than acute, and spontaneous remissions and relapses occur. In some instances there is apparently partial or complete recovery.

No specific therapy is known. Physiotherapy and orthopedic procedures should be used to prevent or correct contractures and deformity. The efficacy of therapy with corticosteroids is in doubt, but it probably should be given a trial early in the course of the disease.

## MORPHEA

### (LINEAR OR LOCALIZED SCLERODERMA)

Morphea is a benign, self-limited localized disease of the skin and subcutaneous tissues; in contrast to scleroderma it does not involve the viscera. In childhood, morphea, although rare, occurs more often than scleroderma.

The first signs are usually patchy lesions of the skin and subcutaneous tissues. These

often have a linear pattern similar to the dermal distribution of peripheral nerves. During the acute phase the involved areas are erythematous and edematous. As the disease progresses the inflammatory process subsides, usually becoming quiescent first at the center of the lesion. The skin lesions in this stage have a violaceous, sometimes elevated, border and a white or yellow waxy-appearing center. The lesions eventually coalesce with the disappearance of the dermatomal pattern, and an entire extremity or a large portion of the body may be involved. With subsidence of inflammation extensive scarring of the area occurs. The resultant fibrosis leads to deformation of the involved tissues; contractures are common and may be severe enough to limit the growth of an affected limb.

Information on the duration of the active phase is lacking. Generally the disease becomes quiescent over a period of months or years. Once it has become quiescent, reactivation is unusual. The prognosis for life is good, but that for deformity is poor. The course is varied and unpredictable, and data relating to the efficacy of the corticosteroids or other forms of therapy aimed at preventing progression of the inflammatory process are not available. When the disease has become quiescent, surgical procedures may be effective in improving function as well as for cosmetic repair.

RALPH J. P. WEDGWOOD

## REFERENCES

### *Rheumatoid Arthritis*

- Ansell, B. M., and Bywaters, E. G. L.: Growth in Still's Disease. *Ann. Rheum. Dis.*, 15:295, 1956.
- Colver, T.: The Prognosis in Rheumatoid Arthritis in Childhood. *Arch. Dis. Childhood*, 12:253, 1937.
- Coss, J. A., and Boots, R. H.: Juvenile Rheumatoid Arthritis. *J. Pediat.*, 29:143, 1946.
- Edstrom, G.: Rheumatoid Arthritis in Children. *Acta Paediat.*, 34:334, 1947.
- Gauchat, R. D., and May, C. D.: Early Recognition of Rheumatoid Disease, with Comments on Treatment. *Pediatrics*, 19:672, 1957.
- Good, T. A.: Juvenile Rheumatoid Arthritis; in Fomon, S. J., and Robertson, W. O.: *Mesenchymal Disease in Childhood*. Report of the 22nd Ross Pediatric Research Conference. Columbus, Ohio, The Ross Laboratories, 1957.
- Grokoest, A. W., Snyder, A. I., and Ragan, C.: Some Aspects of Juvenile Rheumatoid Arthritis. *Bull. Rheum. Dis.*, 8:147, 1957.
- Joint Committee of the Medical Research Council and Nuffield Foundation: Long-term Results in Early Cases of Rheumatoid Arthritis Treated with either Cortisone or Aspirin. *Brit. M. J.*, 1:847, 1957.



- Robinson, W. D., Ed.: Rheumatism and Arthritis. The Eleventh Rheumatism Review. *Ann. Int. Med.*, 45:831, 1956.
- Still, G. F.: On a Form of Chronic Joint Disease in Children. *Arch. Dis. Childhood*, 16:156, 1941.

#### *Schönlein-Henoch Syndrome*

- Ackroyd, J. F.: Allergic Purpura, Including Purpura Due to Foods, Drugs and Infections. *Am. J. Med.*, 14:605, 1953.
- Clark, W. G., and Jacobs, E.: Experimental Non-thrombocytopenic Vascular Purpura. *Blood*, 5:320, 1950.
- Derham, R. J., and Rogerson, M. M.: The Schönlein-Henoch Syndrome, with Particular Reference to Renal Sequelae. *Arch. Dis. Childhood*, 31:364, 1956.
- Gairdner, D.: The Schönlein-Henoch Syndrome. *Quart. J. Med.*, 17:95, 1948.
- Michaels, L., and Walters, G.: Increased Hematuria in Nephritis during Cortisone and Adrenocorticotrophic Hormone Administration. *Arch. Dis. Childhood*, 28:213, 1953.
- Osler, W.: The Visceral Lesions of Purpura and Allied Conditions. *Brit. M. J.*, 1:517, 1914.
- Philpott, M. G., and Briggs, J. N.: The Treatment of the Henoch-Schönlein Syndrome with Adrenocorticotrophic Hormone and Cortisone. *Arch. Dis. Childhood*, 28:57, 1953.
- Wedgwood, R. J. P., and Klaus, M. H.: Anaphylactoid Purpura (Schönlein-Henoch Syndrome). *Pediatrics*, 16:196, 1955.

#### *Dermatomyositis*

- Everett, M. A., and Curtis, A. C.: Dermatomyositis. *Arch. Int. Med.*, 100:70, 1957.
- Keil, H.: Manifestations in Skin and Mucous Mem-

branes in Dermatomyositis, with Special Reference to Differential Diagnosis from Systemic Lupus Erythematosus. *Ann. Int. Med.*, 16:828, 1942.

- Roberts, H. M., and Brunsting, L. A.: Dermatomyositis in Childhood. *Postgrad. Med.*, 16:396, 1954.
- Wedgwood, R. J. P., Cook, C. D., and Cohen, J.: Dermatomyositis. *Pediatrics*, 12:447, 1953.

#### *Systemic Lupus Erythematosus*

- Ayvazian, L. F., and Badger, T. L.: Disseminated Lupus Erythematosus Occurring among Student Nurses. *New England J. Med.*, 239:565, 1948.
- Gajdusek, D. C.: An "Autoimmune" Reaction against Human Tissue Antigens in Certain Acute and Chronic Diseases. I. Serological Investigations. *Arch. Int. Med.*, 101:9, 1958.
- Hargraves, M. M., Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: "Tart" Cell and "L.E." Cell. *Proc. Staff Meet., Mayo. Clin.*, 23:25, 1948.
- Harvey, A. M., Shulman, L. E., Tummulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases. *Medicine*, 33:291, 1954.

#### *Periarteritis Nodosa*

- Rich, A. R., and Gregory, J. E.: Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity. *Bull. Johns Hopkins Hosp.*, 72:65, 1943.
- Ward, R.: Periarteritis Nodosa; in Brennemann, J., ed.: *Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 3, Chap. 13.
- Zeek, P. M.: Periarteritis Nodosa: Critical Review. *Am. J. Clin. Path.*, 22:777, 1952.

# Diseases of the Blood

The formation of blood cells begins in the fetus about the fourth week of gestation in mesenchymal tissue, initially in the yolk sac, then successively in body mesenchyme, in liver, in spleen, thymus and lymphatic tissues and finally in the bone marrow. For the first six months of fetal life the liver is the most active site of hematopoiesis, but after the third month the marrow becomes increasingly active, and at term blood formation resides almost wholly in it, with only limited activity in lymphatic tissue and in the spleen and liver.

In the infant and young child nearly all the marrow is engaged in active hematopoiesis. After completion of growth, blood cell production in marrow is limited to the ends of the long bones, the vertebrae and certain flat bones, all of which contain red marrow. The other marrow is then largely yellow fatty

tissue, but it retains the ability to form new blood cells in times of exceptional need. When all the marrow is actively hematopoietic, as it normally is in children, additional demands for blood may be met by myeloid metaplasia in the reticuloendothelial tissues, especially in the liver, spleen and lymph nodes. This extramedullary hematopoiesis may result in enlargement of the involved organs.

In general, erythrocytes, granulocytes and platelets are formed in bone marrow, and the cells of the lymphocyte family, including the monocytes, are largely formed in lymphatic tissue, some of which is in marrow. It is only by studying directly or indirectly the states of the hematopoietic tissues as well as that of the spleen, as an organ of blood destruction, that it is possible to understand the meaning of what is observed in the peripheral blood.

## DISORDERS OF RED BLOOD CELLS

**Physiology.** The principal function of the red blood cell is to carry oxygen to tissues and carbon dioxide from them. Hemoglobin also contributes buffering action in defense of the pH of blood.

The largest part of the hemoglobin in the fetus (fetal hemoglobin) is biologically different from adult hemoglobin. It is more nearly saturated at low oxygen tensions than is adult hemoglobin. Transfer of oxygen from maternal blood is enhanced by this difference and by a distinctive property of maternal blood during pregnancy which facilitates release of oxygen at tensions suitable to fetal hemoglobin. An analogous relationship exists for dissociation of carbon dioxide and hemoglobin. The production of fetal hemoglobin falls to a low level within a few months, and hemoglobin of adult type is formed in increasing amounts. Under unusual circumstances, as in thalassemia and sickle cell disease, there is interference with production of normal adult hemoglobin, and the production of fetal hemoglobin may persist.

The formation of red blood cells requires the presence of healthy primordial elements in marrow. Vitamin B<sub>12</sub>, folic acid and vitamin C are closely related to the production of red blood cells. The first two are related to, if not jointly identical with, the maturation factor, which is essential to proper maturation of erythrocyte precursors. Vitamin C is thought to be necessary for the conversion of folic acid to its biologically active form, leucovorin (citrovorum factor, CF, folinic acid). These factors are closely related in body economy to the formation of nucleoproteins, particularly as they contribute to the formation of thymidine and thymine. Other vitamins, such as thiamine, riboflavin and pyridoxine, have a more general relation to blood formation as general growth factors.

Adequate stores of iron and protein are necessary for the synthesis of hemoglobin. The iron is derived from antenatal and postnatal dietary sources and from the destruction of hemoglobin in the body, the iron of



which is ordinarily reused. The principal store of iron is in the liver. Other metallic ions, especially copper, seem to be essential to hemoglobin formation, but they are needed in such small amounts that clinical deficiencies rarely, if ever, occur. Clinical experience indicates that thyroid, adrenal and certain pituitary secretions are essential for normal erythropoiesis.

Under ordinary circumstances the production of red blood cells is stimulated by reduced oxygen content of the blood, which may result from hemorrhage, hemolysis, cardiac or pulmonary disease, or the breathing of an atmosphere low in oxygen content. If the necessary elements for blood cell production are available in adequate amounts, chronic anoxia of marrow will lead to polycythemia. The manner in which anoxia stimulates erythropoiesis is unknown, but humoral factors play a role, inasmuch as anemic animals have in their plasma a substance which increases blood production in normal animals. This substance, erythropoietin, appears in increased amounts when there is hypoxia or anemia.

Erythropoietin contains cobalt, but anemia is not known to occur in man as a result of deficiency in this mineral. In large doses cobalt may stimulate polycythemia, but since it apparently does so only by interfering with transport of oxygen in marrow, its use as a therapeutic agent is unwarranted.

The mean number of red blood cells per cubic millimeter of blood varies with the age of the infant or child. Fetal blood is relatively rich in erythrocytes, which number between 5 and 7 million per cubic millimeter. There may be a transient increase during the first few hours after birth due to redistribution of plasma water and electrolytes, but there is a rapid fall to a lower level during the first week and a more gradual fall in the next three months to a level of about 4 million per cubic millimeter. There is a corresponding and somewhat greater fall in hemoglobin concentration. The fall in red blood cells and hemoglobin may be more pronounced in premature than in full term infants, owing to the proportionately greater demands of growth.

The erythrocytes of the newborn infant are somewhat larger than adult cells; they become smaller as they decrease in number. At three to six months of life the red blood cell measures 5 microns in diameter, in contrast to 8 microns at birth; by eight months the cells have attained the adult size of 7 microns.

During childhood the normal red blood cell count is below the standard for adults, ranging between 4 and 5 million cells per cubic millimeter, with correspondingly reduced hemoglobin levels. A hemoglobin level of 11.0 to 13.5 gm. per 100 ml. may be accepted as within the range of normal values

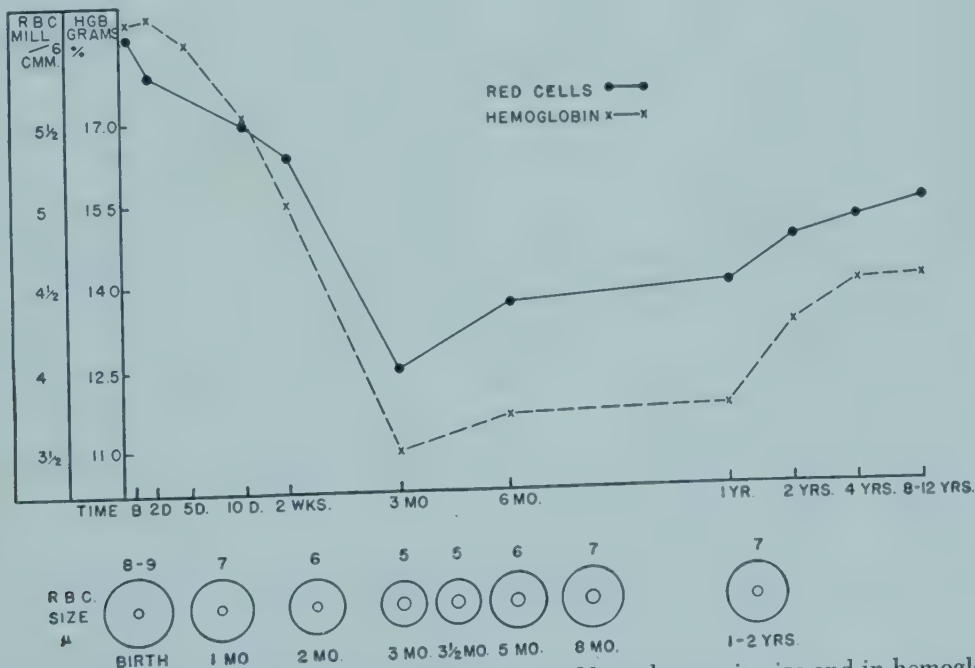


FIG. 301. Average blood values in infants and children. Note changes in size and in hemoglobin content of red blood cells producing microcytosis and hypochromia at ages of 3 to 3 1/2 months with gradual recovery thereafter.

Table 102. Average Normal Blood Values at Different Age Levels

	At Birth	At 2 Days	At 14 Days	At 3 Months	At 6 Months	At 1 Year	At 2 Years	At 4 Years	At 8-12 Years
Red cells/c. mm. (in millions).....	5.1	5.3	5.0	4.3	4.6	4.7	4.8	4.8	5.1
Hemoglobin:									
Grams/100 ml.*.....	17.6	18.0	17.0	11.4	11.5	12.2	12.9	13.1	14.1
Percentage of normal....	113	115	109	73	74	78	83	84	90
White cells/c. mm. (in thousands).....	15.0	21.0	11.0	9.5	9.2	9.0	8.5	8.0	8.0
Platelets/c. mm. (in thousands).....	350.0	400.0	300.0	260.0	250.0	250.0	250.0	250.0	250.0
DIFFERENTIAL SMEARS:									
PERCENTAGES									
Polymorphonuclear neutrophils.....	45	55	36	35	40	40	40	50	60
Eosinophils and basophils.....	3	5	3	3	3	2	2	2	2
Lymphocytes.....	30	20	53	55	51	53	50	40	30
Monocytes.....	12	15	8	7	6	5	8	8	8
Immature white cells...	10	5	—	—	—	—	—	—	—
Percentage of nucleated red cells in total nucleated cells.....	1-5	2	—	—	—	—	—	—	—
Percentage of reticulocytes in total red cells.....	2	3	1	0.5	0.8	1	1	1	1

\* Hemoglobin in whole blood: value of 15.6 gm. per 100 ml. equivalent to 100 per cent.

for children (corresponding to 70 to 90 per cent of the mean normal value for adult males).

The decrease in hemoglobin and red blood cell levels which characterizes the early part of the first year of life is sometimes referred to as "*physiologic anemia of the newborn*," and the accentuation of it in premature infants is referred to as the "*anemia of prematurity*." Neither condition is to be regarded as a morbid state, since both will ordinarily respond without treatment.

Iron is usually given to the premature infant at three to four weeks of age to compensate for depletion of fetal stores by rapid growth. Under exceptional circumstances, as when his erythropoietic function is depressed by infection, the premature infant may need to be assisted over a low point of anemia by transfusions of blood.

The normal red blood cell has a useful life of about 120 days. This period may be shortened to as much as a few days by such factors as exposure to hemagglutinins or hemolysins (erythroblastosis fetalis, favism, transfusion reaction, acquired hemolytic anemia) or abnormalities of shape or structure (hereditary spherocytosis, sickle cell disease, thalassemia).

At the end of its life span the normal erythrocyte probably undergoes intravascular

fragmentation and disintegration. The resulting particles, which contain hemoglobin, are phagocytized by reticuloendothelial tissue. Rapid dissolution of large numbers of red blood cells rarely occurs in the vascular system. When it does occur, the result may be hemoglobinemia and hemoglobinuria, since the human kidney handles hemoglobin inefficiently. Acute renal failure may be the result of severe intravascular hemolysis.

When dissolution of the erythrocyte particles occurs in reticuloendothelial tissue, the hemoglobin molecule is split into two fragments, the protein, globin, which enters the protein metabolic pool, and the heme prosthetic group, which is degraded to bilirubin and excreted by the liver. Iron freed in the process is reused in the formation of more hemoglobin.

Newly formed bilirubin bound to albumin and to alpha and beta globulins is carried in the plasma, where it gives the indirect bilirubin reaction. In the liver, bilirubin is conjugated with glucuronic acid to form a more soluble bilirubin glucuronide. In this form bilirubin is excreted into bile and enters the intestinal tract; there it is changed to urobilinogen, which appears in the feces or may be reabsorbed to be excreted in bile again or in the urine (see pp. 281, 695).

If the pathway for excretion of bilirubin is



blocked beyond the point where the bilirubin glucuronide is formed, this complex may be regurgitated into the blood stream, where it gives the direct bilirubin reaction. If no bile or bilirubin reaches the intestinal tract, no urobilinogen will appear in the feces or in urine.

When the destruction of blood takes place more rapidly than normal, the liver may be unable to excrete the increased load of bilirubin. Bilirubin accumulates in the plasma in the indirectly reacting form, and large amounts may also be excreted, in which case urobilinogen in stools and urine will be increased. Urinary urobilinogen may also be increased during normal hemolytic activity when hepatic function is deficient.

Thus, when there is excessive destruction of erythrocytes, there will be some degree of bilirubinemia, often with clinical jaundice and with large amounts of bile pigment in

the urine and stool, and there may be hemoglobinemia and hemoglobinuria. The spleen and to a less degree the liver may enlarge as a consequence of increased activity of their reticuloendothelial elements. Ordinarily there is responsive activity of erythropoietic tissue in marrow, and occasionally in other tissues, and rapid formation of new red blood cells is manifested by the appearance of relatively immature forms in the peripheral blood. Reticulocytes, normally about 1 to 2 per cent of circulating erythrocytes, may number as much as 30 to 35 per cent of the red blood cells, and normoblasts and even more immature forms may be found. Blood extravasated into body tissues is handled by the reticuloendothelial elements in the manner described, but only if the loss is massive do hyperbilirubinemia and jaundice appear. When the bleeding is external, these signs of increased hemolytic activity are not seen.

## THE ANEMIAS

Anemia is the most common disorder of the blood in children. The deficit of erythrocytes or of hemoglobin always reflects a disturbance of the dynamic balance between production and destruction or loss of these elements. The various anemias may be classified according to the primary disturbance (see Table 103).

**Table 103. Classification of the Anemias**

- I. Inadequate production of red blood cells or hemoglobin
  - A. Inadequate numbers of cell precursors in the marrow
    1. Congenital hypoplastic anemia
    2. Aplastic anemias
      - a. Congenital
      - b. Chemical and physical injury
      - c. Myelophthisis
    3. Hypothyroidism
  - B. Cellular marrow with depressed function
    1. Anemia of chronic infection
    2. Anemia of chronic azotemia
  - C. Cellular marrow with specific nutritional deficits
    1. Anemia due to a deficiency in antipernicious anemia factors (megaloblastic anemias)
    2. Anemia due to a deficiency of iron
- II. Excessive loss of red blood cells
  - A. Hemorrhage
    1. Acute
      - a. Acute hemorrhage in the newborn
    2. Chronic

### B. Hemolysis

1. Congenital abnormalities in erythrocytes or hemoglobin
  - a. Hereditary spherocytosis
  - b. Congenital nonspherocytic hemolytic anemia
  - c. Thalassemia
    - (1) Thalassemia minor
    - (2) Thalassemia major
  - d. Production of hemoglobin S
    - (1) Sick cell trait
    - (2) Sick cell disease
  - e. Production of hemoglobins C, D, E, G, H or I and others
    - (1) As traits (heterozygotes)
    - (2) As homozygotes
  - f. Double heterozygotes of abnormalities in synthesis of hemoglobin
2. Acquired abnormalities of the erythrocyte or its environment
  - a. Toxic hemolytic anemias
    - (1) Chemical poisons
    - (2) Drugs
    - (3) Bacterial toxins
  - b. Infections with parasitization of erythrocytes
    - (1) Malaria
    - (2) Oroya fever
  - c. Hemolytic anemia associated with burns
  - d. Hemolytic anemias due to immune reactions
    - (1) Acquired hemolytic anemia
    - (2) Paroxysmal cold hemoglobinuria
    - (3) Passive immune states
      - (a) Blood transfusion reactions
      - (b) Erythroblastosis fetalis

## *Anemias Due to Inadequate Production of Erythrocytes or Hemoglobin*

Anemias due to deficient production of erythrocytes and hemoglobin have certain features in common, whatever the fundamental defect. In these anemias the onset is insidious. Since only 0.8 per cent of the erythrocyte population of the body is lost each day, even sudden failure in cell production without increased losses will lead to anemia only as rapidly as normal cells are removed from circulation. Such evidence of excessive erythrocyte destruction as bilirubinemia, icterus, increased excretion of bile pigments, or splenomegaly will not be found. Since erythrocyte production is deficient in these anemias, erythroid hyperplasia of the marrow is not found, and there is no reticulocyte response to the demand for blood. Many of these anemias are resistant to therapy and carry a grave prognosis.

### **CONGENITAL HYPOPLASTIC ANEMIA**

(ERYTHROGENESIS IMPERFECTA)

Congenital hypoplastic anemia is characterized by an inability of the bone marrow to produce adequate numbers of erythrocytes. The anemia is not present at birth, but may be manifest as early as three weeks of age. The reduction in the level of hemoglobin does not usually become significant until two or three months of age. The course of the disease is variable, and the prognosis guarded. The patient is usually dependent for years upon frequent blood transfusions.

**Etiology.** The cause of the anemia is unknown; a familial occurrence is often found. Miller et al. have found a disturbance of the intermediary metabolism of tryptophane in six children, each of whom had an abnormal excretion of 3-hydroxykynureine and kynurenin, together with conjugation products of each compound. The relation between this metabolic disturbance and the failure of erythropoiesis is obscure.

**Clinical Manifestations.** These children display the pallor and inactivity associated with severe anemia. Cathie has observed a physical pattern of tow-colored hair, snub noses, a broad vermilion border to the upper lip, and wideset eyes. Growth and development are usually within normal limits, but stunting has been observed in severe cases. Splenomegaly, hepatomegaly, lymphadenopathy and icterus are absent, except as the

liver may become moderately enlarged as the result of hemosiderosis secondary to repeated transfusions. Since the production of leukocytes and platelets is normal, hemorrhagic phenomena and unusual susceptibility to infection are not part of this clinical pattern.

**Laboratory Data.** The diagnosis is established by demonstration of failure of production of erythrocytes with normal production of other formed elements. The red blood cell count may fall below one million per cubic millimeter. The hemoglobin level will be correspondingly reduced, since the anemia is normocytic and normochromic. The reticulocyte count does not exceed 2 per cent in spite of the severe anemia. The leukocyte count is normal, and the leukocytes respond normally to infections. The platelet count is normal. Erythrocyte fragility is normal, as are hemostasis, pigment metabolism and skeletal roentgenograms.

Examination of the bone marrow reveals a deficiency, usually severe, in the number of erythrocyte precursors. There may be a relatively normal number of early erythroid precursors with a distinct failure of maturation beyond the stage of the basophilic normoblast. The marrow contains few reticulocytes.

**Differential Diagnosis.** Congenital hypoplastic anemia is distinguished from hemolytic anemias of early infancy by the absence of splenomegaly, morphologic defects in the red blood cell, reticulocytosis or icterus. Mild or treated erythroblastosis fetalis may present a normocytic and normochromic anemia at seven to eight weeks of age, but at this time a reticulocytosis will usually be present, and further progression of anemia will not occur. The anemia of acute blood loss may be normochromic and normocytic, but there is also reticulocytosis, and the diagnosis is established when the site of loss of blood is demonstrable. Aplastic anemias are accompanied by leukopenia and thrombocytopenia.

**Course and Prognosis.** The disease is characterized by persistent and progressive anemia, and the prognosis is guarded. Spontaneous and complete recovery may occur at any age, but is more likely in the prepubertal period. Cardiac failure may lead to sudden death if the anemia becomes severe. Transfusion accidents and transfusion hemosidero-





FIG. 302. Congenital aplastic anemia with multiple anomalies (Fanconi syndrome) in a boy aged 4½ years. Pallor and inadequate growth and development were present from birth, but became exaggerated at 4 years, when bleeding manifestations appeared. Anomalies included bilateral absence of radii and thumbs, syndactylism, hypospadias, cryptorchism and horseshoe kidney. All formed elements of the blood were depressed. The bone marrow initially showed normoblastic hyperplasia, but subsequently there was increasing evidence of hypoplasia. Whole blood transfusions corrected the anemia temporarily. Iron, liver extract and folic acid administration, singly or combined, produced no response. Splenectomy was ineffective. Death occurred at the age of 5½ years.

sis are a constant threat to these children, who are entirely dependent upon transfusion for survival. With adequate care, however, growth and development of these children are normal, and many lead active, happy lives for many years. In persistent cases hypogonadism may be present in the postpubertal period.

**Treatment.** Transfusions with whole blood or preferably with sedimented erythrocytes should be given as often as necessary to maintain the hemoglobin level at 6 gm. per 100 ml. (40 per cent of normal) or above. Cardiorespiratory embarrassment and frank cardiac failure may occur if the hemoglobin level falls below this point.

Diathermy over the sternum and long bones has been reported to produce a temporary erythropoietic response. It may be repeated, if effective, as often as necessary to maintain blood levels above those necessitating transfusion. In younger patients especially, corticosteroids are efficacious in stimulating the bone marrow to an increased production of reticulocytes with a subsequent increase in peripheral levels of erythrocytes and hemoglobin. Several infants have maintained normal erythrocyte and hemoglobin levels during continuous therapy with small doses of these steroids. Splenectomy has not been of benefit, nor has administration of iron, folic acid, vitamin B<sub>12</sub>, cobalt or other blood nutrients.

## THE APLASTIC ANEMIAS

Aplastic anemia cannot be regarded as a specific clinical entity. Characteristically, failures in granulocyte and platelet production accompany the deficit in erythrocyte formation. The anemia is likely, therefore, to be accompanied by infections and bleeding. The types of aplastic anemia may be classified according to etiology as follows:

- I. Aplastic anemia of genetic origin
  - A. Congenital aplastic anemia (Fanconi)
- II. Aplastic anemias due to chemical and physical agents
  - A. Drugs and industrial and household chemicals
  - B. Radiation injury
- III. Aplastic anemias due to infection
- IV. Myelophthisic aplastic anemias
- V. Aplastic anemias of unknown cause
  - A. Idiopathic aplastic anemias
  - B. Preleukemic states.

### Congenital Aplastic Anemia (Fanconi).

In 1927 Fanconi reported the occurrence of aplastic anemia in association with multiple congenital anomalies in three male siblings. These children had hyperpigmentation, microcephaly, hypogonadism, exaggerated tendon reflexes and congenital strabismus. In other reported instances there have been anomalies of the heart and genitourinary tract and, most consistently, defects of the bones of the

radial sides of the forearm and hand. Cleft palate has also been noted.

Erythropoietic failure may be evident shortly after birth or be delayed for variable periods of time. It is manifest by thrombocytopenia, granulocytopenia and/or anemia and by the associated symptoms of bleeding, infection or distress due to anemia. Treatment is limited to the use of antibiotic drugs and to transfusions of whole blood. Corticotropin and cortisone are of no value. Few patients survive the early years of childhood.

**Aplastic Anemias Due to Drugs and Other Chemical Agents.** Aplastic anemia most commonly results from the toxic action of chemical substances on the bone marrow; these substances include a wide variety of drugs and industrial and household chemicals. Among the drugs are organic arsenicals, bismuth, mercury, the sulfonamides, chloramphenicol, the hydantoins and streptomycin. The main offenders among the chemical agents are paints, lacquers, paint removers, cleaning solutions, gasoline, hydrocarbons which contain crude benzene, and insecticides containing halogenated hydrocarbons. These highly volatile substances may be absorbed through the lungs in poorly ventilated rooms or inhaled directly from such containers as gasoline tanks. There is great individual variation in the degrees of susceptibility to these agents; children are more susceptible than adults.

Many weeks may elapse after exposure to a toxic agent before the resulting aplastic anemia makes its clinical appearance. Hemorrhagic and infectious symptoms may precede the onset of severe, progressive anemia, and usually dominate the clinical picture. Extensive ulcerating and necrotizing infections of the mouth and pharynx and at times of the vagina and rectum are common. Platelet deficiency leads to spontaneous bleeding from the mucous membranes and to the development of extensive ecchymosis from minimal trauma. Recurrent epistaxis and vaginal bleeding may occur and be difficult to control. Intracranial hemorrhage is the most common cause of death.

In some instances exposure to benzene or benzene-containing compounds may be followed by rapid hemolysis. In such cases a hemolytic type of anemia with associated splenomegaly, hyperbilirubinemia and icterus precedes the toxic effect on the bone marrow.

**Aplastic Anemia Due to Radiation Injury** (see also Radiation Injury). Small doses of roentgen rays stimulate granulopoiesis, but

overexposure may lead to aplastic anemia in children. Lymphocytes are the most susceptible of the blood elements to the effects of radiation; granulocytes and platelets are somewhat more resistant, and erythrocyte precursors are the least susceptible. Accordingly, the clinical pattern in radiation anemia is likely to be dominated by infection and hemorrhage.

**Aplastic Anemia Due to Infection.** Only in the newborn period have we encountered aplasia of the marrow as a result of infection. Thrombocytopenia and agranulocytosis do not occur with anemia of chronic infection in the older child. In the newborn infant congenital syphilis, cytomegalic inclusion disease, toxoplasmosis and torulosis have been associated with aplastic anemia, and petechiae and purpura may be present at birth. Anemia is generally not a major clinical feature at the time of birth, but may be rapidly progressive during subsequent weeks.

**Myelophthistic Aplastic Anemia.** Aplastic anemia resulting from invasion or replacement of the medullary cavity of the long and membranous bones by nonhematopoietic tissue is rare in children. It may be caused by leukemia, osteopetrosis (Albers-Schoenberg disease), myelofibrosis, Letterer-Siwe disease and Gaucher's disease.

**Aplastic Anemias of Unknown Cause.** Only after the most careful search for the cause of aplastic anemia may one regard the condition as "idiopathic." Many of the apparently idiopathic cases are subsequently found to be leukemia, and of the remaining ones many are probably due to unrecognized contacts with chemical or physical agents.

**Laboratory Data in Aplastic Anemias.** The anemia is usually a normocytic, normochromic one, but occasionally macrocytes may be seen. Although the total leukocyte count may be near the normal level, the number of granulocytes is generally reduced and may be for days or weeks before a significant anemia occurs. The platelet count is low early in the course of the disease and may persist at levels of 20,000 to 40,000 per cubic millimeter for prolonged periods of time. Reticulocytes are decreased in number.

Except when a hemolytic process is associated with an aplastic anemia at its onset, blood bilirubin levels are normal, and other blood chemical studies are noncontributory. Roentgenograms of the long bones may indicate the primary process in the rare instances of myelophthistic anemia.



The bone marrow consists largely of fatty and fibrous tissue with only small clusters of hematopoietic cells; except in myelophthistic aplastic anemia, when it may disclose the invasive process. If aspiration biopsy reveals only an inadequate amount of functional tissue or if the findings are equivocal, a generous sample of marrow should be removed surgically from the sternum to ensure an adequate specimen and to avoid contamination with peripheral blood.

**Differential Diagnosis.** In *anemias due to nutritional deficiencies* granulopenia and thrombocytopenia are not so marked as in aplastic anemias, and the bone marrow reveals normal or greater than normal cellularity. When *idiopathic thrombocytopenic purpura* is accompanied by anemia due to blood loss, the clinical pattern may suggest aplastic anemia, but a leukocytosis is to be expected, and a reticulocytosis will occur in response to the blood loss. *Secondary hypersplenism* may resemble aplastic anemia, since the peripheral blood may have low levels of those formed elements produced in marrow. In hypersplenism, however, the low levels are the result of excessive destruction of cells, not of inadequate production; the marrow is hypercellular, and there is a reticulocytosis in the peripheral blood. The rare aplastic crises of certain *hemolytic anemias* may be differentiated from aplastic anemia by the transitoriness of the aplastic process and by identification of abnormal erythrocytes characteristic of the hemolytic anemia, such as spherocytes or sickle cells.

**Course and Prognosis.** The course of aplastic anemias in childhood is usually chronic, only temporary relief being obtained from transfusions. Infections are difficult to control, and a tendency to ready bleeding is constantly present.

The prognosis is guarded; recovery or death may occur after months of illness. Cerebral hemorrhage is a common terminal event. The likelihood of recovery depends in large part on the etiologic factor; about half of the children with toxic aplastic anemias will survive with adequate care.

**Treatment.** In most instances treatment is limited to the use of antibacterial agents and to blood transfusions. It is desirable to maintain the hemoglobin level at 7.5 gm. per 100 ml. (50 per cent of normal) or above.

Transfusion of citrated whole blood from glass containers is not effective for the control of hemorrhage or infections, since most of the granulocytes and platelets are destroyed.

If, however, plastic containers and apparatus made nonwetttable by silicone films are used, clinically effective numbers of platelets and possibly of leukocytes can be transfused in fresh blood. The life span of such cellular elements is short, and benefit is of only a few days' duration at most. Striking benefit may result from the transfusion of platelet-rich blood from polycythemic donors. Transfusion of platelet-rich plasma through properly prepared nonwetttable apparatus may also be helpful.

Cortisone and ACTH have not been consistently beneficial in the aplastic anemias produced by toxic agents. Cortisone and prednisone seem to be somewhat more effective than ACTH and may be helpful in relatively large doses early in the course of the disease.

Administration of the various substances necessary for hematopoiesis in larger than normally required quantities is not effective in stimulating the aplastic marrow. Splenectomy is a dangerous procedure.

Anti-infectious prophylaxis with antibiotics and sulfonamides is an important adjunct, but the use of these agents is not without danger, since resistant pathogens may become established. Even the most minor infections are threatening and should be treated promptly with the guidance of adequate bacteriologic diagnosis.

## ANEMIA OF CHRONIC INFECTION

The anemia of chronic infection is a normocytic, normochromic anemia of moderate severity which develops over a long period of time. Erythropoiesis is depressed, and there is no response to the nutrient substances essential for formation of erythrocytes and hemoglobin so long as the infection is active. With advances in therapy of infectious diseases, this type of anemia has become uncommon and accounts for less than 2 per cent of anemias as seen in children in the United States. Severe hemolytic anemias are occasional manifestations of acute infections, but they bear no relation to the anemia of chronic infection.

**Pathogenesis.** The anemia of chronic infection results from an inability of the marrow to incorporate iron into the protoporphyrin molecule. The resulting disturbances in synthesis of heme and of hemoglobin are not related to deficiency of iron and are not corrected by administration of it. Ingested iron is absorbed normally, but disappears

rapidly from the plasma; both the serum iron level and the serum iron-binding capacity are low. The free protoporphyrin of the erythrocytes and the levels of urinary coproporphyrin and blood copper are consistently increased.

**Clinical Manifestations.** The only sign specifically related to the anemia is mild pallor. The anemia is never so severe as to cause symptoms of cardiorespiratory distress; these and other symptoms or signs, such as hepatosplenomegaly or icterus, if present, are related to the infectious process.

**Laboratory Data.** The hemoglobin level is usually in the range of 8.5 to 11.0 gm. per 100 ml., with a proportionate reduction of the red blood cell count. The erythrocytes are often slightly smaller than normal, but slight macrocytosis also may be occasionally observed. Hypochromia is unusual except after prolonged infections. The extent of the anemia may not be accurately reflected by the findings in the peripheral blood, since the blood volume may be as low as 60 to 70 per cent of the normal value. The reticulocyte count is low; the platelet count is normal, and the leukocyte count is consistent with the infection, granulocytes being produced in adequate numbers.

The cellularity of the bone marrow is normal or increased. Hyperplasia, if present, involves principally the myeloid (granulopoietic) elements.

**Differential Diagnosis.** The anemia of chronic infection is differentiated from acute hemolytic anemias by the absence of clinical and laboratory signs of blood destruction. If there are disturbances in the production of white blood cells and platelets, aplastic anemia rather than the anemia of chronic infection is suggested.

**Course and Prognosis.** If the infection is brought under control, the anemia will be gradually corrected within several weeks. The anemia is rarely severe enough to modify seriously the course of the infection.

**Treatment.** Treatment is that of the primary infection. The effect of transfusions is temporary and rarely justifies the expense and danger which accompany them. Administration of supplementary amounts of the nutrients essential for erythropoiesis has no advantage over a well balanced diet. Cobalt chloride results in the formation of erythrocytes and hemoglobin even in the presence of infection, but no symptomatic improvement has been observed, and it is felt to be contraindicated.

## ANEMIA OF CHRONIC AZOTEMIA

This anemia, which is normocytic and normochromic, develops in patients with chronic azotemia of renal or extrarenal origin. Generally it results from inadequate production of red blood cells, but infrequently there may be a hemolytic factor if the azotemia is severe. At such times the anemia may be sudden in onset and progress rapidly. The mechanism responsible for the anemia in azotemia is not known.

The clinical findings are those of the illness responsible for the azotemia, except as the anemia is severe, when it may contribute to cardiac failure. Occasionally azotemic anemia is the first manifestation of serious renal or metabolic disease not otherwise recognized.

**Laboratory Data.** The severity of the anemia is proportionate to the degree of nitrogen retention; in extreme cases hemoglobin levels may be as low as 4 to 5 gm. per 100 ml. The erythrocyte count and hematocrit value are proportionate to the hemoglobin level, since the anemia is ordinarily normochromic and normocytic. In unusually persistent cases a mild degree of microcytosis may be found. The reticulocyte count is low, except as there may be a hemolytic component contributing to the anemia. Leukocytes are increased in number, with a preponderance of granulocytes. The platelet count is normal. The bone marrow is usually hypercellular, with the increase in cells confined to the myeloid elements.

**Course and Prognosis.** These depend upon the primary disturbance.

**Treatment.** As a rule no specific treatment is needed for the anemia. Blood transfusion is not indicated except when the hemoglobin level is very low. The usual nutrient substances necessary for hematopoiesis have no effect. Cobalt chloride may lead to elevation of erythrocyte and hemoglobin levels, but clinical benefit is doubtful and toxic reactions are common; such therapy is rarely indicated.

## THE MEGALOBlastic ANEMIAS

In the absence of certain nucleic acids the normal maturation of erythrocyte precursors in marrow is interrupted. These necessary substances include ascorbic acid, vitamin B<sub>12</sub>, folic acid and certain purines and pyrimidines (thymine and thymidine). Deficits of these substances lead to cytologic alterations in erythrocytes and erythrocyte precursors which are characteristic of megaloblastic



anemias (pernicious anemia-like anemias). The erythrocytes are macrocytic and hyperchromic. Since granulocyte and platelet precursors also share the need for these nutrients, various degrees of granulocytopenia and thrombocytopenia accompany megaloblastic anemias.

Those occurring in infants and children may be classified as follows:

- I. Juvenile pernicious anemia
- II. Megaloblastic anemia of infancy
- III. Megaloblastic anemias of intestinal origin
  - A. Celiac disease
  - B. Cystic fibrosis of the pancreas
  - C. Congenital strictures
  - D. Surgical shunts
  - E. Intestinal infections and infestation
- IV. Megaloblastic anemias of metabolic origin
  - A. Chronic liver disease
  - B. Rare instances of acute leukemia
- V. Others
  - A. With phenytoin sodium therapy
  - B. With chronic hypoparathyroidism

#### JUVENILE PERNICIOUS ANEMIA

In pernicious anemia, which is rare in children, vitamin B<sub>12</sub> is not absorbed from the gastrointestinal tract, owing to a lack of the intrinsic factor in the gastric secretion. The deficiency which results leads to a megaloblastic anemia and to degenerative lesions in the central nervous system. The reason for deficiency of the intrinsic factor is unknown; a genetic factor is a possibility.

**Clinical Manifestations.** The observed age of onset has ranged from four months to fourteen years. The presenting symptoms are usually pallor and easy fatigability. Atrophy of the papillae of the tongue and recurrent glossitis have been consistently found. Neurologic manifestations are more likely to occur in children with prolonged illnesses and include ataxia, paresthesias and absence of tendon reflexes. Clinical jaundice has not been noted, nor is there splenomegaly or lymphadenopathy.

**Laboratory Data.** A severe anemia is usually present, with hemoglobin levels often below 4 to 5 gm. per 100 ml. Since the anemia is macrocytic, the erythrocyte count will be relatively lower than the hemoglobin level or hematocrit value. The mean corpuscular volume may be as high as 130 cubic microns. The reticulocyte count is low prior to therapy. The total leukocyte count is low with neutropenia and a relative lymphocytosis. The platelet count is reduced, but not to levels at which spontaneous bleeding is likely to occur.

The bone marrow is characterized by mega-

loblastic erythropoiesis, with failure of maturation of erythroid elements. The abnormal granulocytic elements seen in adults with pernicious anemia have been found in juvenile cases and consist of giant metamyelocytes, hypersegmented polymorphonuclear leukocytes and atypical mitotic figures.

Blood chemical studies give essentially normal results; the evidences of a hemolytic process which may be found in adults have not been prominent in children. The intrinsic factor is absent in gastric secretion. A histamine-resistant achlorhydria is not always present.

The *diagnosis* of pernicious anemia can be considered only when there is a megaloblastic marrow in association with the absence of the intrinsic factor in the gastric secretion and a continuous need for parenteral therapy with vitamin B<sub>12</sub>.

**Course and Prognosis.** Remissions occur promptly with specific therapy. Relapses should not occur with a well planned program. Death from untreated pernicious anemia or during a severe relapse may be due to infection, to cardiac failure or to overzealous transfusion therapy.

**Treatment.** Parenteral administration of crystalline vitamin B<sub>12</sub> or liver extract containing vitamin B<sub>12</sub> is specific. The recommended dose for initial therapy or for relapses is 15 micrograms, given intramuscularly, every day or two for one to three weeks. The same dose is then given every two to four weeks, according to apparent need. Oral administration is optimally effective only if normal gastric juice is also given to supply the intrinsic factor.

Folic acid, given orally, usually produces a temporary and incomplete hematologic response, but has no effect upon the neurologic manifestations. Iron may be needed by the young patient who has had a diet deficient in iron. A transfusion of blood is rarely necessary.

#### MEGALOBlastic ANEMIA OF INFANCY

Megaloblastic anemia of infancy occurs most commonly in infants of five to eleven months of age and appears to be the result of a relative deficiency of folic acid. The exact pathogenesis is not understood, but it is thought that persistent mild infections may increase the need for folic acid to such an extent that it cannot be met without dietary supplementation. The anemia has been observed especially in infants with deficient intakes of ascorbic acid and in prematurely born ones.

There are no characteristic clinical signs. The spleen may be enlarged.

Complete recovery is to be expected with specific therapy in three to four weeks. Continuation of therapy after recovery is not necessary as it is in pernicious anemia. Untreated, the course is progressive, and severe gastrointestinal and respiratory infections are common terminal events.

**Laboratory Data.** The erythrocyte count is significantly reduced and may be less than one million per cubic millimeter. Hemoglobin and hematocrit levels are low, but not in proportion to the red blood cell count. The erythrocytes are usually macrocytic and hyperchromic. Occasionally they are normocytic; and only examination of marrow will reveal the nature of the anemia. The reticulocyte count is low, and the platelets and granulocytes are reduced in number. The nuclei of the polymorphonuclear leukocytes tend to be hypersegmented.

The bone marrow reveals megaloblastic erythropoiesis, with an arrest in maturation at an early level. Relatively few mature normoblasts are present. Atypical mitotic figures and giant metamyelocytes are found among the myeloid elements. Platelet production is depressed, and there may be a relative increase in mature megakaryocytes. The changes in marrow may vary considerably in degree.

**Treatment.** Folic acid corrects the nutritional deficiency. It is given orally in three or four divided doses, totaling 15 to 20 mg. each day. After two or three weeks the dose can be reduced to 5 mg. daily. The duration of therapy should be adjusted according to the severity of the anemia and the persistence of infection.

Vitamin B<sub>12</sub> is not effective, and ascorbic acid has no effect in the absence of folic acid. Unless there is associated iron deficiency, there is no need for therapeutic iron. Transfusion is not needed, except when the erythrocyte count is extremely low. Appropriate antibiotic agents should be administered for concurrent infections.

#### MEGALOBlastic ANEMIA OF INTESTINAL ORIGIN

Megaloblastic anemia resulting from defective intestinal absorption of antipernicious anemia factors is rare in children. It may occur in association with idiopathic steatorrhea (celiac disease), with fibrocystic disease of the pancreas, and with a variety of anomalies and surgical conditions of the gastrointestinal tract. The studies of Watson and

Witts indicate that megaloblastic anemia associated with anomalies or surgical lesions of the gastrointestinal tract may arise from stagnation and changes in bacterial flora rather than from absorptive losses. The main deficiency appears to be that of vitamin B<sub>12</sub>, but deficiencies of folic acid or closely related substances may occur independently or coexist.

The *clinical picture* is usually dominated by the manifestations of the intestinal disturbance. Lingual atrophy, glossitis and neurologic disturbances may occur if the course is prolonged.

The anemia is normochromic, usually macrocytic, and some anisocytosis is commonly present. The leukocyte count is low, and there is a moderate reduction in the number of platelets. Examination of the marrow reveals hyperplasia of erythroid elements, with a predominance of megaloblasts. The myeloid cells and megakaryocytes show changes similar to those in pernicious anemia. Serum bilirubin levels are ordinarily normal, and the intrinsic factor is usually present in the gastric juice.

The course of the anemia is slowly progressive without treatment. There is a prompt response to replacement therapy or to correction of the intestinal abnormality.

**Treatment.** This should be directed at the intestinal abnormality whenever possible. In addition, specific replacement therapy in the form of liver extract, which supplies vitamin B<sub>12</sub> and other factors related to folic acid, is given daily for one to two weeks in doses of 15 units intramuscularly. The need for further therapy will depend on continuation of the gastrointestinal defect.

#### MEGALOBlastic ANEMIA ASSOCIATED WITH OTHER DISTURBANCES

Severe chronic disease of the liver may occasionally be responsible for megaloblastic anemia. In acute leukemia the rapid growth of leukemic tissue may create an excessive demand for folic acid or related substances; in addition, the relative deficiency of these substances may be accentuated by treatment with folic acid antagonists. Under these circumstances megaloblastic erythropoiesis may be found in the marrow and marked macrocytosis in the peripheral blood.

Megaloblastic anemia occasionally develops in patients receiving prolonged anticonvulsant therapy, particularly with phenytoin sodium. This anemia responds to folic acid, but not to vitamin B<sub>12</sub>. A megaloblastic ane-



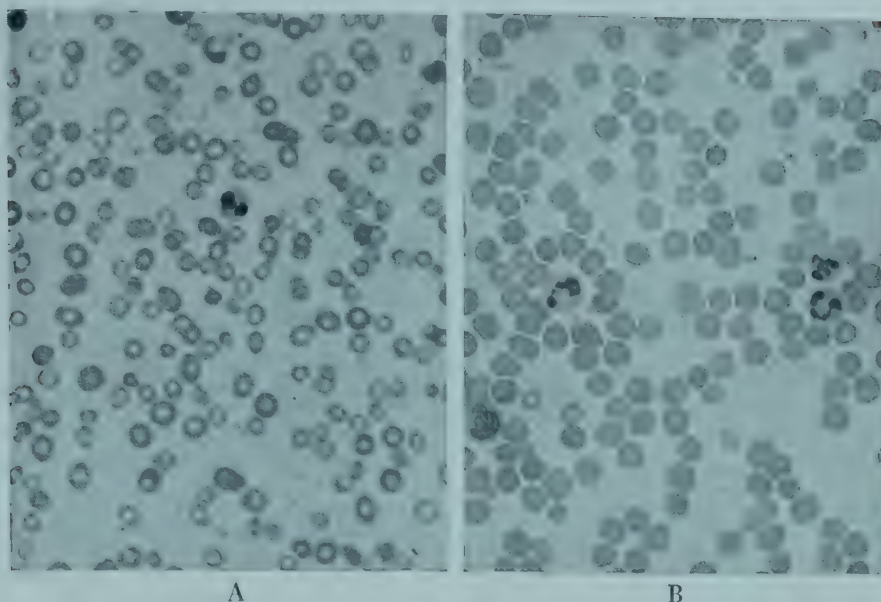


FIG. 303. A, Peripheral blood smear of an infant with *anemia due to iron deficiency* of nutritional origin. The erythrocytes are small and pale and vary greatly in size and shape. B, Peripheral blood smear of an infant with *megaloblastic anemia of infancy*. The erythrocytes vary in size, some being almost as large as neighboring leukocytes, but their shape is well preserved, and they are well filled with hemoglobin. The nuclei of the neutrophils are characteristically multilobate.

mia responding to parenteral administration of vitamin B<sub>12</sub> has also been described in several patients with chronic hypoparathyroidism and moniliasis.

### ANEMIA OF IRON DEFICIENCY

A deficiency of iron is the most common cause of anemia and the most common nutritional deficiency in children in the United States. Either inadequate intake or excessive loss of iron will lead to iron deficiency. The erythrocytes will be small (microcytic) and poorly filled with hemoglobin (hypochromic).

**Etiology.** During the first six months of life the infant is dependent principally upon the adequacy of his storage of iron from late prenatal life for protection against iron deficiency. Iron stores may be inadequate if the mother has been depleted of iron by excessive losses of blood, poor diet or multiple pregnancies. If the infant is born prematurely, the relatively low stores of iron from a shortened pregnancy may be inadequate for the requirements of rapid growth. If the infant is one of twins, he must share maternal iron. Since these causative factors are relatively infrequent, the incidence of iron deficiency anemia is low in the first six months of life.

After the first six months the infant is dependent upon a continuing exogenous source of iron. The incidence of iron deficiency is highest in infants between nine and twenty-four months of age; it drops rapidly there-

after, and iron deficiency due to inadequate intake is relatively rare after three years of age. Subsequently chronic hemorrhage is the principal etiologic factor. Poorly planned meals, feeding problems and behavior disturbances often result in diets made up largely of milk, bread and other foods mainly carbohydrate in content. Absorptive defects as in chronic diarrhea, steatorrhea, gastrointestinal anomalies or colitis may also lead to iron deficiency.

Owing to the limited capacity for absorption of iron even when the demand is increased, iron deficiency of some degree results from acute and chronic hemorrhages. Hemorrhage less commonly causes hypochromic anemia in children (p. 943) than in adults; in the southern United States chronic blood loss associated with hookworm infestation leads to iron deficiency anemia.

**Clinical Manifestations.** The four common manifestations of iron deficiency anemia are pallor, irritability, anorexia and decrease in normal activity. Anorexia leads to a vicious cycle, in which the deficiency of iron is accentuated by an inadequate dietary intake. Anorexia is not due to the anemia itself, since it is not characteristic of anemia from other causes, and since it may disappear, after administration of iron intravenously, *before* an increase in hemoglobin level can be detected. Pica is not uncommon and often disappears with correction of the deficient diet.

Height and weight are usually within normal limits; obesity is more common than underweight. Pallor is usually evident, and mild to moderate degrees of periorbital or dependent edema may be present. The spleen may be moderately enlarged, particularly when there is an associated mild infection. Soft, blowing, apical systolic murmurs may be heard frequently, but cardiac enlargement is unusual. Though glossitis, koilonychia, loss of cutaneous elasticity and changes in texture of hair are common in adults with iron deficiency, they are rare in children.

**Laboratory Data.** The number of erythrocytes in the blood may be normal or slightly less than normal, but the hemoglobin level is always reduced and may be very low. The hematocrit value is also reduced. The red blood cells as seen in blood films are small and pale, with variations in size and shape (anisocytosis and poikilocytosis). In severe iron deficiency there may be an increase in resistance of a small portion of the erythrocytes to hemolysis in hypotonic saline solution. The reticulocyte count is low, even when the anemia is severe. The leukocytes, including the lymphocytes, show no significant change except as their number may be elevated in response to a concurrent infection. The platelet count is normal.

The serum iron level is lower than normal, and the serum level of iron-binding protein is above normal. The blood copper level and the level of free protoporphyrin in the erythrocytes are elevated. Hypoproteinemia is relatively common. Other blood chemical constituents are not significantly altered.

The bone marrow is characterized by hyperplasia of the late normoblastic elements with inadequate hemoglobin in their cytoplasm. Leukocyte and platelet elements and their precursors are not altered.

**Diagnosis.** The anemia of iron deficiency is not likely to be confused with other anemias. It may rarely coexist with megaloblastic anemia of infancy. The small, pale poikilocyte in stained smears of peripheral blood is evidence of iron deficiency, and the diagnosis should not be made in its absence. *Thalassemia* may occasionally be confused with iron deficiency anemia, but there will be evidence of hemolysis and of hyperactivity of marrow in respect to early erythroblastic as well as normoblastic elements.

**Course and Prognosis.** Untreated iron deficiency anemia is slowly progressive. If it becomes unusually severe, cardiorespiratory distress or cardiac failure may occur. The

anemia responds promptly to adequate therapy; a moderate reticulocytosis occurs in four to seven days, followed by a gradual rise in the hemoglobin level. The ultimate prognosis depends in part upon the primary cause of the iron deficiency.

**Treatment.** It must be established whether the deficiency of iron is the result of inadequate dietary intake, absorptive defects or excessive losses. Supplementation of diet with medicinal iron will be ineffective unless all causative defects are corrected.

Since iron deficiency often grows out of faulty feeding habits, education of the parents is frequently indicated. In children with behavior disturbances this may be as difficult as it is essential. A large part of the caloric needs of the child must be supplied by foods rich in iron. Potatoes, spaghetti, bread, cookies and crackers should not be given until a well balanced diet is acceptable to the child. Milk should be limited to one pint a day. In exceptional instances when the mother is unable to effect a change in the child's dietary habits it may be expedient or necessary to carry out the dietary education of the child in the hospital through the sympathetic but firm efforts of nursing personnel.

Ferrous iron is more efficiently absorbed than the ferric salt. The daily intake should be in the range of 0.4 to 0.8 gm. of ferrous sulfate, which is equivalent to 100 to 200 mg. of elemental iron. Since only a small percentage of ingested iron is absorbed, the daily dose is given in at least two or three divided doses; this also reduces the incidence of gastrointestinal complaints. The tendency to discoloration of the teeth by iron can be minimized by taking liquid preparations through a tube and by brushing the teeth after the medication has been given. The discoloration is not permanent.

Owing to the ability of phosphorus-containing phytates and of phosphates to form insoluble salts with iron, medicinal iron should be given when the upper gastrointestinal tract is relatively free of these materials. Milk and milk products contain large amounts of phosphates, and cereals have a high content of phytates. Iron is therefore best given between meals. Colloidal preparations of iron for intravenous use and an iron-dextran mixture for intramuscular use are available. They are rarely indicated, however, and may lead to severe toxic reactions. They are specifically indicated only when there is a disturbance of gastrointestinal absorption and when correction of it is not immediately pos-



sible. They may also be helpful initially in the anemia of hookworm disease (see p. 583).

Transfusion of blood is rarely indicated. If cardiorespiratory distress, cardiac failure or

some other condition warrants transfusion in a severely anemic child, it should be carried out with caution, since the ischemic myocardium has a low tolerance for rapid increases in blood volume.

### *Anemias Due to Excessive Loss of Erythrocytes*

Erythrocytes may be lost by hemorrhage and by hemolysis. Anemias due to excessive loss of erythrocytes, in contrast to those due to failures of erythrocyte production, may be sudden in onset and are generally accompanied by a hyperactivity of the marrow. The severity of the anemia depends upon the ability to respond with increased erythropoietic activity.

#### **ANEMIA DUE TO ACUTE HEMORRHAGE**

The severity of the anemia will depend upon the extent of the blood loss and the rapidity with which it occurred. The anemia is normocytic and normochromic except as it occurs in a person with a pre-existing anemia of another type.

**Clinical Manifestations.** Although the clinical picture is often dominated by manifestations related to the cause of the hemorrhage, certain symptoms are independent of it. These are prostration, restlessness, thirst, rapid and thready pulse, and hypotension. Symptoms of shock may develop only after the child has assumed an erect position. By contrast, *bradycardia* often accompanies large losses of blood in patients who remain at rest. In adults the rapid loss of one third of the blood volume may result in death. Up to half of the volume, however, may be lost over a twenty-four hour period without necessarily a fatal outcome. When bleeding occurs into body cavities or tissues, resolution of the localized accumulation by hemolysis may result in icterus within two to five days.

**Laboratory Data.** Shortly after the sudden loss of blood there is a rise in the platelet count and a shortening of the coagulation time. Within two to five hours a polymorphonuclear leukocytosis appears which may persist for three to five days. Early changes in the hematocrit value may be misleading, since they are modified by redistribution of body fluids and by adjustments of plasma volume which may require several days. In general, there is a gradual fall in the hemoglobin level which does not necessarily indicate further loss of blood. The erythrocytes are normochromic; a hypochromic anemia with acute

loss of blood suggests previous hemorrhage or a nutritional deficiency of iron.

Within a few days regeneration of erythrocytes will be indicated by polychromatophilia, slight macrocytosis and reticulocytosis in the peripheral blood. The marrow will show an increase in the number of erythrocyte precursors and increased activity in the formation of myeloid elements.

After two to four days the serum bilirubin level may be slightly elevated in internal hemorrhage. Other blood chemical constituents are unchanged or will depend upon the cause of the loss of blood.

**Course and Prognosis.** The ultimate outlook depends upon the control of shock and prevention of further loss of blood and upon the primary morbid process. An isolated loss of blood in an otherwise healthy child will be corrected gradually over a period of five to seven weeks; the time required is not closely related to the amount lost.

**Treatment.** The immediate treatment is directed at control of the hemorrhage and shock. Transfusion of whole blood or plasma expanders may be urgently needed for restoration of blood volume. The well nourished child requires no further treatment following an isolated loss of blood other than a well balanced diet. Infants should receive supplemental iron for at least eight to ten weeks.

#### **ANEMIA DUE TO ACUTE HEMORRHAGE IN THE NEWBORN INFANT**

Acute hemorrhage may occur from the infant immediately before, during or just after birth. It may be evident externally when due to placental abnormalities, or it may be occult when it is from the fetus into the maternal circulation. In the latter situation, if the fetal blood is incompatible with the mother's, she may have a transfusion reaction. When vascular anomalies occur in the placenta of twins, bleeding from one twin to the other may lead to severe anemia in the "donor" twin. In infants delivered by cesarean section blood may be lost by poorly timed interruption of the umbilical cord or by accidental incision or rupture of the placenta.

Because the newborn infant has a small

blood volume, the loss of relatively small quantities of blood is often highly significant. The shock and anemia which result present urgent difficulties which must be differentiated from those presented by anoxia or hemolytic disease or other causes of anemia in the immediate newborn period.

The infant may be listless, limp and pale at birth, or he may rapidly become so after delivery. The fall in the hemoglobin level may be extremely rapid and may be apparent within an hour. The need for transfusion may be much more urgent than is suggested by the immediate clinical condition. An amount of blood equal to 10 per cent of the infant's estimated blood volume may be necessary immediately, and subsequently over a period of some hours as much as one quarter to one third of the infant's estimated normal blood volume may require replacement.

### ANEMIA DUE TO CHRONIC HEMORRHAGE

Losses of small amounts of blood over a long time lead to an anemia more severe than would be expected from the amount of blood lost. The unexpected severity results from a depletion of body iron. In the first few years of life anemia of iron deficiency is relatively common, most of the cases being due to dietary deficiency of iron. In later childhood hypochromic anemia is relatively infrequent in the United States, most cases being accounted for by chronic loss of blood.

**Etiology.** The gastrointestinal tract is the most common site of chronic hemorrhage, with bleeding from parasitic infestation, particularly hookworm disease, erosions associated with anomalies and polyps, defects in hemostasis, esophageal varices in association with congestive splenomegaly and ulcerative lesions. Recurrent epistaxes, hemorrhage into the lungs in idiopathic pulmonary hemosiderosis, and bleeding from tumors or ulcerations of the genitourinary tract are additional examples of infrequent causes of persistent hemorrhage.

**Clinical Manifestations and Laboratory Data.** The findings are those of iron deficiency anemia. Additional clinical features may point to the primary cause, and careful investigation, as for example repeated examinations of stools for occult blood, will usually disclose the site of hemorrhage. When there is doubt whether an anemia is of nutritional or chronic hemorrhagic origin, it may be expedient to carry out a short trial with an optimal diet and supplemental iron.

*Treatment* is directed primarily at the source of bleeding. Supplemental iron is also given orally as in other iron deficiency anemias. Transfusion of blood is not ordinarily needed except on occasion in patients requiring operation for correction of the defect responsible for loss of blood.

### HEMOLYTIC ANEMIAS

The hemolytic anemias of infancy and childhood can be separated into those resulting from congenital defects in the production of erythrocytes and/or hemoglobin and those dependent upon acquired defects in red blood cells or in their environment. A general classification is given in Table 103 (p. 933). These anemias have certain features in common. The spleen is a main site of the destruction of blood and is usually enlarged. An excess of bilirubin is formed from the heme of the destroyed cells which frequently leads to an elevation in serum bilirubin level and occasionally to clinical icterus.

In the peripheral blood active regeneration is evidenced by reticulocytosis and polychromatophilia. The marrow is the site of pronounced erythroid hyperplasia, which often leads to widening of the marrow spaces in long and flat bones, with the development of characteristic clinical and roentgenographic skeletal changes.

In severe chronic hemolytic anemias there may be a marked accumulation of iron-containing pigment in body tissues (hemosiderosis), which may be augmented by extensive transfusion therapy. Hemosiderosis may lead to hepatic enlargement and to a distinctive gray-green discoloration of the skin.

### HEREDITARY SPHEROCYTOSIS

(CONGENITAL HEMOLYTIC ANEMIA,  
FAMILIAL ACHOLURIC JAUNDICE,  
CONGENITAL MICROSPHEROCYTOSIS)

Hereditary spherocytosis is characterized by excessive destruction of abnormally shaped cells (spheroidocytes). The defect is inherited as a dominant character. This hemolytic anemia has been most commonly recognized in young adults, but careful study will lead to its recognition in infancy and early childhood.

Recent studies have demonstrated abnormalities in carbohydrate metabolism within the red blood cells of patients with hereditary spherocytosis. The number of energy-rich phosphate bonds in these cells is less than normal, with the apparent result that the cells



are unable to maintain a normal biconcave shape against the osmotic pressure of normal plasma.

The spleen is the principal site of entrapment, stagnation and excessive destruction of the abnormal, spherical erythrocytes. Removal of the spleen generally modifies the intensity of the hemolytic process significantly. It is not known what brings about hemolytic crises in hereditary spherocytosis.

**Clinical Manifestations.** Clinically apparent hereditary spherocytosis in early infancy is ordinarily unaccompanied by symptoms other than mild or moderate pallor. When it makes its appearance in the newborn period, however, icterus and increasing anemia may occur as early as the first or second day of life, and kernicterus may be a sequel. In later childhood the symptoms of a chronic hemolytic process may be more marked. Episodes (crises) of weakness, anorexia, dizziness, nausea, vomiting and abdominal pain, with or without icterus, may be the presenting symptoms in children who seem to be well between attacks, except for pallor. Mild degrees of icterus may occur in severe anemias of long duration, and the urine and feces may be highly colored. Manifestations of gallstone colic or obstruction of the biliary tract may be the first signs. The spleen is always enlarged, but only sufficiently to be palpable in about 60 per cent of patients. A slight fever may be present during crises. Cardiac murmurs of hemic origin are common with severe anemia, and there may be cardiac enlargement.

**Complications.** These are uncommon in children, but there may be chronic ulceration and pigmentation over the lower tibia or malleoli, membranous corneal opacities and optic atrophy. Pituitary dysfunction and hypogonadism have been attributed to hereditary spherocytosis. Motor development and intellectual capacity are not impaired, but linear skeletal growth and gain in weight may be retarded. The combination of hypoplasia at the base of the skull with widening of the marrow spaces of the flat bones of the skull may lead to parietal and frontal bossing and broadening of the face.

**Laboratory Data.** The erythrocyte count is reduced and may be as low as one million cells per cubic millimeter; the hemoglobin level is reduced in proportion. The anemia is normochromic and normocytic. The reticulocyte count is usually elevated and sometimes reaches levels as high as 20 to 30 per cent. A normal or low reticulocyte count may be

found for a day or two at times of aplastic crises. The leukocyte count may be strikingly elevated at times of active hemolysis, but during periods of chronic hemolytic activity both leukocyte and platelet counts may be below normal as a result of secondary hypersplenism. The peripheral blood smear shows anisocytosis. There are many large polychromatophilic erythrocytes, a sizable proportion of apparently normal cells, and variable numbers of small, deeply staining spherocytes. Similar spherocytes are usually seen in at least one parent of the child with hereditary spherocytosis.

The osmotic fragility of the erythrocytes is typically increased, but in 10 to 15 per cent of cases even carefully performed quantitative tests will fail to reveal abnormal fragility. Incubation of the erythrocytes in defibrinated whole blood under sterile precautions for twenty-four hours at 37° C. prior to testing will accentuate the abnormality in osmotic fragility.

In a small proportion of cells, the reticulocytes and immature erythrocytes, there may be increased resistance to destruction in hypotonic saline solution.

The serum level of indirect bilirubin is usually moderately elevated in older children, but rarely in the first few years of life; the direct bilirubin may be elevated if cholelithiasis has resulted in biliary obstruction. There may occasionally be falsely positive reactions to serologic tests for syphilis, which revert to normal after splenectomy. The Coombs' test is negative.

The bone marrow reveals hyperplasia of the erythroid series. Rarely the marrow may be hypoplastic with depression of erythrocytes, myeloid elements and platelets.

Microscopic examination of the spleen after surgical removal shows intense congestion of the pulp. The sinusoids and pulp spaces are lined with prominent endothelial cells. Hemosiderosis may be present.

**Differential Diagnosis.** Neither spherocytosis nor increased osmotic fragility is confined to this disease. Spherocytosis may be found in hemolytic anemias of other causes, including those resulting from acute infection, from iso-immunization, especially to the A or B blood groups, from auto-immunization or from chemical agents. In the absence of the trait of spherocytosis in other members of the family the possibility of some anemia other than hereditary spherocytosis must be carefully explored.

**Course and Prognosis.** The course is ex-

tremely variable. Many patients live active lives of average duration without therapy. When symptoms occur in childhood, however, one can anticipate that without treatment the chronic hemolytic process will lead to limitation of activity, stunting of growth and possibly to biliary tract disease or other complications. The danger of sudden severe crisis has perhaps been overestimated. Death can occur from anemia and cardiac failure if treatment is too long delayed.

With splenectomy and correction of any abnormality of the biliary tract the child can expect to lead a normal life. His offspring should be examined for the hereditary trait, however, in early life; even in the newborn period, if jaundice should occur.

**Treatment.** Splenectomy completely alleviates the anemia and accompanying symptoms in hereditary spherocytosis. After splenectomy striking changes occur in all the cellular elements of the blood. The erythrocyte count increases promptly by one to one and a half million cells per cubic millimeter, and the leukocyte count rises quickly to levels of thirty to forty thousand cells per cubic millimeter. A gradual increase in the platelet count beginning soon after operation reaches its peak by the eighth to tenth day, when it may exceed one million platelets per cubic millimeter. At this level the patient may be particularly susceptible to thrombosis, which in intra-abdominal or intracranial vessels may be serious. Adequate anticoagulant therapy with heparin should be initiated if the daily postoperative platelet count exceeds one million per cubic millimeter and should be continued so long as the platelet count remains above that level.

#### CONGENITAL NONSPHEROCYTIC HEMOLYTIC ANEMIA

A number of patients with familial hemolytic anemia resembling hereditary spherocytosis clinically but without spherocytosis have been studied recently. A dominant mode of inheritance is suggested. The affected children have a severe acute hemolytic anemia soon after birth, which continues as a mild or severe hemolytic process, represented by several ill-defined clinical patterns. Instead of spherocytes in the peripheral blood, varying numbers of macrocytes and, in some instances, ovalocytes are found. The red blood cells have decreased osmotic fragility in saline solution, but increased hemolysis in the autohemolysis test of Selwyn and Dacie. As in hereditary spherocytosis, there appears

to be a disturbance of energy metabolism in the erythrocytes.

Splenectomy is of no value. Steroid therapy was thought to be helpful in one patient with a severe hemolytic process.

#### THALASSEMIA

(COOLEY'S ANEMIA, ERYTHROBLASTIC ANEMIA, MEDITERRANEAN ANEMIA)

Thalassemia is a chronic hemolytic anemia in which the defect leads to the production of cells of abnormal shape, which are deficient in hemoglobin and are destroyed at an excessive rate. The primary defect appears to be inability to produce cells capable of normal incorporation of hemoglobin rather than inability to produce hemoglobin. The delivery of erythrocytes to the peripheral blood is decreased in severely involved patients to as little as 15 per cent of normal.

Thalassemia occurs in two forms. If the gene responsible for the defect is heterozygous, there is a mild anemia with moderate hypochromia, anisocytosis, poikilocytosis, and at times a slight splenomegaly. Carriers of a single gene for thalassemia are free of symptoms and live normal lives. Their asymptomatic condition is called *thalassemia minor*.

The child of two parents with thalassemia minor may be *homozygous* and have a severe, progressive anemia, *thalassemia major*, which is incompatible with long life and is only temporarily responsive to supportive transfusion therapy.

In each form hematopoietic tissue effects a partial compensation by persistent production of fetal hemoglobin at levels above normal values. In thalassemia minor this compensatory activity is relatively inconspicuous; though it is greater in thalassemia major, it falls far short of the need for effective oxygen transport.

Thalassemia, first described by Cooley in Detroit, was for some time found almost exclusively in persons whose familial origins were in certain countries bordering the northern Mediterranean coast, particularly Italy, Greece and Sicily. It has now been described in people of oriental, Jewish, Negro and western European origins.

**Clinical Manifestations.** In thalassemia minor the clinical manifestations are limited to moderate pallor and, on occasion, slight enlargement of the spleen. The condition is usually not recognized unless careful blood studies are obtained as part of a family survey.

Thalassemia major is characterized by the



onset of a severe and progressive anemia early in infancy. Anemia is not present at birth, but seems to develop in relation to the normal gradual decrease in production of fetal hemoglobin. Pallor is usually marked, and there is often mild icterus. Splenomegaly appears early, is progressive and may attain enormous proportions within a few years. In the absence of supportive transfusion therapy the anemia of thalassemia is relentlessly progressive and leads to cardiorespiratory distress and cardiac failure. Hemic murmurs and cardiac enlargement are common.

After months or years of transfusion therapy the clinical features of hemosiderosis usually become manifest. The possibility of a fundamental defect in control of iron absorption has been postulated, since the amount of iron stored in the tissues is far in excess of that accounted for by the blood transfused. The distribution of the iron in tissues resembles more closely that seen in hemochromatosis than in hemosiderosis due to other hemolytic disease or to multiple transfusions. The skin becomes a muddy, bronze color, with which the pallid mucous membranes are in striking contrast. The liver may become enlarged, owing to the changes of hemosiderosis, and together with the splenomegaly (largely due to other aspects of the disease) may produce abdominal enlargement of such an extent as to be disabling at times. A mild degree of lymphadenopathy is common.

With the progression of thalassemia major the skeletal changes associated with chronic hemolytic anemia become strikingly evident and exceed the changes found in other hemolytic anemias. Thickening of the membranous bones of the face and skull leads to a mongoloid facies, with a tendency to protrusion of teeth. The hands become broad and heavy in appearance, owing to alterations in the metacarpal bones. Periodic transfusions of blood may minimize the degree of hyperplasia in bone marrow and consequently lessen the extent of skeletal deformities.

The roentgenographic abnormalities in thalassemia major have been described in detail by Caffey. The first changes occur by the end of the first year of life and consist in widening of the medullary spaces, thinning of the cortices and decrease in size of the bony trabeculae. The small bones of the hand may be the first site of detectable changes in tubular bones. There the cortices may be thinned, and the medullary cavities broadened, so that the bones seem to assume a rectangular rather than a tubular shape. In

older children the changes in the bones of the extremities regress, whereas the changes in the vertebrae, skull and pelvic bones persist and increase in intensity. The membranous bones of the calvarium show striking widening of the diploic spaces, with radiating bony trabeculae traversing the widened space to give a "hair-on-end" appearance to roentgenograms of the skull. Pneumatization of the paranasal sinuses and mastoid regions is retarded and may be absent until late in childhood. Overgrowth of the maxilla is a common finding and may result in serious malocclusion and in a toothy facial appearance.

**Laboratory Data.** The characteristic features of the peripheral blood in thalassemia become apparent within the first few months and persist throughout life. In both the major and minor forms there is a microcytic, hypochromic anemia.

In thalassemia minor the anemia is of only moderate degree. The hemoglobin level is likely to be 9 to 13 gm. per 100 ml. There is a compensatory polycythemia with erythrocyte counts of six to seven million cells per cubic millimeter. Mild or moderate anisocytosis is present, and some polychromatophilia is seen. Reticulocyte counts of 3 to 6 per cent are usual. The leukocyte and platelet counts are not affected.

In thalassemia major there is a severe anemia with profound hypochromia. The erythrocyte count is below the normal range, and the hemoglobin is reduced to an even greater extent. The erythrocytes show anisocytosis and poikilocytosis. There are many microcytes, with a minority of contrasting, large hypochromic cells 12 to 15 microns in diameter. The hemoglobin in these large cells is irregularly distributed, creating many bizarre shapes. The presence of a small central mass of hemoglobin may give them a "target-cell" appearance.

Rapid turnover of erythrocytes is reflected in the moderately elevated reticulocyte count and the presence of nucleated erythrocyte precursors. Stippled cells occur, and Howell-Jolly bodies and polychromatophilic cells may be numerous. The red blood cells in both thalassemia major and minor show a distinctly increased resistance to hemolysis in hypotonic saline solution.

A moderate leukocytosis is present in the early stages of thalassemia major; counts may be as high as twenty-five to thirty thousand per cubic millimeter. Later when secondary hypersplenism dominates the picture, a leu-

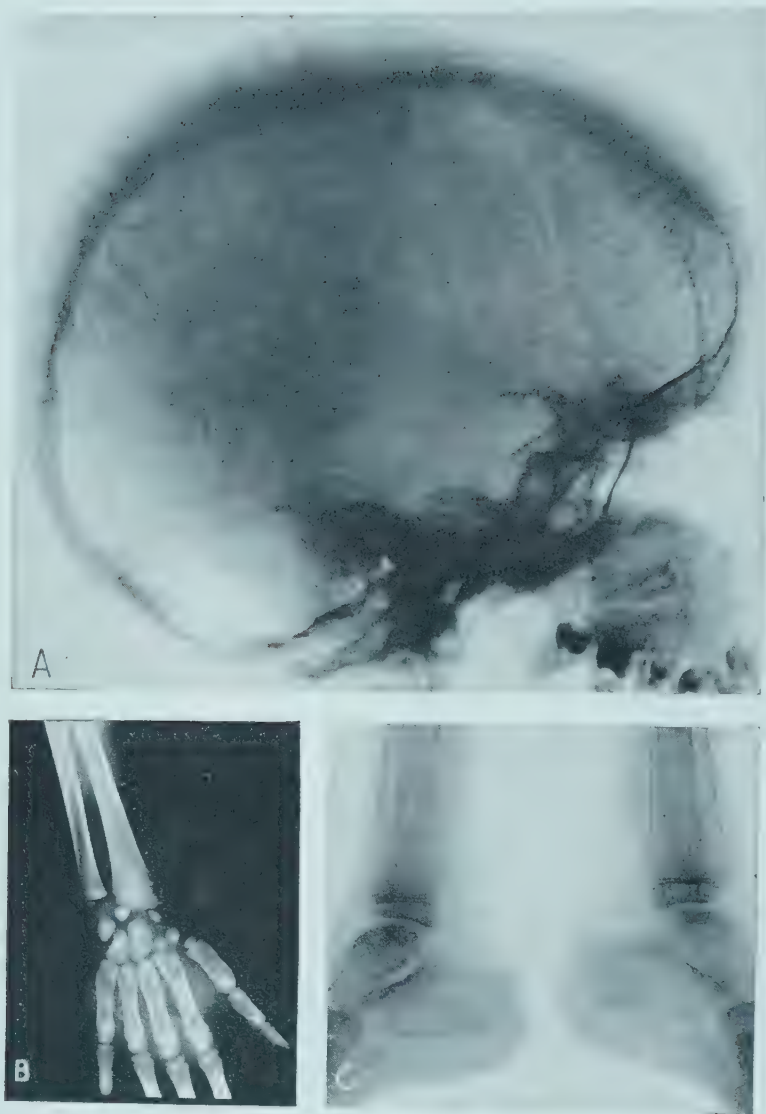


FIG. 304. Roentgenograms of skull and long bones of child with thalassemia. A, Skull: Note rarefaction of bones and spicule formation, creating appearance of "hair standing on end." B, Hand: Rarefaction of bones resulting from expanding marrow cavity is visible earliest in small bones of hands and feet. C, Lower extremity: Extreme rarefaction in a long-standing anemia of severe degree; the excessively wide marrow cavities and the thin cortical bones predispose to pathologic fractures.

kopenia will be found. Granulocytes are the predominant cells. Platelets may be slightly increased in the early phase of the disease, but may be reduced in number when hypersplenism occurs.

The serum level of indirect bilirubin is elevated in thalassemia major to levels of 2 to 3 mg. per 100 ml., with higher levels when hemosiderosis appears. The serum level of iron is in the high range of normal, and the serum iron-binding capacity is less than usual. The free protoporphyrin of the erythrocytes and the serum level of copper are elevated. The erythrocytes contain increased amounts of fetal hemoglobin long after the production of this pigment has practically ceased in normal children.

The bone marrow in thalassemia major is hypercellular, erythrocyte precursors being predominant. In long-standing cases foam cells resembling those of Gaucher's disease may be found. Similar cells are also found in the spleen, where there are numerous foci of extramedullary erythropoiesis, enlargement of fibrous trabeculae and infarcts.

**Diagnosis.** Thalassemia minor must be differentiated from the *anemia of iron deficiency*. This may be difficult on casual examination. In thalassemia minor the erythrocyte count will be normal or elevated. The reticulocyte count will be slightly elevated in thalassemia minor, but usually not in iron deficiency states. Study of the parents of the child with thalassemia minor will always



show that one or both have blood findings compatible with that diagnosis.

Thalassemia major must be differentiated from other hemolytic anemias of early infancy which may be associated with splenomegaly. Usually the hypochromia and anisocytosis in peripheral blood will exclude other hemolytic conditions, as will the finding of decreased rather than normal or increased osmotic or mechanical fragility. Family studies will also aid in the establishment of the diagnosis of thalassemia major; *both* parents will have thalassemia minor.

The *sickle cell trait* may exist in patients with thalassemia minor (p. 952). Ordinarily the clinical pattern of this unusual combination more closely resembles that of sickle cell disease than of thalassemia major.

**Course and Prognosis.** Thalassemia minor is a benign condition and does not interfere with normal activity. Persons with this condition should be cautioned that if they marry another person with the same trait, their children may have the major form. On the average, one quarter of their children would be so affected.

Children with thalassemia major are dependent from early infancy upon transfusion therapy, the frequency of the need often increasing as they become older. Even with the best of care they are usually severely limited in activity and often stunted in growth. Many acquire hemosiderosis, and hemochromatosis may be a terminal complication. Cardiac failure is a constant threat, and only a few patients have survived the childhood years; a few with relatively mild involvement have lived into late adulthood. There may be some lessening of severity after puberty.

**Treatment.** Thalassemia minor requires no treatment. The anemia of thalassemia major is controlled only by transfusion of blood, which should be given as often as necessary to maintain the hemoglobin level above 6 gm. per 100 ml. (40 per cent of normal). More vigorous therapy appears to add little to the comfort or well-being of these children. The use of sedimented cells will increase the efficiency of a given amount of transfusion. Such transfusions, if given slowly and carefully, may also lessen the danger of cardiac embarrassment during the procedure. Although febrile and allergic reactions to plasma occur with some frequency, the washing of transfused cells with saline solution is rarely, if ever, indicated. The prophylactic use of aspirin with antihistaminic drugs may be effective, and in reac-

tions of unusual severity cortisone has been beneficial.

The results of splenectomy are difficult to evaluate. When there is massive enlargement, relief from the mechanical load justifies the operation. Splenectomy has appeared on occasion to prolong the interval between needed transfusions and to result in more nearly normal growth and activity. When leukopenia and thrombocytopenia of moderate or severe degree indicate secondary hypersplenism, some benefit from splenectomy might be expected.

The administration of iron, liver extract or cobalt has no place in the treatment of thalassemia, and oral therapy with iron may dangerously accentuate the hemosiderosis.

It is important that the families of these children be helped to accept the unfortunate situation and to provide the opportunity for them to lead as nearly normal lives as possible. With adequate management and understanding children with thalassemia major are often able to lead satisfactory lives.

## SICKLE CELL DISEASE

### (DREPANOCYTOSIS, MENISCOCYTOSIS)

Sickle cell disease is characterized by a persistent hemolytic anemia with intermittent episodes of painful crises, during which the hemolytic process may be accentuated. The disease is associated with an inherited defect in the synthesis of hemoglobin and occurs almost exclusively in the Negro race. When the defect in synthesis of hemoglobin is inherited in the heterozygous state, an asymptomatic condition (*sickle cell trait*) can be identified; it is found in 7 to 13 per cent of Negroes in the United States. When the inherited abnormality appears in homozygous form, sickle cell disease results.

In both the heterozygous and homozygous forms the presence of an abnormal hemoglobin (hemoglobin S) can be identified by electrophoretic means. This type of hemoglobin has the distinctive property of forming long crystalline structures (tactoids) under reduced oxygen tension. This property is thought to be responsible for the sickled shape of the erythrocytes of both heterozygous and homozygous carriers.

Both parents of the person with the homozygous trait (sickle cell disease) are heterozygous (sickling trait). On the average, three quarters of the children of such parents have the sickling abnormality, and one quarter have sickle cell disease. It has been un-

usual for a parent to have the active form of the disease.

**Pathogenesis and Pathology.** The alterations in sickle cell disease are related to chronic hemolytic anemia and to interference with the blood supply of various tissues. The vascular lesions result from capillary obstruction, which may depend upon the abnormal shape of the erythrocytes. It is believed that at times of crises the number of sickled cells may be increased and that sequestration of them in local areas leads to anoxic changes which promote further sickling and further obstruction. Infarcts may thus occur in many organs, most commonly the spleen, and less often in bone, the gastrointestinal tract, kidneys, lungs, heart and brain. Thrombosis is an occasional complication.

At intercritical times the spleen (and to a less extent other areas) is the site of continuous removal of abnormally shaped cells. Infarctions of the spleen are common, and after the age of five to seven years may lead to striking fibrosis and atrophy. The trabeculae become greatly thickened, and calcium and iron are deposited. Atrophy may be so extreme that the organ effectively disappears after the age of twelve. Hemosiderosis occurs in the liver, largely the result of repeated blood transfusions. As in other chronic hemolytic anemias, cholelithiasis is common in patients living to adulthood.

**Clinical Manifestations.** The sickle cell trait is not accompanied by clinical symptoms unless it is associated with some other defect in the synthesis of hemoglobin (see p. 952), or with exceptional circumstances, such as flight in aircraft at high altitudes, when hypoxia may provoke splenic infarction.

Clinical manifestations of sickle cell disease do not appear until the second or third month of life, when the normal fetal hemoglobin is largely replaced by the abnormal hemoglobin S. In mildly affected children, sickle cell disease may not be evident until late in childhood; 30 to 50 per cent of all affected ones manifest symptoms by one year of age.

The initial manifestation is often the so-called crisis, an acute disturbance accompanied by a variety of manifestations, the most common of which are severe abdominal pain and pain in the legs. The abdominal pain is commonly associated with absence of bowel sounds and with boardlike rigidity of the abdominal wall, and it is often impossible to differentiate conditions requiring surgical intervention. Pain in the extremities may be

muscular, or osseous, or may be localized to joints, which may be hot and swollen. Other less common manifestations are severe flank pain sometimes with hematuria, priapism presumed to be due to thrombosis of small vessels in the penis, convulsions, syncope, stiff neck, coma or localized paralyses. The chronic pallor may be greatly accentuated at the time of crisis. About forty-eight to seventy-two hours after onset of a crisis icterus will usually appear and may become marked.

Except in crisis, the manifestations are those of a chronic hemolytic process, viz., anemia and pallor. Icterus may be persistent in late childhood and in severely affected persons. Older children are likely to have long thin extremities, a short trunk, protruding abdomen and barrel chest, but they usually attain average heights and weights.

Under the age of nine years the spleen will often be palpable; later it is less likely to be felt. Enlargement of the liver is not common. Cardiac enlargement and apical blowing systolic murmurs are common; the latter may be transmitted to the left axilla and be indistinguishable from murmurs of rheumatic heart disease. Ulcerations over the lower tibia and malleolar areas, common in adults with sickle cell disease, are rare in children.

**Laboratory Data.** The "sickled" shape assumed by the erythrocyte under conditions of low oxygen tension is characteristic. At times of crisis sickled forms may be abundantly demonstrated in ordinary smears of peripheral blood. When not so demonstrated, they may be produced in many ways. Commonly a small drop of blood is placed under a cover slip and sealed off from oxygen by petroleum jelly. After incubation for one to twenty-four hours at room temperature sickled forms will usually appear. Other methods include the incubation of erythrocytes with suspensions of aerobic bacteria, or the exposure of erythrocytes to any of several potent reducing agents, such as sodium meta-bisulfite. It is a good rule not to accept less than three negative tests as final evidence when sickle cell disease is suspected.

*Tests for sickling do not distinguish between the sickle cell trait and sickle cell disease.* In sickle cell disease the sedimentation rate of unoxygenated blood is low even in the presence of severe infection. An increase in the sedimentation rate of such blood to more than 20 mm. per hour (Westergren) after oxygenation is a strong indication of sickle cell disease. Occasionally only quantita-



tive electrophoretic determination of the amount of sickle cell hemoglobin can *absolutely* differentiate trait and disease. More than 60 per cent of the hemoglobin in red blood cells is abnormal in sickle cell disease, whereas less than 45 per cent is abnormal in sickle cell trait. Hemoglobin S can also be distinguished by its amino acid content. Fetal hemoglobin as well as hemoglobin S is produced in increased amounts in sickle cell disease.

The erythrocyte count and hemoglobin level are not abnormal in persons with simple sickle cell trait. In sickle cell disease the level of hemoglobin may be in the range of 6 to 9 gm. per 100 ml., except at times of crisis, when it will be lower. Each affected person tends to stabilize at a level at which he is able to balance hemolysis by his increased erythropoietic activity; any increase from transfusion of blood is temporary. Rarely a patient may be able to maintain a balance within the lower limit of the normal range.

There may be a moderate degree of hypochromia, the reason for which is not known, since iron deficiency is not ordinarily present. The reticulocyte count is moderately elevated to 5 to 25 per cent, with the highest values five to seven days after crises. On occasion reticulocytes may be absent early in the course of a crisis, and there may be hypoplasia of erythroid elements in the marrow in contrast to the usual hyperplasia. The osmotic fragility of the erythrocytes shows increased resistance in hypotonic saline solution.

The leukocyte count is moderately elevated and may reach thirty to fifty thousand cells per cubic millimeter at times of crisis. Immature myeloid cells are commonly present, and granulocytes predominate. Platelets are usually normal in number.

Although no defect of renal glomerular or tubular function is characteristically demonstrable, the urine usually has a low specific gravity. Proteinuria is not uncommon, and spontaneous, painless hematuria may occur with sickle cell trait as well as sickle cell disease.

The serum level of bilirubin, principally indirect pigment, is consistently moderately elevated. Four to seven days after the onset of crises the level will increase temporarily. There may be an increase in protein, leukocytes and erythrocytes in the cerebrospinal fluid, when sequestration of cells occurs in the central nervous system at times of crisis or in patients suffering from a cerebral thrombosis. Abnormalities in electroencephalo-

graphic tracings are often found during crises.

Roentgenograms of the skull, long bones, vertebrae, hands and feet may show widening of medullary spaces and thinning of cortices. Infarction of large areas of bone often leads to extensive changes similar to those of osteomyelitis.

**Differential Diagnosis.** There is hardly a clinical pattern which might not be duplicated by sickle cell disease, since any organ system may be the site of vascular occlusion during crises. A test for sickling should be obtained on every Negro patient.

When sickling is demonstrated in the patient and in both parents, the presence of a hemolytic anemia will suggest sickle cell disease. If a hemolytic process of another origin, such as hereditary spherocytosis or acquired hemolytic anemia, were to occur in a patient with sickle cell trait, differentiation from sickle cell disease would rest upon clinical and laboratory features. The sickling trait may be associated with other abnormal hemoglobins or with the trait for thalassemia (p. 952). Occasionally only electrophoretic studies of the hemoglobin will disclose the true nature of the hemic disturbance.

The roentgenographic rarefaction and sclerosis of bone in sickle cell disease may suggest syphilis, tuberculosis, osteomyelitis, aseptic necrosis or a tumor.

Cardiac enlargement and murmurs, joint pains and epistaxis are suggestive of rheumatic fever in children in whom sickling can be demonstrated. Electrocardiographic changes may be similar in the two diseases, but the demonstration of a hemolytic anemia favors sickle cell disease.

**Course and Prognosis.** The crises of sickle cell disease tend to occur less frequently with increasing age; they are more common in the fall and spring months in temperate climates.

The prognosis of sickle cell disease must be guarded, since fatal cerebral, cardiac or hemolytic difficulties may occur with little notice. Cholelithiasis may occur in the older child. Adults with sickle cell disease are said to have hypogonadism and relatively low fertility. The life expectancy of an infant or young child with sickle cell disease is less than average, but with careful supervision many may reach adult life.

**Treatment.** Treatment consists in supportive measures such as blood transfusions, protection against infection and help in social and vocational adjustment.

The treatment of crises involves relief of

pain, maintenance of hydration and, on rare occasions, the transfusion of erythrocytes. Codeine and aspirin may be only partially effective in the control of pain. During the first twenty-four to forty-eight hours of a critical episode vigorous oral hydration with water free of electrolytes may help to reverse sickling and thus help to relieve local vascular obstructions. Prompt and adequate antibiotic therapy should be given for any coexisting bacterial infection.

The advisability of blood transfusion must be evaluated according to individual needs. At times of crisis, when the level of hemoglobin may fall rapidly to 4 gm. per 100 ml. or less, if symptoms of hypoxia are absent, it is often possible through supportive measures, particularly oxygen and hydration, to avoid transfusion. In such cases the hemoglobin level will rise promptly and spontaneously after the crisis to its previous level. Transfusion therapy is indicated much less frequently than is generally considered to be the case.

Iron, liver extract and vitamins have no effect on sickle cell disease. Splenectomy apparently has no effect; secondary hypersplenism is rarely a problem.

#### SICKLE CELL—THALASSEMIA DISEASE (MICRODREPANOCYTOSIS)

An anemia associated with inheritance of genes both for production of sickle cell hemoglobin (hemoglobin S) and for thalassemia minor has been identified. It has been found most often in persons of Italian and Sicilian origin. Most persons affected have a mild, apparently modified form of sickle cell disease, with the onset in late rather than early childhood; on occasion the disturbance may more closely resemble thalassemia. The diagnosis of *combined sickle cell trait and thalassemia minor* is suggested when a chronic hemolytic anemia is found in a person of Mediterranean ancestry whose erythrocytes sickle and show marked hypochromia and when only one of the parents has the sickling trait. The other parent will usually have thalassemia minor. It is possible, however, for a person with the genes for both thalassemia and sickling to transmit *both* to a child.

#### OTHER HEMOLYTIC ANEMIAS ASSOCIATED WITH ABNORMAL HEMOGLOBINS

The identification of many hemoglobins of unusual molecular structure followed the identification of the molecular abnormality in hemoglobin S of sickle cell disease. To date

more than ten distinct varieties of abnormal hemoglobins have been identified in patients with hemolytic disease; probably many more remain to be identified. It has become customary to designate the various hemoglobins by letters as they are reported: hemoglobin A is adult hemoglobin; hemoglobin F, the fetal variety; hemoglobin S, sickle cell hemoglobin; and C, D, E, G, H; I, J, K, and so on, designate other varieties of abnormal hemoglobins.

In a patient with an otherwise unexplained chronic hemolytic process consideration must be given to the possible existence of an abnormal hemoglobin; no geographic or racial group appears to be free of these genetic abnormalities. The abnormality may exist in an asymptomatic, heterozygous state analogous to the sickle cell trait, in a homozygous symptomatic state, or most commonly as a double heterozygote; in the last instance hemolytic disease results from destruction of erythrocytes which contain two abnormal hemoglobins. Hemoglobin S has been commonly found with hemoglobin C, as well as with D and G; other hemoglobins have been described with the trait for thalassemia.

The abnormal hemoglobins are most often recognized through their characteristic electrophoretic patterns; differences in solubility, spectrophotometric patterns and amino acid content can be demonstrated for many and may be essential to the identification of certain ones. Fetal hemoglobin is differentiated from the others by its ability to resist denaturation in alkaline solution.

In persons with these abnormalities of hemoglobin, treatment is limited to blood transfusions when anemia is severe. In most instances hemolysis is only moderately severe and is generally compensated by hyperactivity of the bone marrow.

#### ELLIPTOCYTOSIS

Small numbers of elliptical-shaped erythrocytes may be encountered in peripheral blood films in a wide variety of anemias. A genetically controlled abnormality in which 50 to 90 per cent of the erythrocytes are oval or elliptical occurs in about 0.04 per cent of the population. About one in eight of such persons has a hemolytic process. The abnormality in erythrocyte structure is inherited as a mendelian dominant trait.

Elliptocytes are not found in conspicuous numbers at the time of birth in these patients, but appear in increasing numbers up to the age of three to four months, when the num-



ber becomes constant. The affected person may have no evidence of hemolytic anemia, or may have a mild, well compensated hemolytic process without symptoms, or may have a chronic hemolytic anemia. In the last instance splenectomy is often of symptomatic benefit.

#### ACQUIRED HEMOLYTIC ANEMIAS

The acquired hemolytic anemias of childhood are a heterogeneous group of disorders; among possible causative factors are (1) toxic substances with hemolytic properties, (2) idiosyncratic susceptibility to hemolytic effects of certain drugs or vegetable substances, (3) infections in which the erythrocyte is directly involved, (4) specific antibodies against red blood cells. The last group includes (a) acquired hemolytic anemias associated with autoagglutinins, (b) blood transfusion reactions and (c) iso-immunization (erythroblastosis fetalis). Because these three conditions present unique features, they are discussed separately.

The other acquired hemolytic anemias of childhood have many features in common, as well as distinctive aspects.

The clinical onset is typically abrupt. Nausea and vomiting or fever and abdominal pain may be the first signs, or hemoglobinuria may be the initial evidence. The child becomes irritable, lethargic, pale and often icteric. The liver may become enlarged; the spleen is regularly so after a day or two and may be tender. Hemic murmurs, tachycardia and cardiac failure may accompany severe anemia. If recovery occurs, relapses or recurrences are rare. Chronic forms may be seen, especially when immune bodies occur.

*Examination of the blood* usually shows a normocytic and normochromic anemia, which may be mild or profound. Regenerative activity is manifest by polychromatophilia and reticulocytosis (up to 60 per cent or more) and by a considerable degree of macrocytosis. Nucleated erythrocytes are occasionally found in the peripheral blood, and spherocytes, fragmentation of erythrocytes and Heinz bodies are often present. Erythrophagocytosis is common in peripheral blood and in marrow. When there is spherocytosis, the osmotic and mechanical fragilities may be increased. A granulocytic leukocytosis is common during or after acute hemolytic episodes and may reach levels of 50,000 cells or more per cubic millimeter. Platelet levels may be above normal.

Hemoglobinemia may be demonstrated, and hemoglobinuria may give the urine a bright red or port-wine color. Mild hematuria may also occur. Serum bilirubin may be moderately elevated with respect to indirect-reacting pigment. Large amounts of urobilinogen can be demonstrated in urine and may give the feces an orange tint.

**Specific Features of Certain Acquired Hemolytic Anemias.** Acquired hemolytic anemias of *toxic* origin owe their occurrence (1) to the direct lytic action of drugs, chemicals or bacterial products upon the erythrocyte, or (2) to a defect in the patient which makes his erythrocytes susceptible to hemolysis upon exposure to an otherwise nonhemolytic substance.

In the first category of toxic hemolytic processes are those associated with exposure to lead, potassium dichlorate, benzol and related compounds, the nitro derivatives of toluol and phenol, certain snake venoms and the toxic products of certain bacteria, notably the colon bacillus and hemolytic *Streptococcus* (in infancy) and *Clostridium welchii*.

In the second category hemolytic anemias have been observed in "sensitive" but otherwise normal persons after exposure to a variety of substances, including the sulfonamides, primaquine, naphthalene metabolites, nitrofurazone, vitamin K analogues, fava beans (p. 1388) and probably many other agents. A common enzyme defect, which is genetically controlled and is concerned with glutathione metabolism of the erythrocyte, is responsible for the development of the hemolytic state (p. 264). Red blood cells of affected persons have a low concentration of reduced glutathione as a result of a deficiency of the enzyme glucose-6-phosphate dehydrogenase. The enzyme defect can be demonstrated by measuring the concentration of reduced glutathione or by performing the "glutathione stability test."

Exposure to naphthalene is a relatively common cause of hemolysis in affected children, occurring most often from the ingestion of moth balls. In favism the onset occurs in the susceptible person a few hours to a day or two after ingestion of the broad bean (*Vici fava*) or inhalation of its pollen or dust. The hemolysis in any of these chemically induced anemias can be severe; resulting in prostration, extremely low levels of hemoglobin, icterus and hemoglobinuria. Transfusion of erythrocytes is necessary in severe cases, but in most instances the anemia is self-corrective. Removal of the toxic substance from the environment is essential to

prevent further hemolysis. Determination of the glutathione levels in the red blood cells of other members of the patient's family should be obtained when possible to identify apparently healthy persons who might experience hemolysis from exposure to offending chemical agents.

Severe *burns* are commonly accompanied by hemolysis and hemoglobinuria, which seem to depend upon thermal injury to red blood cells and upon toxic factors.

Direct *parasitization of the erythrocyte* occurs in malaria and in Oroya fever (*Bartonella bacilliformis*). Malaria is probably responsible for more hemolytic anemia than any other single condition (p. 606).

#### ACUTE HEMOLYTIC ANEMIAS ASSOCIATED WITH AUTO-AGGLUTININS

Acquired hemolytic anemia associated with the development of *auto-agglutinins* may occur under a variety of conditions, as, for example, with leukemia or other malignant processes, with infectious mononucleosis, atypical pneumonias and other infections, and at times without apparent association with another process (Lederer's anemia). The condition may be considered the prototype of several blood diseases (idiopathic thrombocytopenic purpura, anaphylactoid purpura, lupus erythematosus) in which the affected person forms antibodies against his own tissues. A hemolytic anemia may accompany *paroxysmal cold hemoglobinuria*, which is encountered in some children with congenital syphilis (p. 1022).

Except for the demonstration of auto-agglutinins, the laboratory findings resemble those described earlier. The agglutinins may be active in the cold (4° C.), but often show a wide thermal amplitude, being demonstrable at 37° C. They are usually pan-agglutinins for human erythrocytes, but unlike the naturally occurring cold agglutinins with anti-A, anti-B, anti-O, anti-M, anti-N or anti-P specificity, may rarely be selective of human blood groups, especially of Rh subtypes. The auto-agglutinins must be differentiated from the foregoing specific agglutinins and from the naturally occurring cold panagglutinins which many normal persons have in their serum in low titer. The titer of abnormal agglutinins is usually high, and they have the property of coating the patient's erythrocytes and almost always producing a positive direct antiglobulin test (Coombs' test). They may also be demonstrated by the indirect antiglobulin technique

and by the technique of trypsin digestion, using erythrocytes of a normal person.

The coating antibodies render the erythrocytes of the patient susceptible to spontaneous agglutination, particularly in normal serum or albumin solution or on glass surfaces at room or body temperature. This effect may seriously interfere with accurate typing of the patient's blood and with the cross-matching procedure. For example, if the patient is erroneously typed AB, no AB blood will be compatible, or, if the patient is correctly typed, blood which is compatible will not be satisfactory in the cross-matching procedure. These difficulties can sometimes be circumvented by washing the patient's cells several times with warm saline solution (37° C.) and by performing all tests at 37° C., using prewarmed reagents, except that the serum of the patient is separated from the clot and warmed only after it has been incubated with the clot at 4° C. for at least an hour or preferably overnight. These precautions tend to secure reagents as free of interfering substances as possible and to permit the cold agglutinins as little activity as possible. If satisfactory results cannot be obtained after cross-matching with as many group O bloods as possible, group O Rh-negative blood may be cautiously used for the transfusion of these patients. A or B blood group substances should be added if the patient is not group O.

Acquired hemolytic anemias associated with auto-agglutinins are usually acute and self-limited. They may need transfusion therapy, but this should be used sparingly, perhaps only when the hemoglobin level is under 5 gm. per 100 ml. Occasionally these anemias become subacute or chronic. Administration of ACTH or cortisone may be effective, and splenectomy may be so in about half of the chronic cases. These measures may suppress the hemolytic process or induce temporary or lasting remissions. With either treatment the production of auto-agglutinins and the positive Coombs' test may persist for months or years, while the hemolytic process remains quiescent.

#### HEMOLYTIC REACTIONS DUE TO TRANSFUSION OF INCOMPATIBLE BLOOD

Hemolytic transfusion reactions may occur as a result of infusion of erythrocytes into a patient who has iso-agglutinins specific for these erythrocytes or as a result of the infusion of plasma containing iso-immune bodies for the recipient's erythrocytes. The most important reactions involve hemolysis



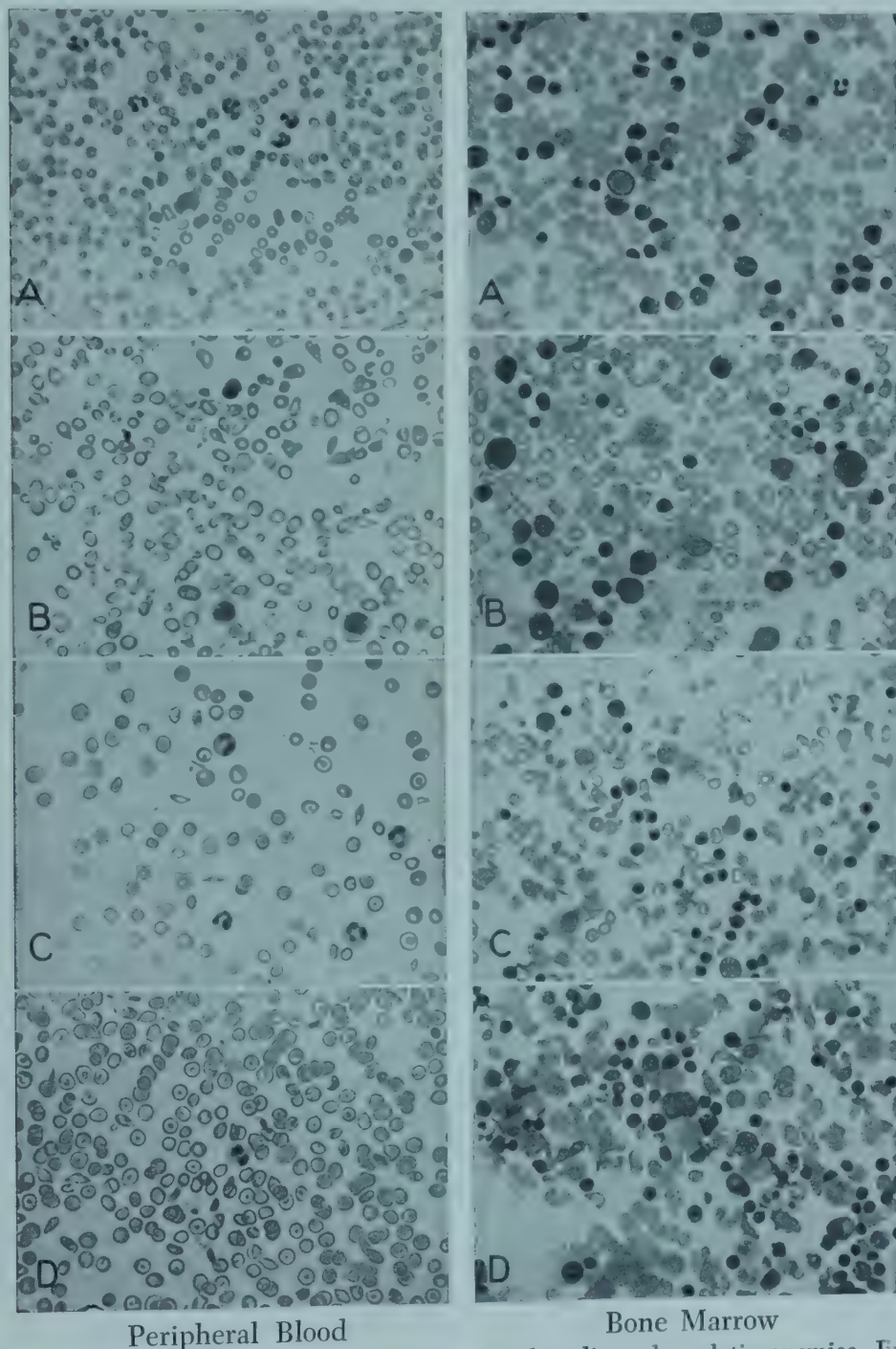
of the donor's cells rather than of the recipient's; at times erythrocytes of both donor and recipient are destroyed (for example, when group A blood is given to a group B recipient).

The safeguards of blood transfusion are outlined elsewhere (p. 200). The *treatment*

of the hemolytic reaction is mainly directed at control of *acute renal injury* (p. 1050).

#### HEMOLYTIC DISEASE OF THE NEWBORN (ERYTHROBLASTOSIS FETALIS)

The term *hemolytic disease of the newborn* includes a number of hemolytic processes



Peripheral Blood

Bone Marrow

**FIG. 305.** Morphologic alterations in erythrocytes in hereditary hemolytic anemias. In *A* the small, dark-staining spherocytes of hereditary spherocytosis are seen. Large polychromatophilic erythrocytes are also present. There is erythroid hyperplasia in the marrow specimen. In *B* the hypochromia, anisocytosis and poikilocytosis characteristic of thalassemia major are evident. The marrow shows corresponding variability in the cytoplasm of normoblasts, which are greatly increased in number. In *C* sickle cells are present, with erythroid hyperplasia in the marrow. In *D* the striking degree of target cell formation is seen as a manifestation of hemoglobin C-sickle cell disease. This chronic hemolytic anemia is accompanied by erythroid hyperplasia in the marrow.

occurring in the fetus and in the newborn infant. The most important of these is hemolytic disease due to iso-immunization with respect to the Rh factor; next in importance is hemolytic disease due to A or B iso-immunization. Hemolytic disease may occur occasionally as a result of hereditary spherocytosis or other conditions uncommon at this age. Hemolytic disease of the newborn due to Rh iso-immunization has long been known as *erythroblastosis fetalis*; this is an unsatisfactory term because it focuses attention on an aspect of illness which is neither specific nor always present in Rh incompatibility. It seems preferable to designate the various hemolytic conditions occurring in the neonatal period as *hemolytic disease of the newborn*, and then in each instance to identify additionally the category of the hemolytic disturbance.

Hemolytic disease of the fetus or newborn infant is generally due to an isohemagglutinin in maternal serum. The antibody produces agglutination *in vitro* of the red blood cells of the infant and of the father and identifies a factor in their erythrocytes which is lacking in the mother. Typically, Rh iso-immunization affecting the fetus is based upon (1) stimulation of an Rh-negative mother by the Rh-positive red cells of the fetus, or on occasion by transfusion or injection of other Rh-positive blood cells; (2) production by her of an anti-Rh agglutinin; (3) passage of this substance across the placenta into the circulation of the infant; and (4) destruction of fetal erythrocytes by specific reaction with the anti-Rh agglutinin. A similar train of events can result when the father and mother have an incompatibility in the ABO system. Clinical manifestations of hemolytic disease are, in fact, more commonly due to incompatibility of a group A or group B fetus with its mother than to Rh incompatibility. A or B iso-immune disease in the newborn is usually mild, however, and most often overlooked. Hemolytic disease may also be caused by incompatibility with respect to other antigens (Rh-Hr system) related to the original Rh antigen (D) or by incompatibilities within other blood groups such as Kell-Cellano (K-k) or the MNS group (factors S and s).

#### HEMOLYTIC DISEASE DUE TO RH INCOMPATIBILITY

**Genetics and Pathogenesis of Rh Sensitization.** Severe hemolytic disease is most often due to Rh or related incompatibilities.

Rh antigens may be regarded as associated with three linked pairs of genes, designated C and c, D and d, and E and e. Each gene determines a red blood cell antigen which has the same identification. The D antigen is responsible for most cases of hemolytic disease, and it is considered practical to regard the terms "Rh positive" and "Rh negative" as meaning "D positive" and "D negative," respectively. The offspring of a D-positive father and a D-negative mother will be D positive in all cases if the father is homozygous; i.e., if he has two D genes and is, therefore, DD. If the father is heterozygous, i.e., if he has only one D gene and is, therefore, Dd, each of his children has a 50 per cent chance of being D positive. Approximately 15 per cent of white persons are Rh negative, about 38 per cent are Rh positive homozygous, and about 47 per cent are Rh positive heterozygous.

Two conditions are prerequisite to the development of Rh antibodies in the Rh-negative mother: (1) Rh antigen (fetal or blood donor) must enter the maternal circulation; (2) the mother must be capable of producing the specific agglutinins. The transfer of small numbers of fetal cells across the placenta into the maternal blood undoubtedly occurs in all pregnancies. The most important initial sensitization in the mother may come, however, at the time of delivery of her first Rh-positive infant and placenta. A mother who is able to produce antibodies easily will likely do so in response to this stimulus, so that the first affected infant of the easily sensitized mother is likely to be her *second* Rh-positive infant. A miscarriage of the first pregnancy may also sensitize the mother. When antibody production is not excited by the first Rh-positive infant, the Rh-negative mother may respond to subsequent pregnancies. Instances are known, however, when twenty or more Rh-positive fetuses did not produce sensitization of an Rh-negative mother. There is evidence that a mother not easily sensitized may produce antibodies of low titer or pathogenicity, and that the affected infant will likely have a mild disease.

Transfusion of the Rh-negative woman with Rh-positive blood is a potent stimulus to sensitization. About half of all Rh-negative recipients of a single Rh-positive blood transfusion will produce Rh antibodies; multiple transfusions will sensitize 90 per cent or more of recipients. Hemolytic disease in the first-born Rh-positive infant of an Rh-negative



mother (5 to 10 per cent of cases) is most often the result of previous sensitization by blood transfusion or intramuscular injections of blood.

Besides the mother's exposure to antigen and her capacity for reactivity, other factors tend to limit the occurrence of hemolytic disease. Thus, when the husband of the Rh-negative woman is incompatible with her in the AB system as well as the Rh one, her sensitization to the Rh factor is less likely than if he is compatible with respect to A and B. Most Rh-positive men are heterozygous with respect to D, so that only half of their infants are antigenic in this respect to the mother. These factors and the tendency toward small families limit the occurrence of hemolytic disease in the Rh system to about one in every 200 births, whereas about 12 per cent of marriages in this country are of Rh-negative women with Rh-positive men.

**Pathology.** The pathologic changes are those of an acquired hemolytic anemia, but certain additional features related to the occurrence in fetal life and in the neonatal period are more or less peculiar and account for the designation erythroblastosis fetalis. There may be no abnormality in mildly affected infants, or there may be alterations which vary from mild splenomegaly to severe hepatosplenomegaly with extensive extramedullary erythropoiesis in liver, spleen, heart, skin and other tissues. Nucleated erythrocytes may be prominent in blood sinuses and vessels, and deposition of iron pigment may be widespread. In severely affected infants there may also be cardiac enlargement, hyperplasia of the islands of Langerhans, lipid infiltration of adrenals and atrophy of lymphatic tissue. Local accumulations of fluid may occur in serous cavities, or there may be generalized edema (hydrops fetalis, universal edema of the newborn), which is thought to be due to anemic cardiac failure, but may also be secondary to or aggravated by hypoproteinemia or anoxic shock. Hydrops fetalis is usually fatal before or just after delivery. The placenta of the hydropic infant is also edematous, large, friable and pale. Hydropic degeneration of the villi is seen microscopically.

These pathologic changes conspicuous in infants dead or dying at birth are found in varying degree in infants who die of hemolytic disease *after the first day of life*, in whom the most characteristic finding is *kernicterus*, or jaundice of the nuclear masses of

the brain in association with severe generalized icterus. This lesion may be seen only grossly, as faint to marked yellow pigmentation of the basal ganglia, amygdala, inferior olive, dentate nucleus of the cerebellum, vegetative centers of the medulla, or gray matter of the spinal cord. Kernicterus may be seen on the surface of the brain in the mammillary bodies, in the flocculi of the cerebellum and on the hippocampal gyrus. There is good evidence that the pigment is indirect-reacting bilirubin.

Microscopic changes of acute kernicterus are variable. Necrobiosis and pigment-laden ganglion cells are seen at times, but often there are no microscopic abnormalities. Some infants with clinical signs of kernicterus survive many weeks or years. In those whose brains have been examined as short a time as a few weeks after the neonatal period the presumed yellow stain is no longer present. There may, however, be gliosis in the areas thought to have been stained.

Kernicterus, which almost never occurs in infants not surviving at least thirty-six hours, is closely related to the degree of immaturity of the infant, the level of maternal antibody, the sex of the infant (more boys are affected) and the level of serum bilirubin attained within the first week of life.

Infants with a severe hemolytic component who live several days or weeks may have plugging of bile canaliculi and changes suggestive of early portal fibrosis.

**Clinical Manifestations.** About 15 to 20 per cent of Rh-positive infants of sensitized Rh-negative mothers have no clinical illness. Of those who do, the manifestations are largely the results of hemolysis. Jaundice is rarely manifest at the moment of birth, but may become evident within a few minutes or hours. The vernix may be normal in appearance or dark yellow, and may give a golden yellow appearance to a severely ill infant whose skin is not icteric. Anemia of some degree is generally present initially or within the first few days of life, and the peripheral blood usually contains immature cells, chiefly of the red cell series. Universal edema and general anasarca (hydrops fetalis) are usually found only in stillborn infants or in those dying shortly after delivery. The placenta is often normal or may be considerably enlarged with characteristic microscopic changes.

Increasing icterus often masks developing pallor, which may increase rapidly after the third day of life. The liver and spleen may

be moderately or greatly enlarged at birth, or may become palpable during the first week of life. Enlargement of the heart and hemic murmurs are common in severely anemic infants. Petechiae and a bleeding tendency occasionally occur in the first day or two.

Kernicterus (p. 1077), when manifest, usually appears between the second and sixth days of life. The signs are increasing lethargy, poor feeding, and loss of the normal Moro response. There may be spasms of rigidity and opisthotonos, during which the infant assumes a characteristic posture with arms stiffly extended and inwardly rotated, and fists clenched. These spasms are particularly likely to result from handling and are often accompanied by a sharp, high-pitched cry.

Most infants with kernicterus due to Rh incompatibility die within the first week, usually with the clinical findings of pulmonary hemorrhage. If they survive the newborn period, they almost always show evidence of extrapyramidal motor difficulties and usually mental retardation. Impairment of hearing is common. Kernicterus occurs predominantly in infants who are severely jaundiced, especially if they are premature by as little as a week or two, and has *no* close relationship to other aspects of the hemolytic process.

**Laboratory Data.** In subclinical illness no abnormality other than a positive Coombs' test (see p. 201) may be found to suggest a hemolytic process. In many instances, however, an outstanding characteristic is an excess number of nucleated erythrocytes in the peripheral blood in the first day or two of life (from the usual 200 to 2000 nucleated red cells to 10,000 to 100,000 per cubic millimeter). There may also be increased numbers of reticulocytes, red cells with nuclear fragments, and macrocytic erythrocytes well filled with hemoglobin. The anemia may be slight or severe in the first twelve hours of life and, as the disease progresses, may worsen rapidly. A profound anemia may ensue by the end of the first or second week in a child not anemic at birth. The nucleated erythrocytes tend to diminish and may even disappear by three to four days; their absence should not confuse the diagnosis.

The erythrocytes may show slight increases or decreases in osmotic fragility. Spherocytes are not common; erythrophagocytosis is frequently demonstrated.

The leukocytes vary from 15,000 to 30,000 per cubic millimeter, with immature forms of granulocytes and lymphocytes predominant. In unusually severe cases a leuke-

moid picture may be found, and the platelets may be reduced in number in the first few days. The bleeding time may, therefore, be prolonged, and a prothrombin deficiency may augment the bleeding tendency. After the first few days the platelets return to normal levels, and the bleeding tendency subsides.

In spite of the absence of jaundice at birth there is often an elevation of serum bilirubin above 3 mg. per 100 ml. in blood of the umbilical cord. In severely affected infants the level of bilirubin may rise at a rate of 1 mg. per 100 ml. per hour for the first three to four days unless treatment is instituted. The pigment is ordinarily almost entirely of the indirectly acting form, but in severely affected infants a substantial portion (up to 50 per cent) may give a direct reaction.

Between the first and fourth weeks of life it is not unusual for the feces to become clay-colored and the urine bile-tinged. This acholic state (the so-called *inspissated bile syndrome*) lasts only a few days or weeks. During the period of active hemolysis both the urine and the feces contain increased amounts of urobilinogen.

It is usually not possible to demonstrate the anti-Rh (anti-D) agglutinins in the mother's serum when the infant's Rh-positive cells are suspended in saline solution; cellular suspensions in several dilutions may be necessary in one of several colloidal media. Appropriate media are *adult* human serum (group AB), 20 per cent bovine albumin, combinations of the two, or certain other substances. Occasionally there will be interference by prozones in the serial titration of maternal serum in these media. Digestion of the Rh-positive erythrocytes by trypsin tends to circumvent this prozone activity; properly digested cells will agglutinate with virtually all anti-Rh antisera, even in saline solution. The slide agglutination test of Diamond and Abelson is another method of value in the demonstration of abnormal Rh agglutinins and detects most prozones. The antiglobulin technique ("indirect" Coombs' test) is the most sensitive method for detecting anti-Rh antibodies and prozone activity. No test for maternal anti-Rh activity is infallible; therefore no serum should be regarded as negative in a suspected case unless all possible tests using as many different reagents as possible (at least two different antiglobulin sera) have been repeatedly negative.

It is as important to show that the infant



is Rh positive as to show that the mother has anti-Rh agglutinins. This is usually not difficult by ordinary techniques, but occasionally the Rh-positive red blood cells of an affected infant are coated with anti-Rh antibody ("blocking antibody" or "incomplete agglutinin"), which prohibits their agglutination with anti-Rh serums in ordinary tests. Its presence can be demonstrated by the "direct" antiglobulin test, which is usually positive even in those infants who will have no clinical disease.

It is frequently possible to demonstrate anti-Rh agglutinins in the serums of affected infants, but only in serum or albumin media. The Rh-negative offspring of mothers who have incomplete anti-Rh agglutinins will also have such antibodies in their serums for a few weeks after birth in approximately the same titer as in the mother's serum. Their presence is not associated with illness, but transfusion of Rh-positive blood should, as always, be avoided.

**Diagnosis.** The definitive diagnosis of hemolytic disease of the newborn rests upon the *demonstration of an abnormal maternal agglutinin which has specific activity for the erythrocytes of the fetus or infant*. The tentative diagnosis should be made *before* the birth of the infant through demonstration of anti-Rh antibody in the blood of the Rh-negative mother; the diagnosis is confirmed when the newborn infant is shown to be Rh positive. There are no other clinical or laboratory tests which can make or exclude the diagnosis with confidence, since some affected infants destined to have severe illness appear normal at birth, and since the changes usually associated with hemolytic disease may be those of another process.

When antenatal study is inadequate, the diagnosis of hemolytic disease due to Rh incompatibility is suggested whenever conspicuous icterus occurs within the first thirty-six hours of life. If, in such circumstances, incompatibility in the Rh group can be excluded by laboratory tests, A or B incompatibility will likely be demonstrable or, rarely, hereditary spherocytosis.

Toxoplasmosis, cytomegalic inclusion disease, sepsis, congenital syphilis, thrombocytopenic purpura or congenital leukemia may occasionally resemble hemolytic disease clinically. Infants of diabetic or prediabetic mothers may occasionally have normoblastemia and hepatomegaly and perhaps other suggestive signs, but the hemolytic element is usually minimal or absent. A severe anemia in a new-

born infant, with no signs of hemolysis, may occur if fetal blood has been lost through retroplacental hemorrhage in abruptio placentae or during the second stage of labor.

**Course and Prognosis.** Hemolytic disease may result in (1) stillbirth, with or without hydrops fetalis; (2) death, as a rule within twenty-four hours after delivery, from overwhelming anemia, usually with hepatosplenomegaly, often with edema, but rarely with evidence of kernicterus; (3) death, usually after the first day and before the sixth day, from kernicterus and pulmonary hemorrhages; (4) survival, with kernicterus manifest in residual central nervous system damage; (5) recovery from an illness of mild to great severity, in which the pressing therapeutic problems, if any, will be either anemia or hyperbilirubinemia; or (6) spontaneous recovery, without clinical manifestation of illness.

If an infant with hemolytic disease survives the first week of life without development of signs of kernicterus, the prognosis is favorable, provided the development of severe anemia is carefully watched for and treated. After the first week of life the hemolytic tendency diminishes, but the bone marrow enters an aregenerative phase which may last four to six weeks. Improvement is signalled by a fairly marked reticulocytosis. Normal hemoglobin and erythrocyte levels are usually attained by the fifth month, and thereafter there are no sequels related to the anemia.

The prognosis of hemolytic disease in the first infant born after maternal sensitization is in general favorable. About 5 to 10 per cent of the first affected infants will be stillborn, but over 90 per cent of the remainder will recover with adequate treatment. When there is a history of a previously affected offspring, the prognosis for subsequent Rh-positive infants is somewhat less good; more will have clinical illness; the case fatality rate will be higher; and the stillborn rate will increase to 30 per cent. Often, but not invariably, the pattern in a given family is that of a nearly uniform degree of illness in the involved infants, which may be mild or severe.

Premature birth, even as little as two weeks, carries a high risk of kernicterus in affected infants. The incidence of kernicterus in spontaneously delivered affected infants treated only for anemia is about 5 to 15 per cent. The incidence can be reduced to less than 1 per cent by adequate exchange trans-

fusions or may be raised to 30 per cent or more by premature induction of labor when multiple exchange transfusions are not performed. The likelihood of kernicterus is closely related to the level of serum bilirubin; it rarely occurs when serum levels do not exceed 20 mg. per 100 ml.

**Treatment.** Management of the newborn infant with hemolytic disease properly begins with its *anticipation* through routine typing of every woman in each pregnancy and performance of at least one test for Rh antibody within four weeks of delivery of every Rh-negative woman. If no maternal anti-Rh antibody is detected at or after thirty-six weeks of gestation, no illness is to be expected in the infant. If antibody is found, irrespective of its titer, a potentially sick infant should be prepared for. Such preparation should include examination of the infant *at the moment of birth* for evidence of need for immediate treatment.

No method is known to alter favorably the sensitization of the mother prenatally, nor to increase the resistance of the infant to her antibodies. Cortisone has been used in pregnant, sensitized women and in affected infants, and ACTH in the latter; the results of such therapy have been disappointing in mothers and inconclusive in infants. There is no evidence that an Rh hapten has therapeutic properties.

The likelihood of stillbirth is to a great extent related to the titer of antibody in the mother, but irrespective of the titer the probability of stillbirth is high in the offspring of a mother who has had a previously stillborn infant as a result of hemolytic disease. Chown and Allen have shown that if stillbirth is to be prevented in a substantial number of infants of such mothers, then birth may need to be induced before term. Chown reports improved results when the delivery is as early as thirty-two to thirty-four weeks and the infant is treated by multiple exchange transfusions. Allen, however, has had unfavorable results in infants delivered by cesarean section at such an early date and recommends that the infant in such cases be delivered at thirty-seven weeks' gestation or as soon thereafter as medical induction of labor seems possible. When early delivery is contemplated in a mother who has had a previous stillbirth, any subjective sign of impending fetal death may be one of the best indications for immediate delivery.

Such early delivery adds the increased risk of kernicterus to the normal hazards of

prematurity. Within the past few years, however, it has become apparent that kernicterus can be prevented even in premature infants by *multiple* exchange transfusions. It is not to be inferred that multiple exchange transfusions offer easy control; hyperbilirubinemia may be controlled only with great difficulty in such infants, if at all, and as many as six or more exchange transfusions may be necessary.

The delivery of the potentially affected infant should be managed with as little sedation or anesthesia as possible, and the Rh type of the cord blood should be obtained immediately after delivery.

If the potentially affected infant *appears* by direct typing to be Rh negative, a direct antiglobulin test (Coombs') must be carried out to exclude the possibility that the infant is Rh positive with coated cells. If both tests are negative, *and if there are no clinical signs of hemolytic disease*, the infant may be considered Rh negative and free of illness.

If the infant is Rh positive and has clinical signs of illness, an *exchange transfusion with Rh-negative blood* should be carried out as soon as possible. An exchange transfusion should be carried out if there are no signs of clinical illness, if the maternal titer of anti-Rh antibodies is 1:64 or more, if the infant is two weeks or more premature or if there has been a previously affected infant with hemolytic disease of clinical severity requiring treatment, and especially if kernicterus has occurred. If none of these indications is present, the hemoglobin and bilirubin levels are determined *immediately* in the cord blood, and an exchange transfusion is carried out if the hemoglobin level is less than 14 gm. per 100 ml. or if the level of serum bilirubin is above 3.5 mg. per 100 ml.

If no indication for exchange transfusion exists at birth, the infant must be closely watched. If the infant becomes jaundiced within eight to twelve hours, or if the level of serum bilirubin exceeds 10 mg. per 100 ml. within the first twenty-four hours, an exchange transfusion is indicated. If, after an initial exchange transfusion, the level of serum bilirubin exceeds 18 mg. per 100 ml., a second exchange transfusion is indicated. Three or more exchange transfusions are occasionally necessary in severely affected or premature infants in order to keep the level of serum bilirubin within the safe range (below 20 mg. per 100 ml.).

It cannot be too strongly emphasized that adequate facilities must be available for mul-



multiple exchange transfusions in the hands of experienced personnel and for continuing and skillful nursing care. No hospital should accept responsibility for these infants which cannot provide on short notice an accurate determination of the level of serum bilirubin at any hour of the day or night.

The umbilical vein, which is usually available for at least five days, is the preferred channel for exchange transfusion. The infant is kept in a heated bassinet, and a polyethylene or polyvinyl cannula is placed in the umbilical vein under aseptic conditions. Small amounts (10 to 20 ml.) of the infant's blood and Rh-negative blood are withdrawn and injected, respectively, until about 500 ml. of blood have been exchanged. In some of the most severely ill infants there is an increase in venous pressure and in blood volume at birth; any further increase in blood volume may be very dangerous. When the venous pressure at the level of the umbilicus of the supine infant exceeds 8 to 10 cm. of saline solution, it may be advisable to carry out the exchange transfusion so that the infant's blood volume is decreased by as much as 50 to 100 ml., if his blood cell count is restored to normal. This situation is unlikely when the infant's clinical condition is good or when additional transfusions are required after the initial one.

Blood for exchange transfusions should be as fresh as possible and in no instance stored longer than four days, since there may be dangerous increases in plasma levels of potassium. *The blood should always be compatible with the mother's serum by the indirect antiglobulin technique* (Coombs' test). If this requires that group O blood be given to a group A or group B infant, A or B group-specific substance may be added. Blood is best given at body temperature and should not be exposed to higher temperatures after removal from the refrigerator.

Infants with hemolytic disease who do not require exchange transfusions should be watched carefully for at least three weeks for the development of anemia, even when they appear to have no clinical illness. Determinations of hemoglobin levels daily during the first week and twice a week for the next two weeks will usually suffice to determine an anemia requiring treatment. A fall in hemoglobin level below 9 gm. per 100 ml. within the first two weeks of life can usually be considered an indication for a small transfusion of sedimented erythrocytes. After three weeks of age a somewhat lower level of hemoglobin

can be tolerated, since the aregenerative phase of this disease ends at five to six weeks. At this time a reticulocyte response occurs, and the hemoglobin level, which may now be 7 to 7.5 gm. per 100 ml., begins to rise. Transfusion is not ordinarily necessary between three and six weeks of age unless the level of hemoglobin is below 7 gm. The infant does not need iron or other antianemic substances. Infants who have received exchange transfusions rarely need additional transfusions for anemia.

Although anti-Rh agglutinins may be demonstrated in the milk of mothers who have appreciable titers of these agglutinins in their serums, they are not a contraindication to breast feeding. It is doubtful whether ingested agglutinins significantly affect circulating erythrocytes.

#### HEMOLYTIC DISEASE DUE TO A OR B INCOMPATIBILITY

Relatively mild hemolytic disease associated with A or B incompatibility appears to be at least as common as clinical Rh incompatibility, but usually escapes attention because it is rarely accompanied by significant anemia, and extremely rarely by hydrops fetalis. The main clinical manifestation is jaundice ("icterus praecox"), which usually has its onset within the first thirty-six hours of life. Hepatosplenomegaly is mild or absent. Kernicterus occurs with some frequency (perhaps 5 per cent) and may be more common with B incompatibility than with A. The first-born is affected as often as subsequent infants.

There is usually little or no anemia, but there may be spherocytosis and pronounced reticulocytosis. The leukocytes and platelets show no distinctive changes. The direct antiglobulin test (Coombs' test) is usually negative, but may be weakly positive. The coated cells of the infant are usually susceptible to spontaneous agglutination in adult serum (group AB) or in certain other media (glues). Anti-A or anti-B in maternal serum is easily demonstrable as an agglutinin in saline solution and may act as a hemolysin against appropriate cells. The *titer* of ordinary (saline-active) anti-A or anti-B agglutinins may be high or within the normal range, but has no diagnostic or prognostic significance. Witebsky has shown, however, that in nearly all cases of clinical A or B incompatibility other A or B antibodies are generally present which remain active in adult serum or in certain other media after

the saline-active agglutinin has been neutralized by its group-specific polysaccharide. These are the so-called immune anti-A or anti-B antibodies. They may at times be demonstrated, after neutralization, by using *adult* erythrocytes of group A or B digested by trypsin or by the indirect antiglobulin technique, using adult cells.

Hemolytic disease due to A or B incompatibility is not commonly anticipated antenatally unless a previous infant in the family has been affected. Attention is usually called to the affected infant by the early onset of icterus. Laboratory examination of the infant's and the mother's blood will establish whether potential incompatibility exists, and, if so, with respect to what blood antigen. Unanticipated Rh incompatibility and icterus neonatorum will most often need to be differentiated. Rarely, hereditary spherocytosis will simulate hemolytic disease due to A or B incompatibility and may be especially difficult

to distinguish if coincidental A or B incompatibility exists.

Because in all these conditions kernicterus may be associated with a high level of bilirubin, the observation of jaundice in a newborn infant should always be considered an indication for critical appraisal; if he is less than thirty-six hours old, it should be considered a pediatric emergency.

*Treatment* of A or B incompatibility is aimed solely at prevention of kernicterus. The level of serum bilirubin is probably the most effective guide to treatment. Exchange transfusion is done as necessary to keep the bilirubin level below 20 mg. per 100 ml. Group O blood of appropriate Rh type is used. A or B substance may be added, so that the additional anti-A or anti-B in the blood of the donor will aggravate the condition as little as possible, but it may be more important to show that the donor blood does not have "immune" anti-A or anti-B agglutinins.

## POLYCYTHEMIA, ERYTHROCYTOSIS AND ERYTHREMIA

The term "polycythemia" designates a higher than normal level of circulating erythrocytes and hemoglobin. Polycythemia is unusual in children, but may arise as a result of many different conditions.

Since the arterial oxygen content is a controlling factor in the production of hemoglobin and of erythrocytes, many conditions associated with reduced oxygen content of arterial blood will lead to a compensatory increase in the number of erythrocytes released from bone marrow. This *true* increase in numbers of circulating red blood cells is spoken of as *erythrocytosis*. By contrast, severe loss of fluid from the vascular compartment may result in a *relative* polycythemia. Such losses of fluid may occur with persistent vomiting or diarrhea, profuse sweating, burns or adrenal cortical insufficiency.

In cyanotic congenital heart disease erythrocytosis occurs as a result of decreased arterial oxygen content and may reach extreme degrees. Erythrocytosis rarely occurs in acquired heart disease, but may be seen in severe mitral stenosis when the diffusion of oxygen across thickened alveolar membranes is impaired. Other chronic pulmonary conditions which may be associated with compensatory erythrocytosis are emphysema, silicosis, cavernous hemangiomas, arteriovenous fistulas and neoplasms.

Chronic mountain sickness (*Monge's dis-*

*ease*), which occurs in persons living at high altitudes, is characterized by a striking erythrocytosis, headache, paresthesias, lethargy, and severe pain in the extremities. The illness abates in an environment of higher oxygen content.

Cushing's syndrome and certain brain tumors for some unknown reason may be associated with erythrocytosis, which is relieved upon correction of the primary process.

Prolonged erythrocytosis is accompanied by an increased demand for nutrients necessary for the production of erythrocytes and hemoglobin. An iron deficiency anemia may be present paradoxically even when the hemoglobin level is 16 to 18 gm. per 100 ml., as in children with cyanotic congenital heart disease. The judicious administration of iron is indicated in such instances. The hypochromia associated with erythrocytosis in thalassemia minor is *not* due to iron deficiency and should *not* be treated with iron.

*Erythremia*, or *polycythemia vera*, is characterized by overactivity of erythroid precursors in bone marrow in response to an unknown stimulus, which leads to an absolute increase in the circulating erythrocytes and usually in platelets. The disease is extremely rare in children. Clinical features in children resemble those in adults. A few instances of familial erythremia have been recorded.



## DISORDERS OF THE LEUKOCYTES

The peripheral blood contains leukocytes of three distinct types: granulocytes, lymphocytes and monocytes. All leukocytes are motile cells having characteristic ameboid activity. Each reacts in its own manner to various stimuli; all serve the body principally as agents of defense. Variations in their number and kind are significant indicators of the reaction of the body to many situations.

Recent studies indicate that three to five days elapse from the beginning of differentiation of the most immature precursor of the granulocyte to the delivery of a mature cell into circulating blood. The life span in the peripheral circulation is four to six days. The basophilic leukocyte and eosinophilic leukocyte have somewhat longer circulating spans: approximately seven to ten days.

The lymphocytes include two distinct kinds of cell with strikingly different life spans. A short-lived group has a mean span of three to four days; a larger group remains in the circulation 100 to 200 days. Abrupt changes in lymphocyte numbers, including such as may be induced by ACTH, generally involve the short-lived cells. The differences in life span of lymphocytes are not clearly related to differences in morphology.

Only a small fraction (estimated 1:400) of the total leukocyte population is in the circulation at one time. The reservoir of these important defense units is, therefore, ordinarily large.

The leukocytes contain zinc, vitamin C, thiamine, folic acid and alkaline phosphatase; alteration in cellular content of these materials is found in leukemia, and offers a field for further investigation.

**Granulocytes.** Granulocytes are produced in bone marrow. Both folic acid and vitamin B<sub>12</sub> seem to be necessary for their production. No other clearly defined nutritional requirement is known. Granulocytic leukocytes include the neutrophilic, eosinophilic and basophilic polymorphonuclear granulocytes.

The *neutrophilic* cells serve primarily as phagocytes, particularly in relation to pyogenic infections. When such infections occur, the number of neutrophilic cells in the blood is increased by mobilization from the marrow, and they accumulate in large numbers at the sites of acute inflammation, which they tend to localize. Other stress-provoking stimuli,

including vigorous exercise, may augment the production of neutrophils. Infants and children more readily deliver immature cells than do adults under similar stressful circumstances; myelocytes and even promyelocytes may be seen in peripheral blood. In severe infections or other toxic states the neutrophils may contain fine, deeply basophilic granules (toxic granules) or larger basophilic masses (Doehle bodies). Administration of ACTH and cortisone causes an increase in neutrophilic cells. Less common causes of neutrophilic leukocytosis in children include certain severe disturbances such as uremia, acidosis, burns, poisonings, infarctions and anoxia associated with hemorrhage or hemolysis. Malignant overproduction of neutrophils and their precursors occurs in myeloid leukemia.

In severe sepsis or extremely toxic states an unexpected leukopenia may indicate an inability to respond to a stressful situation (p. 964).

The functions of the *eosinophils* are poorly understood, but they seem closely related to immunologic mechanisms in the body, and are particularly involved in allergic conditions and reactions to invasion of tissue by parasites. The levels of eosinophils in the peripheral blood are strikingly related to the activity of the pituitary and adrenal cortical hormones. Under a variety of conditions of stress, or with the administration of these hormones, the number of eosinophils in peripheral blood shows a sharp decline. The disappearance of eosinophils from the peripheral blood in acute infections and other toxic states indicates the seriousness of the illness, and the reappearance of them often heralds clinical improvement.

The parasitic infestations associated with increase in eosinophils are predominantly those in which there is invasion of body tissues by parasites. Such diseases include trichinosis, echinococcus disease and infestation with *Toxocara canis* or *cati*.

Eosinophils are increased in a variety of allergic states and in certain hematologic disorders such as leukemia, pernicious anemia and Hodgkin's disease. Familial eosinophilia has been described.

*Basophils* occur in small numbers in the blood of children. Their function is unknown, and they appear to have clinical significance

only in that they are consistently elevated in chronic myelogenous leukemia in children.

**Lymphocytes.** Lymphocytes are produced by lymphoid tissue throughout the body, including the thymus, lymph nodes and bone marrow. Active production of lymphocytes is associated with hypertrophy of lymphoid tissue. These cells are closely related to processes in the body concerned with resistance and immunity to infection. The plasma cell is regarded as the probable source of the gamma globulin fraction of plasma proteins. ACTH and cortisone promote lysis of lymphoid tissue and of short-lived lymphocytes, presumably with release of immune bodies. The thymus and lymph nodes regress rapidly in size with treatment by these agents. In the event of decreased function of lymphocytes it might be expected that humoral immunity would be low. Agammaglobulinemia may represent a special form of defect in lymphocyte function.

Lymphocytes are likely to be found in association with chronic or subacute inflammatory processes, especially of a nonpyogenic variety. Like the eosinophil, they are increased in numbers in the convalescent phase of many infectious conditions.

*Relative* increases in the lymphocyte count may occur with many conditions when granulocytes are reduced in number. Such relative increases should be clearly differentiated from actual increases in numbers of circulating lymphocytes which may at times accompany such infections as mumps, German measles, tuberculosis, brucellosis and syphilis. Lymphocyte production is increased in a number of specific infections, such as pertussis, acute infectious lymphocytosis and infectious mononucleosis.

Malignant overproduction of lymphoid tissue occurs as lymphatic leukemia, lymphosarcoma and plasma cell leukemia.

**Monocytes.** The function of the monocyte is not known. An increase in their number is associated with such chronic bacterial infections as tuberculosis, typhus, brucellosis and subacute bacterial endocarditis, many protozoan infections and certain xanthomas and Hodgkin's disease. There is a marked monocytosis in monocytic leukemia.

**Leukopenia.** In certain overwhelming infections failure of production or mobilization of leukocytes with the occurrence of a leukopenic state is a grave prognostic sign. On the other hand, certain bacterial infections, such as typhoid and paratyphoid fevers, and many virus and rickettsial diseases

are characteristically accompanied by a leukopenia. The mechanism responsible for leukopenia under these circumstances is poorly understood, though a number of physical and chemical agents are known to depress leukopoiesis.

In a variety of conditions accompanied by splenomegaly (Gaucher's disease, Banti's syndrome, and so forth) the sequestration of large numbers of leukocytes in the spleen leads to leukopenia.

A leukopenia may also accompany severe malnutrition, and regularly accompanies the specific nutritional deficiencies of folic acid, vitamin B<sub>12</sub>, pantothenic acid, riboflavin and protein. Aplastic anemias are characteristically accompanied by inadequate production of white blood cells.

Glanzmann et al. have described three patients in whom a striking *lymphopenia* (*alymphocytosis*) was present with extensive infection of the alimentary tract and respiratory organs with *Monilia*. All three cases ended fatally.

In the early phases of anaphylactoid shock and after the intravenous administration of certain colloids as gelatin, globulin and fibrinogen, a reduction in the number of circulating lymphocytes appears to be due to their redistribution in the body. Leukopenia may also be associated with the production of antibodies against the white blood cells. The situation is analogous to that existing in thrombocytopenia, in which auto-immune bodies against platelets are found, or in acquired hemolytic anemia, in which there are auto-immune bodies against red blood cells.

## AGRANULOCYTOSIS

### (MALIGNANT NEUTROPENIA)

The term "agranulocytosis" is commonly used for a syndrome characterized by fever and acute necrotizing lesions of the pharynx associated with leukopenia and pronounced granulocytopenia, but without significant anemia or thrombocytopenia. Agranulocytosis may follow the administration of small amounts of certain coal tar derivatives, particularly amidopyrine. It has also been related to the administration of barbiturates, sulfonamides, dinitrophenol, thiouracil, trimethadione and Mesantoin. The fundamental process may be an allergic or hypersensitive state. The wide appreciation of the dangers of drugs causing agranulocytosis has led to a greatly lowered incidence of this disease.

**Clinical Manifestations.** Fatigue and



weakness are often the initial symptoms, which may then be followed by the sudden onset of a much more striking illness with chills, fever, severe prostration and irritability. Within a few hours, or a day or two, the more characteristic features of agranulocytosis develop; these are extensive necrotic and ulcerative lesions in the skin, the oral cavity, gastrointestinal tract, vagina or uterus. The tissues of the mouth and pharynx are the ones commonly involved. Mental confusion may develop, and coma soon follows; the severely involved patient may die within three to five days. Antibacterial therapy may alter the course of this devastating illness and permit recovery.

**Laboratory Data.** The total leukocyte count is depressed and is usually in the range of 1000 to 4000 cells per cubic millimeter. The leukocytes present are principally lymphocytes, with many basophilic forms. Anemia and thrombocytopenia are not present. Bacteriologic cultures of the blood and of the areas of local infection will usually reveal pathogenic organisms.

The bone marrow reveals a reduction in granulocyte precursors, especially the more mature ones, with normal erythropoiesis and normal numbers of megakaryocytes.

**Diagnosis.** Careful inquiry about the ingestion of an agent known to be causative of agranulocytosis is of utmost importance. Aplastic anemias are accompanied by thrombocytopenia and anemia. The combination of lymphadenopathy, splenomegaly, thrombocytopenia, anemia and the presence of immature leukocytes in the peripheral blood will suggest acute leukemia; examination of bone marrow may be diagnostic. In infants and children with overwhelming sepsis, leukopenia and granulocytopenia may be difficult to differentiate from agranulocytosis.

**Course and Prognosis.** Untreated, acute agranulocytosis ordinarily runs a rapidly fatal course. Chronic forms of agranulocytosis have been observed, however, which follow a protracted course. Mortality rates have been reduced from previous rates of 75 to 90 per cent by appropriate antibiotic therapy and other supportive measures.

Patients who have agranulocytosis from therapy with a particular drug are likely to get the disease again if the causative agent is ingested later.

**Treatment.** Appropriate treatment of the infection with antibiotic drugs is the prime factor in the therapy of agranulocytosis. Direct attempts to stimulate production of

granulocytes in bone marrow have met with failure. Transfusions of whole blood are of little value. Adrenal steroids and ACTH are of doubtful benefit.

## PERIODIC NEUTROPENIA

### (CYCLIC NEUTROPENIA)

Periodic neutropenia is a rare disease of unknown cause characterized by regularly recurring episodes of neutropenia. The onset is usually in infancy or childhood, although some affected persons have not been detected until old age. Symptoms are related to infection, which may take the form of stomatitis, conjunctivitis, furunculosis, or localized abscesses of the skin. Lymphadenopathy, fatigability and fever are often associated. The neutropenia recurring at intervals of about three weeks and lasting four to seven days is often associated with infection. Agammaglobulinemia is suggested, and Good has observed the two conditions in the same patient. Hypergammaglobulinemia accompanying the neutropenia, but fluctuating independently of it, has also been observed.

The erythrocyte count and blood platelets are not affected. The leukocyte count usually falls to 4000 or less per cubic millimeter and the percentage of neutrophilic leukocytes to less than 15 per cent during the period of neutropenia. The bone marrow, which is normal between episodes, shows failure of maturation of leukocytes beyond the early metamyelocyte stage during the neutropenic phase.

*Treatment* is nonspecific and supportive. The infection can often be controlled by prophylactic antibiotic therapy as the period of neutropenia approaches. The neutropenia has been prevented in some patients by administration of ACTH. Splenectomy is reported to have been beneficial.

## CHEDIAK-HIGASHI SYNDROME

An increasing number of infants are being found who have an abnormality of granulocytes first described by Chediak in 1952. The condition is genetically transmitted, probably as a recessive trait. The abnormality of granulocytes is associated with progressive granulocytopenia, increasing susceptibility to pyogenic infections, and a fatal termination in early childhood. Associated stigmata include partial albinism with photophobia, decreased production of tears, and excessive sweating. There is increasing

splenomegaly and moderate generalized lymphadenopathy. An unusual encephalomyelitis observed at postmortem examination was reported by Donohue and Bain.

## THE LEUKEMIAS

Leukemia is a fatal disease of unknown cause characterized by uncontrolled proliferation of leukocytes and their precursors.

The various forms of leukemia are classified according to the anticipated acute or chronic course of the disease and according to the predominant type of cell involved. Leukemia in childhood is usually an acute disease of relatively short duration (over 90 per cent), but chronic leukemia is being recognized with increasing frequency in children and may run a course of several years. The response of some children with leukemia to suppressive therapeutic agents makes separation into acute or chronic forms increasingly meaningless. The type of cell predominantly involved in leukemia offers a basis for classification. Myelocytic, lymphocytic, monocytic and other much less common leukemias (eosinophilic, megakaryocytic) are differentiated. In children, however, the predominating cell is often so undifferentiated morphologically ("stem cell") that a specific diagnosis according to origin of the cell cannot be made.

Leukemia occurs more often in the first five years of life than at any other age period, with a second peak at eight to nine years. Congenital leukemia is rare.

Leukemia is somewhat more common in males than in females, but not to the same degree in children as in adults. There are no detectable relationships to race, geographic factors or social or economic conditions. An unexpectedly high incidence of acute leukemia is found in association with mongolism, especially on a congenital basis.

**Pathology.** The pathologic changes in leukemia are related to the extensive primary proliferation of leukopoietic tissue and to secondary changes consequent upon disturbed function of involved organs.

Lymph nodes, spleen, liver and kidneys are usually enlarged, owing to the large amounts of proliferating leukemic tissue. There is ordinarily almost complete replacement of fatty marrow by grayish-red leukemic marrow. On section the normal splenic architecture is lost in an overgrowth of homogeneous red pulp. The liver is smooth and often made grayish-yellow by the excessive content

of leukopoietic tissue. The kidneys show leukemic infiltration extending along the medullary cords into the cortex. Extensive proliferation of leukemic foci, which is being found with some frequency in and about the central nervous system, may depend upon failure of antileukemic agents to cross the blood-brain barrier in effective concentration. Osseous changes can probably be explained by vigorous osteoblastic and osteoclastic activity and by destruction of bone by leukemic cells in areas which become free of endosteal covering.

Extensive hemorrhages may occur into parenchymal organs, into the retroperitoneal space, into subserosal areas of the bowel and pleura and into the central nervous system. Areas of ulceration and of extensive secondary infection may be encountered anywhere in the body.

**Clinical Manifestations.** The symptoms of leukemia are due (1) to hypermetabolism associated with rapid growth and destruction of leukemic tissue, (2) to bone marrow dysfunction, and (3) to disturbances of organs involved in leukemic proliferation.

The increase in metabolism is manifest by fever, weight loss, weakness and fatigue. Evidence of bone marrow dysfunction is reflected by the inability to produce adequate numbers of erythrocytes, platelets and normal leukocytes. Pallor and weakness accompany anemia; bleeding and easy bruising are associated with thrombocytopenia; and extensive infections, especially of the oral cavity and pharynx, are associated with the deficiency in normal granulocytes. These symptoms may develop with striking rapidity early in the course of leukemia in children. The overgrowth of leukemic tissue in various organs will give rise to local and systemic symptoms of varying severity. Lymphadenopathy and splenomegaly may be found early. Bone pain due to extensive osseous involvement is often a striking feature. Leukemia in other organs may lead to enlargement of liver, kidneys and testes and to symptoms of central nervous system involvement. Icterus, altered protein metabolism and azotemia may reflect functional disturbances, but usually not until late in the course.

Skin infections are common. Necrotic erythematous areas may be encountered late in the course of the disease in the submandibular and axillary areas as an extension from involved lymph nodes. Leukemic involvement of the skin is rarely seen in chil-



dren, but may occur as small yellow, well circumscribed, elevated nodules, which appear with amazing rapidity, especially in infants with myelocytic leukemia.

The hemorrhagic tendency universally present in acute leukemia is strikingly manifest by petechiae, purpura and extensive ecchymoses. Bullous, necrotic lesions may develop which rapidly become secondarily infected.

The mucous membranes are often involved; gums and oral mucous membranes, especially, may be involved early in bleeding and in necrotic ulcerations likely to be covered with a characteristic gray membrane. The gums may be greatly hypertrophied and at times painful.

Enlargement of lymph nodes in acute leukemia is usually not marked and may be absent. Deep-seated lymph nodes are usually more strikingly enlarged than the peripheral ones. Mediastinal involvement may be extensive and infrequently lead to respiratory distress or to pleural effusion. Enlargement of abdominal nodes may be extensive and may explain the rather common episodic abdominal pain.

Enlargement of the spleen is usually present in acute leukemia, but not so marked as in chronic leukemia. It usually has a soft edge and is often somewhat tender.

Though early symptoms referable to the gastrointestinal tract are unusual, anorexia, nausea and abdominal pain are often present. A hemorrhagic diarrhea may be troublesome, and extremely painful necrotic ulcerative lesions of the lower rectum and perirectal areas may occur when agranulocytosis is marked.

Hematuria may be the presenting complaint, and painful episodes of ureteral colic may occur. The kidneys are usually enlarged, and there may be alterations in the pyelogram. Overgrowth of leukemic tissue and extensive hemorrhage may lead to renal failure.

Patients with acute leukemia are frequently first seen because of bone pain or arthralgia. Roentgenograms usually demonstrate changes in the bones of symptomatic areas.

Retinal hemorrhages are common. Exophthalmos may result from retrobulbar hemorrhage or leukemic overgrowth, and bleeding into the lids, vitreous or scleras is not unusual. Deafness may develop after hemorrhage into the labyrinth or auditory nerve. Intracranial hemorrhage is the most common immediate cause of death in children with acute leukemia. Proliferative or hemorrhagic in-

volvement of the central nervous system may lead to a variety of symptoms in acute or chronic leukemia, depending on the areas of the brain or spinal cord involved.

*Chronic leukemia* is uncommon in children, is almost always myelocytic in origin and usually has its onset after the age of eight years. Males seem to be more frequently affected than females. Chronic lymphocytic and monocytic leukemias are rarely, if ever, seen in children.

The onset of symptoms in chronic myelocytic leukemia is insidious, and first knowledge of it often comes from examination of the blood for an unrelated circumstance or because of an asymptomatic splenomegaly. Splenomegaly, slight anemia, and weakness are the only consistent manifestations; bone pain is an occasional complaint. In early infancy such manifestations of disturbed hematopoiesis as thrombocytopenia and hemorrhage may be more prominent.

Splenic enlargement is progressive and may attain enormous proportions, giving rise to anorexia, vomiting and left upper quadrant discomfort. Progressive anemia of moderate degree with pallor and weakness may develop over a period of months. Susceptibility to infections and to hemorrhagic manifestations does not usually occur until late. Terminally, the child has fever, infection, rapidly progressive splenomegaly and hemorrhagic symptoms with a predominance of immature forms in the blood and extreme leukocytosis.

**Laboratory Data.** A diagnosis of leukemia should never be made if the laboratory evidence is equivocal. Abnormalities are usually found in peripheral blood, bone marrow, certain chemical constituents of the blood and in roentgenograms of the long bones.

A moderate to severe normochromic anemia with absent reticulocyte response is usual. There is nearly always a marked thrombocytopenia in acute leukemia, but in chronic myelocytic leukemia there may be a marked increase in platelets with counts up to 1 million per cubic millimeter or more.

Leukopenia is found at the initial examination in over 65 per cent of children with acute leukemia; occasionally there are moderate to marked degrees of leukocytosis. In chronic leukemia counts over 200,000 per cubic millimeter are common. Much more important than the numbers of leukocytes are the morphologic characteristics of the leukemic cells. Careful examination of properly prepared blood films will almost always reveal immature and morphologically abnor-

mal leukocytes. The origin of the abnormal leukocytes should be identified if possible, since certain therapeutic agents are more effective against one cell type than another. In acute leukemia, however, this is most often impossible. The majority of mature cells in peripheral blood are lymphocytes, but this does not mean that the immature forms are necessarily of lymphatic origin, but rather that the leukemic overgrowth in marrow has reduced the production of normal granulocytes.

In chronic myelocytic leukemia identification of the cell type is usually not difficult, the great increase in leukocytes consisting of mature granulocytes, metamyelocytes, myelocytes and, at times, a few myeloblasts. Eosinophilic and basophilic granulocytes are also ordinarily increased.

*The diagnosis of leukemia should not be made without examination of aspirated or surgically removed bone marrow.* Except in most unusual circumstances the marrow will show overgrowth of abnormal leukopoietic tissue; few normal hematopoietic elements are found. Megakaryocytes and erythropoietic precursors are greatly decreased. At times the bone marrow in acute leukemia may present the picture of aplastic anemia without evidence of abnormal leukopoietic tissue. In such instances the diagnosis of leukemia *should be deferred* until confirmation is possible, and exhaustive search should be made for other causes of aplasia of marrow, which might be amenable to therapy.

In chronic myelocytic leukemia the disturbance in bone marrow is less striking, but the experienced morphologist can readily recognize alterations in myeloid cells and an interference in erythropoiesis. Megakaryocytes may be greatly decreased or present in abnormally high numbers. Differentiation from granulocytic leukemoid reactions may be difficult.

Excessive production and destruction of leukocytes lead to an elevation of the uric acid level in the blood, which may be augmented by leukocytotoxic agents. Urinary excretion of uric acid may be so much increased by a rapid reduction of a high leukocyte count that precipitation of urate crystals may obstruct the urinary tract.

The blood levels of glutathione, phosphorus and alkaline phosphatase are also commonly increased. Increases in the pressure, protein content and leukocyte count of the cerebrospinal fluid may also occur.

A wide variety of roentgenographic abnor-

malities may be demonstrated in acute and in chronic leukemia. These include enlargement of mediastinal lymph nodes, pneumonitis, pleural effusion and enlargement of the liver, spleen or kidneys. Certain alterations in bones are highly suggestive of leukemia and are found in over two thirds of children with the disease. There are four general types of lesions: osteolytic lesions, irregular areas of osteosclerosis, areas of diminished density traversing the metaphysial ends of long bones, and subperiosteal new bone formation. Such lesions may be responsible for spontaneous fractures and for collapse of vertebral bodies. The skeletal lesions may disappear in response to antileukemic or to local roentgen ray therapy.

**Differential Diagnosis.** The bone pain and arthralgia of early leukemia often suggest osteomyelitis, rheumatic fever, Still's disease or brucellosis. Leukemia may be suggested by the lymphadenopathy of tuberculosis, pyogenic lymphadenitis, Hodgkin's disease, lymphosarcoma or cat-scratch fever. The generalized lymphadenopathy and cellular changes in the blood of infectious mononucleosis may require bone marrow biopsy for differentiation.

Hemorrhagic phenomena in the form of petechiae and purpura may be the presenting symptoms in acute or advanced chronic leukemia and may suggest scurvy, aplastic anemia, idiopathic thrombocytopenic purpura or purpura of other causes. The differentiation of leukemia from aplastic anemia may be particularly difficult and should not be attempted without a generous specimen of surgically removed marrow.

The increased number of lymphocytes in the blood in pertussis, infectious mononucleosis or infectious lymphocytosis may suggest leukemia and must be differentiated by clinical and laboratory means.

**Course and Prognosis.** Without antileukemic therapy the course of acute leukemia is generally one of progressive deterioration. Infections of the mouth and pharynx leading to pneumonia or septicemia may result in early death. Intracranial hemorrhage is the most common terminal event. In somewhat less than 10 per cent of patients a period of complete normality may occur without "specific" therapy, during which time it is impossible to find clinical or laboratory evidence of the disease. Such "spontaneous remissions" usually follow infections, or the transfusion of large quantities of blood, and usually last only a few weeks. The duration of acute leu-



kemia may be only a week or so, but is more likely to be six to nine months. With suppressive antileukemic therapy, life can be prolonged in the majority of instances for months to a year or so. Chronic myelocytic leukemia is compatible with relatively normal activity for two or more years.

**Treatment.** When the diagnosis has been made beyond any possible doubt, the nature and prognosis must be frankly discussed with the parents. Efforts should then be directed to attaining as many happy and comfortable days as possible for the child.

Supportive measures such as blood transfusions, chemotherapy and sedative and analgesic drugs should be used judiciously. Antibiotic drugs should be used when indicated, but prolonged administration should be avoided, since it may lead to infections with resistant organisms. Prophylactic use is unwarranted. The tetracyclines should not be used in conjunction with the folic acid antagonists, since they may counteract their effect.

A number of agents may have a depressant or lytic effect of variable duration upon the proliferation of leukemic tissue. Such agents include the folic acid antagonists, cortisone, and a purine analog, 6-mercaptopurine. In chronic leukemia temporary modification of the leukemic process may also be obtained through the use of urethane, roentgen ray therapy or certain compounds related to nitrogen mustards.

The introduction by Farber of antagonists of folic acid to the group of antileukemic agents has been the most significant therapeutic measure to date. These agents are thought to exert their beneficial effects by interference with the use of folic acid by intracellular enzyme systems. Leukemic cells require much more folic acid than normal cells, and their division is impaired with antimetabolite therapy, while metabolism of normal cells is not significantly altered. With the administration of these antimetabolites from 25 to 50 per cent of children with acute leukemia experience complete remissions, and an additional 20 or 30 per cent have significant clinical improvement with partial remissions. Of the many analogs of folic acid, aminopterin and Methotrexate are most effective; owing to its lesser toxicity, the latter is most often used. Methotrexate is given orally in doses of 2.5 to 5 mg. a day. The therapeutic effect may be noted within a few days, but usually a remission will occur only after two to five weeks of therapy. When remission has occurred, therapy may be con-

tinued with smaller doses. Eventually the response to therapy becomes less satisfactory, and other therapeutic agents should be substituted.

In toxic doses the antagonists of folic acid exert devastating effects upon normal cells. Those of the gastrointestinal mucous membranes appear to be most susceptible. Nausea, vomiting, diarrhea and ulceration of the buccal mucous membranes are the common early signs of toxicity and necessitate prompt discontinuation of therapy. Hematopoietic activity may also be suppressed by these agents. Peripheral blood cell counts should therefore be performed frequently, and therapy discontinued before dangerous leukopenia or thrombocytopenia develops.

Cortisone in divided doses totaling 100 to 200 mg. daily is also helpful in the management of acute but not chronic leukemia; nearly all patients receive some clinical benefit, and about 60 per cent show hematologic improvement as well. Improvement is often of only a few weeks' duration.

The purine analog, 6-mercaptopurine, induces temporary remission in acute leukemia and in some cases of chronic myelocytic leukemia. The drug is given in doses of 2 mg. per kilogram of body weight per day until a fall in leukocyte count is observed. Since leukocytes may be very sensitive to this drug and since the maximal effect of a given dose is often delayed a few days, the leukocyte count should be closely followed during therapy and the drug discontinued at the first sign of a decrease in the number. The chief manifestation of toxicity is interference with hematopoiesis, which may be severe and irreversible. If no response is obtained within three to four weeks, the dose may be doubled, but this is rarely necessary.

Among other cytotoxic agents which have been used for chronic leukemia are a nitrogen mustard, such as CB1348, triethylene melamine (TEM), thio-triethylenephosphoramide (thio-TEPA) and urethane. These substances are contraindicated in acute leukemia in children.

Roentgen ray therapy may be helpful in temporary control of the recurrent bone pain. Twenty-five to 50 roentgens over the site of pain on three or four successive days will usually produce relief. Roentgen ray therapy may also be useful in chronic myelocytic leukemia.

In acute leukemia the choice of therapeutic agents will depend upon the clinical status, hematologic findings and previous therapy.

The following generalizations may be helpful, but individualization of therapy is essential. If the child when first seen is acutely ill with a leukocyte count of more than 50,000 per cubic millimeter, cortisone is given, since an early beneficial clinical effect may be expected. If the leukocyte count is low and the patient is not in poor clinical condition, therapy with folic acid antagonists is preferable. Benefit is apt to be of longer duration than that obtained from cortisone, but may be delayed two to three weeks in appearance.

When, after prolonged or recurrent courses of therapy, the patient fails to respond to folic acid antagonists, 6-mercaptopurine may be given if the patient is not in a poor clinical state. If the leukemic process is active and the patient's condition poor, cortisone is given initially. When there is no longer a response to administration of 6-mercaptopurine, folic acid antagonists may be given again in the hope that resistance to the drug may have

lapsed. Ultimately leukemia becomes unresponsive to any currently available agent.

The child with leukemia is happiest and most comfortable in his usual environment. Therapy should aim at minimal hospitalization, with as few diagnostic and therapeutic procedures as are compatible with good care. The attitudes of parents and friends toward the seriously ill child should permit him to live as normal a life as possible. Pampering, segregation, puzzling attitudes toward the child and unusual arrangements by which it is hoped to cheer him may provoke more anxiety and bewilderment in him than pleasure. The child's activities should be governed by his own desire and abilities. There are no unusual dietary needs.

So long as satisfactory relationships can be maintained, home care is preferable, but parents are at times unable to cope with the situation, and hospitalization offers desirable respite.

## DISEASES OF THE BLOOD ASSOCIATED WITH DEFECTS IN HEMOSTASIS

When very small vessels, such as arterioles, venules and capillaries, are injured, reflex contraction of smooth muscle in the small arterioles and the precapillary sphincter occurs which leads to reduced flow. There is a local accumulation of platelets at the site of injury to endothelial surfaces forming a hemostatic plug, which seals the defect in the vessel. Disintegrating platelets release a factor (serotonin) producing prolonged local vasoconstriction. The retention of blood within injured small vessels thus appears to depend upon the integrity of the vessel endothelium and normal function of adequate numbers of platelets. There is no evidence that the formation of a fibrin clot is important here. For example, the patient with hemophilia, who cannot form a clot, does not bleed abnormally from trauma confined to small vessels.

*Defects in hemostasis in small vessels* may reside in the vessel or in the platelets. Regardless of the cause, the amount of blood lost will not be large, even if the petechial or purpuric lesions are widespread. Large extravasations in the forms of hematomas, hemarthroses or hemorrhages are not expected in vascular or platelet disorders unless a large number of vessels are traumatized at one time. Epistaxis, however, is an exception, and

bleeding from a small local lesion may lead to prolonged and severe blood loss.

The integrity of vascular endothelium depends upon many factors. Ascorbic acid is essential for production of the intercellular cement substance of endothelial cells. Rutin (vitamin P, eriodictyol, hesperidin) is apparently also involved in capillary permeability, but its mode of action is unknown, and it has no proved therapeutic role. Anoxia may lead to local or general increases in permeability of capillary endothelium, and allergic factors may produce localized or general injury. In many instances the hydrostatic pressure in the vessels will determine the likelihood of extravasation at a site of injury.

*Bleeding from injuries to large vessels* is controlled in part by the same mechanisms which control bleeding from small vessels. There is local spasm of both small and large vessels and accumulation of platelets at the site of injury. There is, in addition, eventual formation of a fibrin clot which bridges and seals the area of injury.

The *formation of the clot* is a complicated process depending upon local upset of a dynamic equilibrium between formation and dissolution of clotting factors. The final step in the process is the conversion of the solu-



protein fibrinogen to an insoluble form, fibrin, which forms a mesh of protein strands trapping red cells, white cells and platelets. Contraction or retraction of the clot occurs, which tends to close the defect in the injured vessel. An adequate supply of functional platelets is essential to retraction of the clot.

Fibrinogen is formed in the liver. It is present in the blood normally in concentrations ranging from 250 to 400 mg. per 100 ml., an amount which represents the average need for about three days. The transformation of fibrinogen into fibrin occurs when thrombin is formed from a protein precursor, prothrombin. Prothrombin is formed mainly in the liver and, like fibrinogen, exists in the blood stream in an amount equal to the needs for about three days. Vitamin K is necessary for the synthesis of prothrombin.

The conversion of prothrombin into thrombin depends upon an increase in thromboplastin activity. Several substances present in small amounts in blood plasma contribute to the elaboration of active thromboplastin, in addition to a factor present in platelets and in tissue juices. These substances in plasma include AHG (thromboplastinogen, antihemophilic globulin), PTC (plasma thromboplastin component) and PTA (plasma thromboplastin antecedent), each of which may have an inactive and an active form.

In addition to thromboplastin activity three other factors regulate the conversion of prothrombin into thrombin. The first is ionized calcium, in the absence of which the conversion cannot take place. The other two are catalytic enzymes which affect mainly the rate of prothrombin conversion. One is known as *labile factor*, since its activity is lost in stored blood in a period of two weeks. The other retains activity under these circumstances and is known as *stable factor*. Both accelerators have many synonyms. Vitamin K is necessary for production of stable factor, which with labile factor is produced in the liver. Each probably exists in inactive and in active forms, and their activation is probably accomplished by small amounts of thrombin.

Many of these clotting factors have associated antifactors, which actively neutralize them as they are formed and tend thereby to preserve the fluidity of blood. In man a heparin-like substance displays predominantly antithrombin activity and is apparently formed for the most part in the mast cells of the reticuloendothelial system. A fibrinolytic enzyme is normally present in blood in an inactive form (profibrinolysin or plasmino-

gen) and in an active form (fibrinolysin or plasmin). Abnormal anticoagulants may be formed in a variety of conditions (shock, transfusion reactions, disorders of pregnancy, prostatic cancer). Antithromboplastic substances have been observed in hemophilia and in lupus erythematosus.

The clot-promoting substances may be only sluggishly responsive initially to the call for clot formation. The process is rapidly accelerated through a feedback mechanism which gives thrombin the property, not only of first initiating fibrin formation, but also of labilizing platelet activity, of accelerating thromboplastin formation and of activating the labile and stable factors which increase the rate of prothrombin conversion.

The formation of fibrin ceases when the free thrombin which activated the clotting process is inactivated. Further clot formation will then depend upon the further addition of active thromboplastin to the blood.

**Platelets.** Blood platelets are small, refractile, oval or irregularly shaped bodies, 2 to 5 microns in greatest diameter, with finely granular basophilic cytoplasm, but without well defined nuclear structure. They are produced in bone marrow from megakaryocytes. Accurate counts of platelets are difficult to obtain, owing to the ease with which these elements undergo lysis and agglutination. Normal counts vary from 150,000 to 400,000 per cubic millimeter. The life span of the platelet in the blood stream in man is four to eleven days. In the dog, after removal of all circulating platelets, the platelet count returns to normal in three to four days.

In the elucidation of the functions of platelets at least four active "factors" and certain other properties have been identified. Platelet factor I accelerates the conversion of prothrombin to thrombin; factor II accelerates the conversion of fibrinogen to fibrin; factor III has thromboplastic activity and with other thromboplastin factors (AHG, PTC, PTA, and the like) converts prothrombin to thrombin; and factor IV neutralizes heparin. Serotonin can be found in lysed platelets in a concentration of 0.5 to 1.3 micrograms per  $10^9$  platelets. This important substance produces vasoconstriction by action on the smooth muscle of small vessels and initiates the release of epinephrine from the adrenal medulla.

Much of the activity of platelets is associated with their agglutination. Agglutination is enhanced in vivo by contact with roughened endothelial surfaces or foreign particles,

by vascular stasis and by thrombocytosis. Owing to the readiness with which platelets agglutinate on contact with a foreign surface, a universally satisfactory system for examining their agglutination in vitro is not available. Current evidence indicates that the immunologic and antigenic properties of platelets reside in two major platelet antigens which give rise to four major platelet groups, analogous to the major red blood cell groups. Iso-immunization to platelets may occur after heterospecific blood (platelet) transfusion or pregnancy. Auto-immunization is the suggested mechanism for many instances of idiopathic thrombocytopenic purpura.

Thrombocytosis may accompany splenectomy, trauma, hemorrhage, lead poisoning, rheumatic states, bacterial infections, polycythemia vera, myeloid leukemia and hyperadrenalism.

#### LABORATORY TESTS USEFUL IN THE STUDY OF PATIENTS WITH A BLEEDING TENDENCY

The evaluation of patients with an abnormal bleeding tendency includes tests of vascular integrity, of platelet function and of adequacy of the clotting mechanism. The bleeding time and the tourniquet test are helpful in evaluating the integrity of the mechanisms responsible for hemostasis in small vessels. Each will be abnormal if there is a generalized defect in vascular integrity or platelet function, as in scurvy, cutis hyperelastica or thrombocytopenia. The *tourniquet test* is the more generally useful. It should be performed with a blood pressure cuff inflated to a pressure midway between systolic and diastolic pressures and maintained there for eight minutes. The *bleeding time* is widely used, but is subject to great error. A careful examination of the formed elements in the peripheral blood, with estimation of the number of *platelets*, is essential. If there is a decreased number of platelets, an examination of *bone marrow* should be made to establish whether an adequate number of megakaryocytes is present, and to account, if possible, for their absence. Observation of *clot retraction* provides evidence of the adequacy of platelet function.

A wide variety of tests can be used to measure the functional adequacy of the clotting mechanism. In hypofibrinogenemia clotting time is normal, but the clot is small and friable. In the absence of fibrinogen (afibrin-

ogenemia) the blood is incoagulable. The clotting time is prolonged in deficiencies of plasma thromboplastin factors. Deficiencies in platelet thromboplastin factors may also occur, but rarely give rise to prolonged clotting time; if the formation of active thromboplastin is impaired, the *prothrombin consumption test* will usually be abnormal.

Certain tests are helpful in distinguishing deficiencies of the various plasma thromboplastin factors. Antihemophilic globulin loses its activity in stored plasma, so that a clotting defect corrected by stored plasma must be the result of PTA or PTC deficiency. Plasma thromboplastin component is adsorbed on barium sulfate, so that normal plasma so treated will not correct the defect in PTC deficiency, whereas it will readily correct the defect in clotting due to AHG, if fresh, and will correct PTA deficiency even if stored. Serum retains PTC and PTA activity, but loses AHG activity. Differentiation of AHG, PTC and PTA deficiencies will be most certain when samples of blood from known cases of each of the three deficiencies are available. It will then be possible to demonstrate that the addition of a tenth part of the plasma of any one to either of the other two will correct the clotting defect, whereas the homologous defect will not be corrected. By similar mixing techniques deficiencies of other newly found factors (such as Hageman, Stuart or Car) may be identified.

The most sensitive test for adequacy of thromboplastin factors is the *thromboplastin generation test*. When plasma adsorbed by barium sulfate, serum and platelets are brought together, all factors needed for thromboplastin formation should be present. When, after incubation, aliquots of such a mixture are added with calcium ion to normal plasma, the time needed for clotting is a measure of the developing thromboplastin activity. Substitution of the adsorbed plasma, serum or platelets of a patient with a hemorrhagic disorder into a system of normal reagents makes possible specific identification of deficiencies of AHG, PTC, PTA or platelet factors.

Defects in the formation of thrombin do not result in increases in the clotting time, except in unusually severe instances. The *one-stage prothrombin test*, however, which measures the clotting time of citrated blood when thromboplastin and calcium are added in adequate amounts, will ordinarily reflect disturbances in thrombin formation. A prolonged prothrombin time reflects an inade-



quate level of prothrombin or a deficiency of prothrombin accelerators. The deficiencies can be differentiated in a variety of ways. For example, if one part of stored plasma is added to nine parts of the plasma of a patient with labile factor deficiency, no correction of the prolonged prothrombin time of the patient will occur, whereas fresh normal plasma will correct the clotting defect. Further, plasma adsorbed on barium sulfate loses both prothrombin and stable factor. Such plasma will not correct the defect in thrombin formation in a patient deficient in either of these substances. Normal serum is ordinarily free of prothrombin and labile factor, but retains stable factor activity. Serum, then, will accelerate prothrombin conversion in a system containing adequate amounts of prothrombin, labile factor, calcium and thromboplastin. Failure of acceleration would indicate an absence of stable factor.

The *two-stage prothrombin test*, which measures the amount of thrombin produced, may give additional useful information, but is cumbersome for routine use.

Increases in anticoagulant factors are not common in children. Increase in antithromboplastin activity may be encountered most commonly in the patient with hemophilia, as a complication of replacement therapy with AHG in any form. Increases in normal antithrombin factor rarely, if ever, occur, but heparinoid substances are increased in states of shock, during intensive radiation therapy or during administration of nitrogen mustard.

One or more fibrinolytic substances may be present in blood under normal or pathologic conditions. They are detected principally by their interference with the stability of the clot. They may on occasion cause such rapid lysis of the clot that its formation may not be detected, and the blood may appear to be incoagulable. The anticoagulant formed under circumstances of surgical or anaphylactic shock or in severe liver disease may be a fibrinolysin. Bleeding disturbances due to abnormal anticoagulants have rarely been demonstrated in children, but it is anticipated that they may be met with greater frequency as knowledge of them increases.

Heparin therapy is occasionally used for anticoagulant purposes in children, particularly after splenectomy, when hypercoagulability due to thrombocytosis may be present. The dose is determined principally by the clotting time, which must be measured in *venous blood* with great care. Protamine sulfate, given intravenously, rapidly counteracts the effects of an overdose of heparin.

Unlike that of heparin, the action of Dicumarol and related anticoagulant substances is on the production of prothrombin in the liver. The therapeutic use of Dicumarol must be regulated by the prothrombin time rather than by the clotting time. The effect of Dicumarol is delayed until preformed prothrombin can be depleted. The action of Dicumarol is reversed by adequate doses of vitamin K within a few hours or by the transfusion of blood.

## DEFECTS OF HEMOSTASIS IN SMALL VESSELS

Petechiae and purpura, characteristic of bleeding from small vessels, may be cardinal features of a wide variety of diseases. The major conditions may be classified according to their vascular or platelet origin as follows:

- I. Vascular defects
  - A. Congenital
    1. Cutis hyperelastica (Ehlers-Danlos)
    2. Pseudoheremophilia
    3. Hereditary hemorrhagic telangiectasia
    4. Pulmonary hemosiderosis
    5. Idiopathic hematemesis and melena
  - B. Acquired
    1. Scurvy
    2. Anaphylactoid purpura (Henoch-Schoenlein)
    3. Toxic angitis due to bacterial or toxic agents
- II. Defects in platelet function
  - A. With normal platelet count
    1. Hereditary thrombocythemia
    2. Thrombocytopathic purpura

### B. With thrombocytopenia

1. With normal numbers of platelet precursors in marrow (megakaryocytes)
  - a. Idiopathic thrombocytopenia
  - b. Thrombocytopenia due to iso-immunization in the newborn
  - c. Thrombocytopenia due to secondary hypersplenism
  - d. Thrombotic thrombocytopenia
2. With deficient platelet precursors in marrow
  - a. Aplastic anemia
  - b. Leukemias

## ANAPHYLACTOID PURPURA (See p. 920)

## OTHER VASCULAR DEFECTS ASSOCIATED WITH BLEEDING TENDENCY

Congenital defects in the structure of small blood vessels may give rise to purpura or to bleeding tendency in children.

In *hereditary familial telangiectasia* small dilatations of capillaries may occur at the finger tips, on the face and in the mucous membranes of the mouth and the nose, which may bleed profusely. This disease is rarely encountered before the age of eleven or twelve years.

In *cutis hyperelastica* (Ehlers-Danlos syndrome, p. 1277) an inherited anomaly of connective tissue is manifest by overproduction of elastic tissue. The skin is hyperelastic, joints are hyperextensible, and there is poor connective tissue support for small cutaneous vessels, which bleed profusely upon slight trauma. Wounds heal with delicate "tissue paper" scars. Serious hemorrhage may follow skin biopsy in these patients.

*Toxic vascular purpura* may be a manifestation of many infections and poisons in children. Acute meningococcemia may be associated with extensive purpura (Waterhouse-Friderichsen syndrome), as may septicemia due to other organisms. Rarely the platelet count will be reduced in such instances. In some infections, such as subacute bacterial endocarditis, petechiae or purpura may be embolic in origin, but more often the vascular injury associated with infection appears to be due to a toxin.

Iodides, arsenicals, salicylates, atropine, belladonna and other drugs have been reported to be responsible for purpura without thrombocytopenia. Such reactions to drugs appear to depend upon idiosyncrasy. Snake venoms, on the other hand, may have a specific toxic action for endothelium which results in purpura. In scurvy the intercellular endothelial cement substance is not produced in adequate amounts, and purpura may be a prominent aspect of this disease.

### IDIOPATHIC THROMBOCYTOPENIC PURPURA

Idiopathic thrombocytopenic purpura (ITP) is characterized by spontaneous small hemorrhages into skin, mucous membranes and many other tissues, and is associated with a striking deficit in the number of circulating platelets and with normal or increased numbers of megakaryocytes in the bone marrow. Sixty-five to 85 per cent of all cases occur in children under twelve years of age, the highest incidence appearing to be between the ages of three and seven years. The predominance of female patients in adults does not occur in children. The disease is uncommon in Negro children.

**Etiology and Pathogenesis.** The role of preceding "sensitizing" infections, which occur in about 60 per cent of instances, is not clear. It has been suggested that the autoimmune type of acquired hemolytic anemia and idiopathic thrombocytopenia are due to similar immunologic abnormalities, and "platelet agglutinins" have been demonstrated in patients with thrombocytopenia, analogous to the auto-agglutinins for erythrocytes. It appears that the spleen may (1) produce substances adversely affecting capillary permeability, (2) be the site of production of anti-platelet antibodies, and (3) be the most active site of removal of "sensitized" platelets from the circulation.

It seems clear that the platelet deficiency is due to factors outside the platelet, since the life span of normal platelets infused into patients with thrombocytopenic purpura is markedly shortened. By contrast, the life span of transfused platelets is generally normal in patients with thrombocytopenia due to hypoadactivity of the bone marrow.

**Clinical Manifestations.** Idiopathic thrombocytopenic purpura occurs in two distinct forms: an acute self-limited form most common in children and a chronic, recurrent form relatively infrequent in children.

In the acute form the onset is sudden and often occurs one to four weeks after a mild respiratory infection or occasionally after one of the exanthems, especially measles.

The first signs are usually spontaneous petechiae and purpura involving the skin and buccal and conjunctival mucous membranes. Bleeding may be especially prominent over bony prominences or at the sites of mild trauma, where large ecchymoses may appear. The lower extremities, the buttocks and the extensor surfaces of the arms are almost always involved, and in the more severe instances hemorrhages are widely scattered over most of the body surface. At the onset the child rarely has other significant symptoms and usually does not appear acutely ill.

Hemorrhages from the urinary tract, vaginal and nasal mucous membranes or the gastrointestinal tract occur in severely ill patients. Hemorrhage into joints or into the pleural or peritoneal spaces is unusual. Intracranial hemorrhage is an uncommon complication, but is the most common cause of death. The neurologic manifestations vary widely; for example, from transient localized paresis to decerebrate rigidity. The spleen is not regularly palpable and is never greatly



enlarged. Generalized lymphadenopathy is not characteristic.

Approximately 10 to 15 per cent of the cases in children are of the chronic variety. The onset is less dramatic than in the acute form. The presence of a hemorrhagic disorder is often recognized only when there is profuse bleeding with such trauma as that of dental extraction or other surgical procedures or with epistaxis or menarche. The history in such instances, however, often discloses a tendency to easy bruising and excessive hemorrhage from minor wounds for months or years. Periods of excessive bruising and bleeding may alternate with periods of prolonged good health. In about one fourth of instances there is a family history of bleeding tendency.

Physical findings are usually less extensive in the chronic form than in the acute one. Small ecchymoses may be found at sites of minimal trauma, and a few petechiae are commonly seen in the oral cavity.

**Laboratory Data.** The platelet count is always below 100 thousand per cubic millimeter and may be less than ten thousand. A normochromic anemia with a compensatory reticulocytosis may be present if bleeding has been severe. In the chronic form, if epistaxis or menorrhagia has recurred frequently, iron deficiency may result from loss of blood. A moderate leukocytosis with an increase in the granulocytic forms is to be expected when intracutaneous bleeding is extensive, and there may be a slight increase in eosinophilic leukocytes.

The tourniquet test is usually strongly positive, and the bleeding time is generally prolonged. The clotting time is normal, but clot retraction is delayed and incomplete, and the prothrombin consumption test shows defective utilization of prothrombin.

The changes in the bone marrow are difficult to evaluate. Megakaryocytes are thought by some to be increased in number, to be immature and to have less than normal "budding" activity. There may be an increase in eosinophils, a feature thought by some to indicate an ensuing remission.

Some affected children have substances in their plasma which produce thrombocytopenia. They may be demonstrated *in vivo* by injecting serum from the thrombocytopenic patient into normal persons, or *in vitro* as agglutinins of platelets by the techniques of Harrington.

**Diagnosis.** In all patients with thrombocytopenia the bone marrow should be studied, since aplastic anemia and leukemia are prom-

inent diagnostic possibilities. If megakaryocytes are present in normal numbers and granulopoiesis and erythropoiesis are not altered, and if the patient is free of symptoms other than those associated with the low platelet level, the diagnosis of idiopathic thrombocytopenia is strongly suggested.

Since splenomegaly is never marked in idiopathic thrombocytopenia, a moderate to marked enlargement in association with thrombocytopenia suggests the possibility of some other disturbance, especially leukemia, a primary reticuloendotheliosis or hypersplenism due to congestive splenomegaly.

In Banti's syndrome, thalassemia, Gaucher's disease and certain parasitic infections secondary hypersplenism may lead to reduction in the number of platelets and occasionally to hemorrhagic manifestations.

In the older child the possibility of lupus erythematosus must be considered; the demonstration of L.E. cells supports this diagnosis. Thrombotic thrombocytopenic purpura has reduced platelet counts and bleeding with a normal marrow; a hemolytic anemia and cerebral symptoms and the acuteness and severity of the illness are additional distinguishing factors.

**Course and Prognosis.** Seventy-five per cent of children recover within two months with supportive therapy, and another 10 to 15 per cent within four to six months. Occasionally spontaneous recovery is delayed for as long as a year. During the active phase the severity of symptoms may vary greatly. Recurrence of the acute form of the disease is rare.

About 10 per cent of children with this disease have the chronic form. Even during improvement in the clinical state the platelet count will remain low. About two thirds of these patients recover after splenectomy. Since the chronic form is encountered more commonly in girls, the possibility of excessive menstrual bleeding is an important consideration. Limited experience indicates that the initial menses may be accompanied by profuse and irregular blood loss, but that after the first few months relatively normal flow can be expected. Approximately 50 per cent of infants of mothers with chronic idiopathic thrombocytopenia have transient thrombocytopenia in the neonatal period.

**Treatment.** Initially a conservative program consisting in careful observation and supportive measures is usually justified. Transfusions of whole blood may be given to correct excessive blood loss. Infections

and carrier states involving pathogenic organisms should be treated with appropriate antibiotic agents. The patient with moderate or severe bleeding should be confined to bed in as atraumatic an environment as possible.

Unusual instances of severe bleeding may call for infusion of platelet-rich plasma or whole blood. In order to preserve blood platelets in useful form, it is necessary to transfer blood as directly as possible from donor to patient with tubing of nonwetable plastic material and glassware treated with silicone agents and preferably with ethylenediamine tetra-acetic acid (EDTA) as the anticoagulant. The survival of platelets even when transferred under optimal circumstances is only a few hours, but during this time bleeding may be controlled. The efficacy of platelet transfusions can be increased by using blood of persons with polycythemia vera. Platelet transfusions become less efficient with repetition.

The use of either ACTH or cortisone is best limited to the temporary control of severe bleeding. The effect of these agents on the platelet count is unpredictable.

Generally, splenectomy is considered only after the disease has been present for six to twelve months. It may be considered earlier when hemorrhagic manifestations are unusually severe and not controlled by ACTH or cortisone, or when adequate protection against trauma cannot be secured. Splenectomy may also be considered when a patient is approaching the menarche, or when an intracranial hemorrhage has occurred, with the hope of avoiding a repetition. Complete and lasting remissions can be expected in 60 to 70 per cent of children with chronic idiopathic thrombocytopenia. The remaining 30 to 40 per cent will have a persistence of the disease, but possibly with some lessening of the manifestations.

### THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura is a rare and, so far, invariably fatal disease, the salient features of which are extensive purpura with thrombocytopenia, hemolytic anemia and bizarre mental and neurologic manifestations. The cause is unknown, but available evidence suggests a state of hypersensitivity. There are no sex or racial predilections.

The primary process appears to be in small blood vessels with inflammatory and degen-

erative changes in their walls, and multiple small aneurysms in arterioles. The capillaries contain masses of amorphous material, thought to be agglutinated platelets, and proliferated endothelial cells. The widespread occlusion of small vessels leads to small infarcts and to foci of necrosis in the heart, brain and other organs.

**Clinical Manifestations.** The onset is usually sudden with extensive purpuric eruption, high fever, pallor and various neurologic findings. Occasionally the onset is insidious with weakness, vertigo and mild anemia. Usually the disease is of only a few days' duration, with rapidly falling hemoglobin level, icterus, coma and convulsions, leading to death. Splenomegaly and hepatomegaly may become marked.

**Laboratory Data.** There are anemia, reticulocytosis and erythroblastemia of varying degrees. The leukocyte count may be slightly or greatly elevated. The platelet count is always reduced. L.E. cells may frequently be encountered in appropriate preparations of the blood.

In the bone marrow there is a reactive myeloid and erythroid hyperplasia, and erythrophagocytosis and leukophagocytosis may be prominent. The characteristic vascular lesions have been observed in sections of marrow and can usually be demonstrated in biopsy specimens of the cutaneous lesions.

**Treatment.** Currently available therapy has failed to alter the course of this disease. Cortisone and ACTH have had no apparent effect.

### THROMBOCYTOPENIA IN THE NEWBORN

In the newborn infant thrombocytopenia most commonly accompanies a severe prenatal or postnatal infection, such as septicemia, syphilis, toxoplasmosis, torulosis or cytomegalic inclusion disease, which may greatly depress marrow activity. Congenital aplastic anemia (Fanconi), congenital leukemia and congenital absence of megakaryocytes are rare causes of thrombocytopenia in the newborn. In these conditions megakaryocytes will be few or absent in marrow.

In many infants of mothers with thrombocytopenic purpura there is a transient thrombocytopenia of four to six weeks' duration, due to transplacental passage of antiplatelet substances. A similar transient thrombocytopenia may occur when an infant is born to a mother who has been iso-immunized by a heterospecific platelet transfusion or



through pregnancy. The thrombocytopenia occasionally seen in association with hemolytic disease of the newborn may have such an origin. In these immunologic disorders the numbers of megakaryocytes in marrow are normal, and no specific measures are ordinarily necessary. In exceptional instances a platelet transfusion may be helpful.

### THROMBOCYTOPENIA AND GIANT HEMANGIOMA

A severe hemorrhagic disorder, with thrombocytopenia, has been encountered in infants

with large hemangiomas, due apparently to sequestration of platelets within the extensive vascular bed of the tumor. Platelet production in bone marrow appears to be normal.

Extensive hemorrhage into the hemangioma may cause rapid enlargement of the tumor and accentuation of the thrombocytopenia. Radiation therapy may be used in the hope of initiating regression of the tumor, but may be difficult, owing to its great size. Steroid therapy is of doubtful help; splenectomy is contraindicated. The prognosis is guarded.

## DISTURBANCES OF THE MECHANISM FOR CLOTTING

See also page 253.

### THE HEMOPHILIAS

Hemophilia can no longer be considered a single disease entity; it should be recognized as a syndrome representing several distinct inborn errors of metabolism. Hemophilic states are now identified as being due to defects in any of several substances necessary for thromboplastic activity. The major ones are the antihemophilic globulin (AHG, thromboplastinogen, plasma thromboplastin factor), plasma thromboplastin component (PTC) and plasma thromboplastin antecedent (PTA). The clinical conditions associated with deficiencies in these substances are now termed hemophilias A, B and C, respectively.

Clinical states resembling these more common forms of hemophilia are known, which involve faulty generation of thromboplastin, but in which no deficiency of AHG, PTC or PTA can be found. Lack of other plasma factors is presumed, each factor generally being named after the patient in whom the rare defect was first found, e.g., Hageman factor and Stuart factor.

Defects in the formation or activity of prothrombin (p. 980) or fibrinogen (p. 982) may also give rise to hemorrhagic tendencies with prolonged coagulation and normal bleeding times, but the associated clinical states are not classified with the hemophilias.

All the hemophilias are characterized by an unusual tendency to bleed both externally and into tissues, and particularly into joint spaces, after minimal or no trauma. The coagulation time is usually prolonged, the

bleeding and prothrombin times being normal.

#### HEMOPHILIA A

(TRUE OR CLASSIC HEMOPHILIA, AHG DEFICIENCY)

Hemophilia A occurs in all races and is inherited as a sex-linked recessive trait, occurring almost exclusively in males. The extremely rare exception of the disease in a female may occur when an affected male weds a female carrier. The male hemophiliac is a "bleeder" and has a demonstrable inability to produce antihemophilic globulin (AHG) in adequate amounts. Though it may be shown that the female carrier has less than normal levels of AHG in her plasma, only rarely does she have a mild bleeding tendency.

**Clinical Manifestations.** Clinical symptoms may occur within the first few days after birth in the form of hemorrhage from the umbilical cord or following circumcision, either of which may threaten life. Otherwise, excessive bleeding is not likely to occur until the infant begins to walk. Then a tendency to excessive bruising may be encountered, with large hematomas at the sites of minor trauma. External hemorrhage at this time is most often the result of trauma to the mouth or nose. In older children uncontrollable bleeding following extraction of teeth or removal of tonsils may be the first serious sign of hemophilia. Bleeding may involve the liver, spleen, pleural or peritoneal cavities, urinary tract, gastrointestinal tract or central nervous system. Death may result from intracranial bleeding, from exsanguination or from interstitial hemorrhage into the tissues of

the neck, resulting in respiratory obstruction.

Hemarthrosis is a characteristic lesion of hemophilia. It may occur early in life, but usually occurs first when the child begins to walk. Ankles, knees and elbows are particularly likely to become involved, but any joint may be affected. Painful swelling and severe discomfort accompany hemorrhage and may prohibit walking for days or weeks. Hemorrhage may also occur into the juxta-articular bone. Initially the hemorrhage is readily absorbed, but after repeated hemorrhages some fluid remains in the joint. Chronic inflammatory and degenerative changes occur which limit motion and may lead to eventual fixation of the joint. In late childhood or early adult life the large, tender, fixed joint is common in the hemophiliac.

**Laboratory Data.** The defect in coagulation is usually indicated by a prolongation of the clotting time. The prothrombin time and bleeding time are normal. The prothrombin consumption test, which reveals excessive residual prothrombic activity in serum after coagulation has taken place, demonstrates that the defect is in inadequate activation of thromboplastin. This test is more reliable than the clotting time, which may often be within the wide range of normal limits.

The thromboplastin generation test (p. 972) may be even more sensitive. That the defect in thromboplastic activation is actually due to absence of AHG may also be shown by "mixing" tests. The diagnosis is established if normal fresh plasma (in a 1:10 mixture with the patient's plasma) corrects the defect, and fresh plasma from a patient with proved hemophilia A does not correct it. The mixing test may occasionally be disturbed by the presence of an anticoagulant (antithromboplastic) substance in the blood of the patient with hemophilia A. This may be detected by showing that the plasma of the hemophilic patient in a 1:10 mixture disturbs the coagulation of normal blood or plasma.

Other studies of the blood are not diagnostic. Anemia, mild leukocytosis and moderate elevation in platelets may occur if loss of blood has been significant.

Roentgenograms of involved joints initially show the joint cavity to be distended, and there may be evidence of acute synovitis. After several hemorrhages into a joint there will be areas of subchondral erosion, with demineralization of epiphysal bone. Varying degrees of synovial thickening and contracture eventually occur. With repeated hemorrhages increased vascularization of the joint

space may lead to acceleration of bone growth and the premature appearance of centers of ossification. The articular surfaces may ultimately be completely destroyed. Juxta-articular cysts may develop as an aftermath of intraosseous hemorrhage at the epiphysal line and may erode into the joint space.

**Differential Diagnosis.** The family history may establish the typical pattern of recessive sex-linked inheritance. Since, however, female carriers may transmit hemophilia A for many generations without affected sons, and since new mutations appear to occur rather frequently, sporadic cases number as many as 30 per cent.

Hemophilia A can be differentiated from hemophilia B and hemophilia C by proper "mixing" tests, using the bloods of persons with known defects or through differential use of the thromboplastin generation test. The hemophilias can be separated from congenital hypoprothrombinemia and from parahemophilia by the prolongation of prothrombin time which occurs in the latter illnesses. Congenital afibrinogenemia is clinically indistinguishable from hemophilia, but shows incoagulability of the blood rather than simple prolongation of the clotting time, and a low level of fibrinogen may be demonstrated quantitatively. Certain platelet and vascular defects may occasionally be confused with the hemophilias, but they can be distinguished by abnormalities in the platelet count, clot retraction or tourniquet test.

**Course and Prognosis.** The hemophiliac lives under the constant threat of serious disability or death from his disease. Recurrent and ultimately crippling hemarthroses may progressively decrease the child's activities. Hospitalization is necessary more often for the younger patient than for the older child, whose periods of disability tend to become less frequent and may be of shorter duration. Occasionally a cyclic pattern may be manifest, in which periods with little or no bleeding as the result of moderately severe trauma will alternate with periods when severe hemorrhages appear to occur spontaneously. Infection often appears to accentuate the hemorrhagic tendency. Families in which the hemophilic members have a partial deficiency of AHG with a mild form of hemophilia have been recorded. In general it is impossible to prognosticate in early life the eventual degree of involvement.

**Treatment.** A major obligation is to help the patient and his family make the necessary adjustments in family and community life



that this disease imposes. A realistic picture must be presented to the parents, but they should know that many hemophiliacs live useful, active and productive lives. The joint efforts of physician and family should be directed toward preparing the child for a satisfactory role in adult life.

In early years responsibility for prevention of injury to the hemophiliac rests largely with the parents. The careful selection of toys, the padding of crib and playpen and intelligent supervision of play are important prophylactic measures. Sponge rubber pads over knees and buttocks may be helpful to the infant just learning to walk. At school age the boy should attend classes with normal children, but the understanding help of his teachers and classmates must be elicited. The older child becomes familiar with his limitations and, with guidance, seeks his proper level of activity among normal companions. Tolerable normal activity should not be denied, lest emotional crippling from overprotection be more disabling than the effects of repeated hemorrhages.

Since antihemophilic globulin loses its activity rapidly in blood stored in a fluid state, transfusion of *fresh* whole blood or plasma, or its equivalent, is essential for treatment of acute hemorrhage. Inasmuch as 10 to 20 per cent of the normal concentration of AHG must be present in the blood to assure adequate coagulation, fresh plasma should be given in the amount of 10 ml. per kilogram, at a rate of 1.5 to 2.0 ml. per minute, to initiate hemostasis. Further slower infusion must follow if hemostasis is to be maintained, at times for three to five days. When blood loss has been severe, rapid infusion of blood is necessary to restore blood volume and to relieve shock. When operation is necessary, fresh blood should be given for three to four hours prior to the operation and for seventy-two or more hours postoperatively.

In the frozen state fresh plasma loses its antihemophilic property slowly, and may be used effectively months after preparation for the control of hemorrhage in the hemophiliac. Frozen plasma has the additional advantage that the danger of sensitization to red blood cell antigens is minimized for children who are likely to receive multiple transfusions. Cohn's fraction I of plasma, which contains AHG in addition to fibrinogen, produces effective control of bleeding in the hemophiliac, but the material must be prepared from *fresh* blood plasma, is expensive, and is likely to transmit serum hepatitis if pre-

pared from pooled plasma. A lyophilized concentrate of fresh plasma is available (Anti-hemophiliac Plasma, Hyland Laboratories) and has been found helpful.

The appearance of an anticoagulant substance in the blood of the hemophilic patient is a serious complication of therapy, since subsequent administration of fresh plasma or blood may be much less effective in the control of hemorrhage. These substances are found in the pseudoglobulin fraction of plasma and counteract the effect of AHG through antithromboplastic activity. Van Creveld has found that ACTH may temporarily depress these abnormal substances and permit more effective action of fresh plasma or blood. Since repeated infusions of blood and plasma are thought to predispose to the development of anticoagulants, local measures for the control of hemorrhage should be tried whenever reasonable before the use of plasma or blood is considered.

Any wound should be thoroughly cleansed, and any foreign matter, including clotted material, should be removed. Powdered thrombin may then be applied to the injured area, although, if the lesion is extensive, topical application will often have little effect. Judicious local pressure should also be applied when possible, and cold applications to the traumatized area may reduce bleeding through vasoconstriction. Closure of a wound by sutures should be avoided whenever possible, since even this mild trauma may aggravate hemorrhage. Local application of epinephrine solution sometimes aids in hemostasis, but astringents and styptics usually do more harm than good.

The control of hemorrhage into joint cavities is extremely important if prolonged or lasting disability is to be prevented. Ice bags should be applied immediately, and the involved joint wrapped in an elastic bandage. Parents of children prone to develop hemarthroses should keep one or two plastic icebags in the refrigerator at all times for immediate use if hemorrhage occurs. This local therapy should be continued for at least forty-eight hours if the hemorrhage is controlled; if it is not promptly controlled, a transfusion of plasma should be given. After bleeding has been controlled for forty-eight hours or longer, cautious application of heat will aid in absorption of the fluid in the joint cavity. This is followed by gentle passive exercise and massage. With such attention much chronic disability may be avoided. When ultimate fixation of a joint seems in-

evitable, an effort should be made to ensure fixation in a position as functionally effective as possible. Results of injecting hyaluronidase into recently affected joints have been disappointing.

### HEMOPHILIA B

(PTC DEFICIENCY, CHRISTMAS FACTOR DEFICIENCY)

The hemophilic state due to deficiency of plasma thromboplastin component (PTC) is responsible for about 15 per cent of all patients with hemophilia. It is inherited as a sex-linked recessive trait; so far it has been reported only in males.

The clinical manifestations, course and prognosis of hemophilia B do not in any way differentiate it from hemophilia A. The clotting abnormality is typical of the hemophilic state: the clotting time is prolonged, or occasionally normal; prothrombin consumption is abnormal, owing to inadequate activation of thromboplastin. The plasma of the patient with hemophilia B readily corrects, *in vitro*, the coagulation defect in the plasma of patients with hemophilia A or C, and vice versa.

PTC is relatively stable in stored blood or plasma, so that the patient with hemophilia B can be effectively treated by the infusion of *stored* blood or plasma, whereas only *fresh* blood or plasma is effective in hemophilia A; otherwise therapy is similar for both hemophilias A and B.

### HEMOPHILIA C

(PTA DEFICIENCY)

Hemophilia C is the result of a defect in the synthesis of plasma thromboplastin antecedent (PTA). The abnormality is inherited as a mendelian dominant trait and therefore affects males and females alike. No sporadic cases have been reported to date.

The hemorrhagic tendency is not so great as in hemophilias A and B. It may appear within the first few hours of life and is manifest as a tendency to bleed excessively from mild trauma or laceration. Loss of blood following dental extraction or tonsillectomy may be especially prominent. Hemarthrosis apparently does not occur.

The clotting time in hemophilia C may be prolonged or within normal limits. The defect in utilization of prothrombin is readily demonstrated by the prothrombin consumption test. Plasma from patients with PTA defi-

ciency readily corrects the clotting defect in the bloods of patients with hemophilias A and B, and vice versa.

Therapy in hemophilia C is similar to that of hemophilias A and B. Although bleeding is generally less severe, the need for treatment may be just as urgent. Since PTA is relatively stable, the clotting defect in hemophilia C can be corrected by the use of stored blood or serum.

### VON WILLEBRAND'S SYNDROME

(VASCULAR HEMOPHILIA OR PSEUDOHEMOPHILIA)

Von Willebrand described many years ago a familial hemorrhagic disorder characterized by prolonged bleeding time with normal coagulation time. The syndrome closely resembles hemophilia A; there are massive hematomas in infancy, and hemarthroses, epistaxes and bleeding following dental extractions in subsequent years. Genetic transmission is as a mendelian dominant, affecting both sexes.

Recent evidence indicates that at least two groups of patients can be identified who present the clinical findings and genetic pattern of von Willebrand's disease. In the first group a vascular abnormality identified by capillary microscopy is the only demonstrable factor contributing to deficient hemostasis. Except for prolonged bleeding time there is no other abnormality in coagulation. In the second group the clinical pattern is similar with an identical vascular abnormality, but there is, in addition, a variable degree of deficiency of antihemophilic globulin. In patients of this second group infusion of plasma containing AHG corrects the hemostatic defect both clinically and *in vitro*. The deficiency of AHG is not so severe as in hemophilia A and is often detected only by the thromboplastin generation test. The clotting time and prothrombin consumption may be normal.

Schulman and his co-workers, who first differentiated the two groups of patients with von Willebrand's syndrome, have suggested that the condition with both vascular defect and AHG deficiency be termed *vascular hemophilia*, and the condition with isolated vascular defect be called *pseudohemophilia*.

### DEFICIENCIES IN PROTHROMBIN AND ACCESSORY FACTORS

Prothrombin is converted to thrombin through the actions of activated thrombo-



plastin in the presence of ionized calcium and of the stable and labile accelerator factors. Deficiencies of these substances may arise from faulty production or faulty utilization when abnormal antifactors are elaborated against them. Congenital defects in synthesis are known for each of these factors. Vitamin K is necessary for the synthesis of prothrombin and stable factor. Since all three substances are formed in large part in the liver, in far advanced hepatic disease clinical deficiencies may occur involving one or all factors.

Deficiencies in prothrombin or related substances are manifest clinically as more than usual hemorrhage from slight trauma or surgical incisions. Epistaxis, hematuria, gastrointestinal and intracranial hemorrhages and extensive hematomas occasionally occur, but hemarthroses are rare.

Only when deficiencies of prothrombin factors are unusually marked is the defect in coagulation shown by a prolongation of the clotting time. The one-stage prothrombin time (Quick), however, is always prolonged, regardless of whether the defect is in prothrombin or in an accelerator factor; the prothrombin consumption test has no practical advantages. The platelet count, fibrinogen level, tourniquet test, bleeding time and thromboplastin generation test are normal in patients with defects in the prothrombin complex.

#### DEFICIENCY OF PROTHROMBIN

The synthesis of prothrombin depends upon adequate hepatic function and an adequate supply of vitamin K. Defects in either will lead to hypoprothrombinemia.

**Hypoprothrombinemia in the Newborn.** In most newborn infants the one-stage prothrombin time is considerably prolonged within a few hours after birth; it reaches a maximum prolongation by about three days, and rises to normal levels gradually within five to ten days. The defect in neonatal prothrombin activity is due to defects of both prothrombin and stable factor, which apparently depend upon a transient deficiency in available vitamin K. Administration of this vitamin produces a prompt increase in plasma. Whether hypoprothrombinemia of the newborn is in small or large measure responsible for *hemorrhagic disease of the newborn* is not clearly established.

**Congenital Defect in the Synthesis of Prothrombin.** Several instances have been

reported in which there appeared to be a congenital absence of prothrombin production. These reports are difficult to evaluate, since defects in stable or labile factors were not excluded. There is no reason, however, to expect that congenital defects in synthesis of prothrombin may not occur.

**Hypoprothrombinemia Due to Avitaminosis K** (see p. 379).

**Hypoprothrombinemia with Severe Hepatic Disease.** In a number of conditions in which hepatic parenchyma is severely injured the synthesis of prothrombin may be primarily disturbed, so that there is no response to parenteral administration of vitamin K. There are usually deficiencies of other coagulation factors, such as of fibrinogen and stable and labile factors, which contribute to the severe hemorrhagic state which accompanies hepatic failure.

#### DEFICIENCIES IN STABLE FACTOR

Since both stable factor and prothrombin are formed in the liver and need vitamin K for their synthesis, acquired deficiencies in these substances usually occur together. Several instances of isolated deficiency of stable factor have been reported, however, in which the defect is genetic. The affected patients have shown a tendency to excessive bleeding in early life, with recurrent epistaxis, excessive bruising, subarachnoid hemorrhage and melena, and later menorrhagia. Owren reported a family in which the defect was inherited as a dominant trait of uncertain penetrance. Decreased activity of stable factor was found in many maternal relatives, but only those with less than 10 per cent of normal activity had evident hemorrhagic tendencies.

The *diagnosis* of congenital stable factor deficiency may be established by appropriate "mixing" tests, using the fresh and stored bloods of persons with known defects in coagulation. The prothrombin time is prolonged, but the clotting time may be normal even when the deficiency is severe. Vitamin K does not alter the defect, but the disturbance may be temporarily relieved by transfusion of stored blood or plasma.

#### DEFICIENCIES IN LABILE FACTOR

Low levels of labile factor activity have been found in patients with severe hepatic disease, in acute leukemia, in postoperative states and in the late stages of cancer. The activity of labile factor is normally present in the neonatal period.

Deficiencies of labile factor may occur as congenital defects in synthesis, which may be inherited as a mendelian dominant trait (parahemophilia, Owren's disease). *Parahemophilia* affects both sexes and may be responsible for a hemorrhagic disorder of moderate severity from early life. Excessive subcutaneous bleeding, recurrent epistaxis, profuse menorrhagia and severe hemorrhage following dental extractions and other surgical procedures have been recorded.

There are only moderate prolongations of the one-stage prothrombin time and the clotting time. The deficiency is corrected by small amounts of *fresh* plasma or blood.

## DISORDERS INVOLVING FIBRINOGEN AND FIBRIN

Mention has been made of the hypofibrinogenemia which may accompany severe diseases of hepatic parenchyma. Other rare disorders of clotting closely related to the formation or utilization of fibrinogen or fibrin include congenital afibrinogenemia and the hemorrhagic disorders associated with fibrinolysins.

### CONGENITAL AFIBRINOGENEMIA

Congenital afibrinogenemia is a rare hereditary defect in the synthesis of fibrinogen, affecting both sexes and probably due to an autosomal recessive gene; consanguinity has been frequently noted in the parents of affected children.

Hemorrhagic manifestations commonly make their appearance in the neonatal period. Clinically the disorder is indistinguishable from hemophilia; the blood, however, instead of clotting only after a prolonged time, proves to be absolutely incoagulable after many hours or days, and no fibrin deposit is produced in plasma on heating it at 56° C. for twenty minutes. The latter is a quick and simple test for afibrinogenemia. The sedimentation rate of the erythrocytes is exceptionally slow.

Specific *treatment* is limited to transfusions of whole blood, plasma or concentrated fibrinogen (Cohn fraction I). Therapy should be planned to maintain the blood level of fibrinogen at 60 mg. per 100 ml. or higher. Injections may be given according to need, or prophylactically at intervals of three to four weeks. Supportive management in other respects resembles that suggested for hemophilia.

## A HEMORRHAGIC DISORDER DUE TO FIBRINOLYSINS

### (FIBRINOLYTIC PURPURA)

Normal plasma contains a fibrinolytic enzyme, usually in an inactive form (profibrinolysin). The mechanism of activation of profibrinolysin to fibrinolysin is not known; it is postulated that activation occurs through a fibrinolysokinase related to, if not identical with, streptokinase. Apparently many tissues normally contain an inhibitor of fibrinolysokinase (antifibrinolysokinase), which exerts control over activation of profibrinolysin.

A hemorrhagic disorder caused by excessive activation of fibrinolysin has been identified in a variety of clinical conditions, though rarely in children. Trauma, hemorrhage and shock are recognized as potential initiators of excessive fibrinolysis. The lungs and uterus contain the highest concentrations of fibrinolysokinase, which may explain why bleeding disorders due to fibrinolysins have been most commonly encountered as complications of pulmonary and gynecologic surgery and in certain disorders of the placenta. Excessive fibrinolysis may also cause severe hemorrhage in leukemia, severe bacterial infections or cyanotic congenital heart disease or in association with a variety of malignant neoplasms. Excessive fibrinolysis in such unrelated diseases is not accounted for by any single factor.

Bleeding associated with excessive fibrinolysis is usually severe and difficult to control, and may begin at a number of sites without apparent provocation. Detection of excessive fibrinolysis is ordinarily not difficult; the blood will usually clot readily enough, but if a sterile sample of clotted blood is incubated at 37° C., the clot will disappear within twenty-four hours. The degree of abnormal activity is inversely proportional to the time required for dissolution of the clot.

*Therapy* may be urgently needed and has two aims: to correct the faulty excessive activation of fibrinolysin and to replace clotting proteins being destroyed in the process. Replacement of blood may also be urgently needed. The replacement of clotting proteins can best be accomplished by the liberal administration of concentrated fibrinogen (Cohn's fraction I) or large amounts of plasma; fraction I is the more effective. Cortisone has appeared to be effective in reducing the activity of fibrinolysin.

NATHAN J. SMITH  
VICTOR C. VAUGHAN, III  
LOUIS K. DIAMOND



## REFERENCES

*Erythropoiesis*

- Cartwright, G. E.: Dietary Factors Concerned in Erythropoiesis. *Blood*, 2:111, 256, 1947.
- Schulman, I., and Smith, C. H.: Fetal and Adult Hemoglobins in Premature Infants, with Observations on the Mechanism of the Anemia of Prematurity. *Am. J. Dis. Child.*, 86:354, 1953.

*Hypoplastic and Aplastic Anemia*

- Abt, A. F.: Aplastic Anemias in Childhood. *Am. J. Dis. Child.*, 78:516, 1949.
- Hunter, D.: Industrial Toxicology. *Quart. J. Med.*, 12:185, 1943.
- Lawrence, J. S., Dowdy, A. H., and Valentine, W. N.: Effects of Radiation on Hemopoiesis. *Blood*, 3:593, 1948.
- Smith, C. H.: Hypoplastic and Aplastic Anemias of Infancy and Childhood. *J. Pediat.*, 43:457, 1953.

*Iron Deficiency Anemia*

- Josephs, H. W.: Iron Metabolism and The Hypochromic Anemia of Infancy. *Medicine*, 32:125, 1953.
- Smith, C. H., Schulman, I., and Morgenthau, J. E.: Iron Metabolism in Infants and Children; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1952, Vol. 5, p. 195.
- Smith, N. J., and Rosello, S.: Iron Deficiency in Infancy and Childhood. *J. Clin. Nutr.*, 1:275, 1953.

*Megaloblastic Anemias*

- Reisner, E. H., Jr., Wolff, J. A., McKay, R. J., Jr., and Doyle, E. F.: Juvenile Pernicious Anemia. *Pediatrics*, 8:88, 1951.
- Watson, G. M., and Witts, L. J.: Intestinal Macrocytic Anemias. *Brit. M. J.*, 1:13, 1952.
- Zuelzer, W. W., and Rutzky, J.: Megaloblastic Anemia of Infancy; in *Advances in Pediatrics*. Chicago, Yearbook Publishers, Inc., 1953, Vol. 6, p. 243.

*Anemia Due to Blood Loss*

- Barer, A. P., and Fowler, W. M.: Effect of Iron on Hemoglobin Regeneration in Blood Donors. *Am. J. M. Sc.*, 205:9, 1943.
- Ebert, R. V., Stead, E. A., Jr., and Gibson, J. G., Jr.: Response of Normal Subjects to Acute Blood Loss. *Arch. Int. Med.*, 68:578, 1941.

*Hemolytic Anemias*

- Caffey, J.: Cooley's Erythroblastic Anemia; Some Skeletal Findings in Adolescents and Young Adults. *Am. J. Roentgenol.*, 65:547, 1951.
- Idem*: Skeletal Changes in Chronic Hemolytic Anemias. (Erythroblastic Anemia, Sickle Cell Anemia, and Chronic Hemolytic Icterus.) *Am. J. Roentgenol.*, 37:293, 1937.
- Chernoff, A. I.: The Human Hemoglobins in Health and Disease. *New England J. Med.*, 253:322, 365, 416, 1955.
- Crosby, W. H., and Akeroyd, J. H.: The Limit of Hemoglobin Synthesis in Hereditary Hemolytic Anemia. *Am. J. Med.*, 13:273, 1952.
- Etteldorf, J. N., Tuttle, A. H., and Claybon, G. W.:

Renal Hemodynamics in Children with Sickle Cell Anemia. *Am. J. Med.*, 18:243, 1955.

- Henderson, A. B.: Sickle Cell Anemia: Clinical Study of Fifty-Four Cases. *Am. J. Med.*, 9:757, 1950.
- Kaplan, E., Zuelzer, W. W., and Neel, J. V.: A New Inherited Abnormality of Hemoglobin and Its Interactions with Sickle Cell Hemoglobin. *Blood*, 6:1240, 1951.
- Lipton, E. L.: Elliptocytosis with Hemolytic Anemia: The Effect of Splenectomy. *Pediatrics*, 15:67, 1955.
- Loutit, J. F., and Mollison, P. L.: Hemolytic Icterus (Acholuric Jaundice), Congenital and Acquired. *J. Path. & Bact.*, 58:711, 1946.
- Neel, J. V.: Inheritance of Sickle Cell Anemia. *Science*, 110:64, 1949.
- Owren, P. A.: Congenital Hemolytic Jaundice. The Pathogenesis of the "Hemolytic Crises." *Blood*, 3:231, 1948.
- Pranker, T. A. J., Altman, K. I., and Young, L. E.: Abnormalities of Carbohydrate Metabolism of Red Cells in Hereditary Spherocytosis. *J. Clin. Investigation*, 34:1268, 1955.
- Smith, E. W., and Conley, C. L.: Sicklemia and Infarction of the Spleen during Aerial Flight. *Bull. Johns Hopkins Hosp.*, 96:35, 1955.
- Sturgeon, P., and Finch, C. A.: Erythrokinetics in Cooley's Anemia. *Blood*, 12:64, 1957.
- Young, L. E., Izzo, M. J., Platzer, R. F., and Ervin, D. M.: Hereditary Spherocytosis. *Blood*, 6:1073, 1099, 1951.
- Zinkham, W. H., and Childs, B.: A Defect of Glutathione Metabolism in Erythrocytes from Patients with Naphthalene-Induced Hemolytic Anemia. *Pediatrics*, 22:461, 1958.

*Hemolytic Disease of the Newborn*

- Allen, F. H., Jr.: Induction of Labor in the Management of Erythroblastosis Fetalis. *Quart. Rev. Pediat.*, 12:1, 1957.
- Allen, F. H., Jr., Diamond, L. K., and Vaughan, V. C., III: Erythroblastosis Fetalis. VI. Prevention of Kernicterus. *Am. J. Dis. Child.*, 80:779, 1950.
- Chown, B., and Bowman, W. D.: The Place of Early Delivery in the Prevention of Fetal Death from Erythroblastosis. *Pediat. Clin. North America*, 5:279, 1958.
- Hsia, D. Y.-Y., Allen, F. H., Jr., Diamond, L. K., and Gellis, S. S.: Serum Bilirubin Levels in the Newborn Infant. *J. Pediat.*, 42:277, 1953.
- Levine, P., Vogel, P., and Rosenfeld, R. E.: Hemolytic Disease of the Newborn; in *Advances in Pediatrics*. Chicago, Yearbook Publishers, Inc., 1953, Vol. 6, p. 97.
- Mollison, P. L., and Walker, W.: Controlled Trials of the Treatment of Haemolytic Disease of the Newborn. *Lancet*, 1:429, 1952.
- Pickles, M. M.: Hemolytic Disease of the Newborn. Springfield, Ill., Charles C Thomas, 1950.

*Polycythemia*

- Dykstra, O. H., and Halbertsma, T.: Polycythemia Vera in Childhood. *Am. J. Dis. Child.*, 60:907, 1940.

*Disorders of Leukocytes*

- Bernhard, W. G., Gore, I., and Kilby, R. A.: Congenital Leukemia. *Blood*, 6:990, 1951.

- Chediak, M.: Nouvelle anomalie leucocytaire de caractère constitutionnel et familial. *Rev. Hemat.*, 7:362, 1952.
- Donohue, W. L.: A lymphocytosis. *Pediatrics*, 11:129, 1953.
- Finch, S. C., Ross, J. R., and Ebaugh, F. G., Jr.: Immunologic Mechanisms of Leukocyte Abnormalities. *J. Lab. & Clin. Med.*, 42:555, 1953.
- Follis, R. H., Jr., and Park, E. A.: Some Observations on the Morphologic Basis for the Roentgenographic Changes in Childhood Leukemia. *Bull. Hosp. Joint Dis.*, 12:67, 1951.
- Page, A. R., and Good, R. A.: Studies on Cyclic Neutropenia. *A.M.A. Am. J. Dis. Child.*, 94:623, 1957.
- Reimann, H. A., and deBerardinis, C. T.: Periodic (Cyclic) Neutropenia, An Entity. *Blood*, 4:1109, 1949.

#### *Hemorrhagic Disorders*

- Alexander, B., and Goldstein, R.: Parahemophilia in Three Siblings (Owren's Disease). *Am. J. Med.*, 13:255, 1952.
- Barondess, J. A.: Thrombotic Thrombocytopenic Purpura. *Am. J. Med.*, 13:294, 1952.
- Clement, D. H., and Diamond, L. K.: Purpura in Infants and Children. *Am. J. Dis. Child.*, 85:259, 1953.
- Dameshek, W.: Acute Vascular Purpura. *Blood*, 8:382, 1953.
- Epstein, R. D., Lozner, E. L., Cobbey, T. S., Jr., and Davidson, C. S.: Congenital Thrombocytopenic Purpura; Purpura Hemorrhagica in Pregnancy and in Newborn. *Am. J. Med.*, 9:44, 1950.
- Harrington, W. J., and others: Immunological Mechanisms in Idiopathic and Neonatal Thrombocytopenic Purpura. *Ann. Int. Med.*, 38:433, 1953.
- Newton, W. A., Jr., and Zuelzer, W. W.: Idiopathic Thrombopenic Purpura in Childhood. *New England J. Med.*, 245:879, 1951.
- Schulman, Irving and Smith, C. H.: Coagulation Disorders in Infancy and Childhood; in *Advances in Pediatrics*, Chicago, Year Book Publishers, Inc., 1957, Vol. 9, pp. 231-76.
- Soulier, J. P.: Study of Prothrombin Consumption. Practical Interest for Diagnosis of Hemorrhagic Diseases; Study of 89 Cases. *Acta med. Scandinav.*, 137:1, 1950.
- Stefanini, M., Chatterjea, J. B., Dameshek, W., Zannos, L., and Santiago, E. P.: Studies on Platelets. II. The Effect of Transfusion of Platelet-Rich Polycythemic Blood on the Platelets and Hemostatic Function in "Idiopathic" and "Secondary" Thrombocytopenic Purpura. *Blood*, 7:53, 1952.



# The Spleen

The diversified functions of the spleen include activities related to its lymphoid tissue (antibody formation and other mechanisms of defense), to its reticuloendothelial tissue (removal of degenerating blood cells) and to its unique circulatory structure (storage, sequestration and destruction of blood cells).

The parenchyma is made up of two distinct types of tissue: the lymphoid follicles (malpighian corpuscles) and the splenic pulp, which consists of reticuloendothelial tissue containing erythrocytes and other blood cells. The lymphoid follicles surround small arteries and share in alterations of the lymphoid tissue of the body such as occur in leukemia, tuberculosis, sarcoidosis, infectious mononucleosis and less specific infections. The reticuloendothelial elements of the splenic pulp share with similar tissue elsewhere the pathologic deposition of lipid material in Gaucher's disease, Niemann-Pick disease, and the like, and are typically altered in nonlipid reticuloendotheliosis (Letterer-Siwe disease). The splenic pulp has vascular arrangements found nowhere else in the body, consisting of arterioles and venules, the pulp spaces and the venous sinuses. The pulp spaces are large open channels which wander among cords of reticular tissue and contain an abundance of reticuloendothelial elements, including many motile phagocytes. Blood apparently passes from the arterioles either into the pulp spaces, where it is brought into contact with these scavenger cells, or directly into the venous sinuses. An "open" and a "closed" circulation appear to coexist. Plasma is relatively easily lost from the pulp spaces, leaving a high concentration of cells which then enter the venous sinuses through a unique arrangement of slitlike openings. The length of time during which the cells are held in the spleen is dependent upon the ease with which they can pass through these openings and upon the contractile capacity of the organ. Structurally or metabolically abnormal erythrocytes have difficulty in traversing this complicated pathway, and stasis and destruction occur in the vascular spaces.

The spleen appears to have some control over the production and release of blood cells from marrow. Its removal is associated with the appearance of immature erythrocytes in peripheral blood, with granulocytic leukocytosis and with increased numbers of platelets in the circulation. In animals as little as 10 per cent of residual spleen inhibits such changes. These changes are transient; within a few days most splenic functions are assumed by other tissues. An unusual susceptibility to overwhelming or recurrent severe infection appears to follow splenectomy in some instances.

The spleen is an important source of new blood cells in some vertebrates and in the human fetus, but not after birth in man. Blood storage, against sudden increases in the demand for blood, is an important function of the spleen in many vertebrates, but is of minor importance in man.

With shielding of the spleen or with injection of homogenates of spleen, animals survive otherwise lethal doses of radiation. The demonstration by Lindsley that heterologous splenic cells survive and multiply when injected into the radiated animal implies that actual seeding of splenic cells exerts the protective influence. Human experience with this property of the spleen is not available.

**Clinical Evaluation of the Spleen.** On occasion the spleen can be felt at or slightly below the costal margin in apparently healthy infants and children. Light or superficial palpation is more apt to be effective in locating the organ than deep palpation, particularly if the supine infant is turned slightly toward his right side and the finger tips are lightly pushed toward the costal margin during inspiration. Since the spleen must be enlarged to about three times its usual size before it becomes palpable, the possibility of a pathologic disturbance should be considered whenever it is felt. The ease with which it can be felt depends upon a number of factors. Unusual depression of the diaphragm may displace a normal spleen downward, or displacement of abdominal contents upward may

make it impossible to feel a significantly enlarged spleen.

If a question arises about a mass in the left upper quadrant, the following considerations may be helpful: (1) the upper margin of the spleen is almost always concealed by the ribs; (2) the splenic notch may usually be identified; and (3) intestines do not cover the spleen, as they do renal or other retroperitoneal tumors.

At birth the weight of the spleen is about 10 gm.; at one year, about 30 gm.; at five years, about 40 to 50 gm.; at puberty, about 80 gm.; and at maturity, about 150 to 190 gm.

**Anomalies.** Congenital absence of the spleen is rare, occurring at times with cardiac and other congenital defects, especially situs inversus. Blood findings resemble those in patients with splenectomy: leukocytosis, siderocytosis, decreased osmotic fragility of red blood cells and mild normoblastemia. Some susceptibility to infection may be present; an isolated instance is known of repeated attacks of sepsis in asplenia.

Unusually small as well as large spleens are occasionally observed in infants without demonstrable cause or relation to function.

Various anomalies of shape have been recorded, among them an unusual elongation of the organ and an increased number of notches on the ventrocaudal margin.

When there is a complete transposition of the abdominal viscera, the spleen is on the right side. Elongation of the splenic pedicle permits descent of the spleen to a lower level than usual, so-called *splenoptosis*.

Supernumerary spleens are not rare and may undergo hyperplasia after removal of the principal splenic structure. They are usually located in the region of the splenic pedicle, but may be widely scattered, occasionally being in the scrotum, usually on the left side; a testicular tumor may be suspected.

**Rupture of the Spleen.** Traumatic rupture of the spleen may occur from a sharp blow to the left flank, as, for example, in automobile accidents, from a direct blow or from striking a projecting object while running, sledding, bicycling or the like.

The symptoms vary, but there are usually some or all of the following: vomiting; abdominal pain, which may not be located in the left flank; muscle spasm, tenderness and fullness in the left flank; shoulder pain, especially in the area of the left scapula; and shock. A complaint of thirst is not unusual. There is no correlation between the external

manifestations and the extent of the damage to the spleen. An increase in the pulse rate, a decline in the systolic blood pressure and an increase in the number of leukocytes, especially neutrophils, are strongly suggestive of active internal hemorrhage. Later, the decrease in the number of erythrocytes in the peripheral blood will become manifest. The lesion following injury to the spleen may be a subcapsular hematoma, which may rupture with resultant fatal hemorrhage several days after the initial injury.

When other trauma is not too extensive, removal of the spleen, as soon as adequate treatment for shock has been instituted, offers the greatest possibility for recovery. There is usually no effect upon the subsequent growth and development of the child. Occasionally the peritoneal cavity will be "seeded" by implantation of splenic fragments; intestinal obstruction may result.

Rupture of a pathologic spleen is more likely to occur than that of a normal one, and may be either spontaneous or traumatic. In the child such rupture most commonly occurs in infectious mononucleosis. In the newborn infant splenic rupture may occur in severe hemolytic disease.

**Splenomegaly in Disease.** Enlargement of the spleen may result from increase in its vascular, lymphoid or reticuloendothelial elements. The more common conditions which may be accompanied by clinical splenomegaly are listed in Table 104.

## CONGESTIVE SPLENOMEGALY

### (SPLENOPORTAL HYPERTENSION, BANTI'S SYNDROME)

In 1893 Banti described a syndrome of anemia, leukopenia, thrombocytopenia and unexplained splenomegaly, in which, as the disease progressed, the liver became enlarged and ascites and other evidence of portal cirrhosis became manifest. Death occurred as a result of hepatic insufficiency or gastrointestinal hemorrhage. Banti interpreted the disturbance as a primary one of the spleen. The syndrome is now considered to result from obstruction of the splenic venous system. Primary disturbances may be located in the liver, in the extrahepatic portal vessels or in the splenic vein.

Portal cirrhosis is the most common primary condition responsible for congestive splenomegaly. It is rare in childhood. In the Near and Far East the hepatic lesions of schistosomiasis commonly produce porto-



splenic venous hypertension and congestive splenomegaly ("Egyptian spleen"), but in the United States and western Europe the most common cause of congestive splenomegaly in children is extrahepatic vascular obstruction, usually inflammatory, which involves the portal or splenic vein, or both. Such thrombophlebitis most commonly follows omphalitis or generalized infection in early life. Neoplasms, especially pancreatic, and post-traumatic strictures of the splenic or portal veins are rare causes of congestive splenomegaly. There are at least three recorded instances of congestive splenomegaly in more than one member of a family.

**Pathology.** When persistent and severe venous hypertension leads to enlargement of the spleen, there are increases in reticular and fibrous tissues, which encroach upon the vascular spaces. The original pulp spaces become reduced to rigid channels lined with endothelium and communicate directly with venous sinuses rather than through the normal slitlike openings. The latter become occluded; and the splenic circulation eventually becomes a closed one similar to that elsewhere in the body. The circulation of blood cells becomes retarded, and deficits in erythrocytes, leukocytes and platelets in the peripheral blood accompany these alterations for some unexplained reason.

**Clinical Manifestations.** The age at onset of congestive splenomegaly varies with the primary disturbance. The onset may be insidious, splenomegaly being noted in early infancy and progressive enlargement and mild anemia developing over a period of months or years. Recurrent bouts of diarrhea may occur, and epistaxis is not uncommon. The older child may complain of a feeling of fullness or pain in the left upper quadrant. Unless splenectomy is performed, the spleen continues to enlarge and may attain enormous size.

In more than half of the patients gastrointestinal hemorrhage ultimately becomes the predominant problem. Loss of blood may be microscopic or massive, leading rapidly to death, and may arise from the upper or the lower part of the gastrointestinal tract. It may be the first event calling attention to portosplenic hypertension. There may be other signs of portal obstruction, such as extensive collateral circulation, particularly in advanced cases. Excessive bruising and recurrent epistaxis occur when significant thrombopenia develops.

**Laboratory Data.** Early in congestive

splenomegaly there are few, if any, abnormalities in the peripheral blood. As splenomegaly becomes marked, a leukopenia develops with counts as low as 1800 cells per cubic millimeter; there is a relative lymphocytosis. The platelet count is reduced to 100,000 to 160,000 per cubic millimeter, and anemia is almost always present. It may be normochromic in response to sudden loss of blood or hypochromic and microcytic in response to a deficiency of iron secondary to chronic loss of blood. Anemia may also result from excessive destruction of erythrocytes within the enlarged spleen (secondary hypersplenism),

*Table 104. Causes of Splenomegaly*

I. Vascular
Congestive splenomegaly (Banti's syndrome)
Venous obstruction
Intrahepatic
Extrahepatic
Portal
Splenic
Chronic cardiac failure
Polycythemia vera
Vascular neoplasms
Hemangiomas
Lymphangiomas
Infections
Septicemia
Typhoid fever
II. Lymphoid
Benign hyperplasia
Infectious mononucleosis
Hyperthyroidism (Graves' disease)
Malignant hyperplasia
Lymphoblastic and lymphocytic leukemias
Giant follicular lymphoma
III. Reticuloendothelial
Chronic infection
Hemolytic anemias
Primary splenic hematocytopenias (hypersplenism)
Thrombocytopenic purpura
Myeloid metaplasia
Myelocytic leukemias
Myelophthisic anemias
Agnogenic myeloid metaplasia
Malignant growth of reticuloendothelial tissue
Reticulum cell sarcoma
Endotheliomas
Hodgkin's disease and related conditions
Reticuloendothelioses
Amyloidosis; diabetic and familial (?) lipemias
Gaucher's disease; Niemann-Pick disease
Schüller-Christian disease
Nonlipid reticuloendotheliosis (Letterer-Siwe)
IV. Other
Cysts—true and false
Abscess
Metastatic neoplasm (rare)

in which case the anemia will be normochromic and normocytic with moderate reticulocytosis.

The bone marrow is normal or hyperplastic in respect to erythroid elements.

If hepatic disease with intrahepatic portal obstruction is responsible for congestive splenomegaly, abnormalities of hepatic function will be demonstrable. If portal hypertension is present, esophageal varices may ultimately be shown roentgenographically.

It is possible, with splenic puncture, to obtain a measurement of intrasplenic pressure indicative of pressure in the splenic vein. At the same time material may be aspirated for microscopic study, and a radiopaque medium injected for splenic venography. Such procedures should be done only with the opportunity immediately at hand for blood transfusion and necessary or definitive surgery.

**Prognosis.** The prognosis is dependent upon the origin of congestive splenomegaly. A localized obstruction of the splenic vein or portal system may be remedied by direct surgical means or by creation of a shunt to bypass the obstruction. If the original difficulty lies within the hepatic parenchyma, the outlook for full recovery is guarded, but many years of symptomatic relief may follow surgical diversion of the portal hepatic flow into the renal vein or the vena cava. In a few instances, after years of hemorrhagic manifestations, some decrease in bleeding may result from establishment of extensive collateral circulation to the portal vein. If surgical therapy is not possible, congestive splenomegaly eventuates in death from severe bleeding or hepatic failure.

**Diagnosis.** The diagnosis can be made only after exclusion of other conditions responsible for anemia, leukopenia, thrombocytopenia and splenomegaly. If the onset is in early life, there may be a history of omphalitis or sepsis, or a history of trauma to the upper abdomen may suggest the diagnosis in an older child. The peripheral blood and bone marrow must be carefully studied to exclude leukemias, aplastic anemias and Gaucher's disease, Niemann-Pick disease or other reticuloendothelioses. Tuberculosis, sarcoidosis and other chronic infections must also be excluded.

**Treatment.** The site and cause of vascular obstruction must be established as accurately as possible. When vascular obstruction is limited to the splenic vein, splenectomy will be curative. More commonly when larger portions of the portosplenic venous system are

involved or the obstruction is the result of intrahepatic abnormality, therapy is directed, if possible, at relief of the portal hypertension with the hope of postponing or averting hepatic failure or serious gastrointestinal hemorrhage. Splenectomy alone is rarely indicated and removes the possibility of using this vein in the creation of a vascular shunt. A splenorenal anastomosis is indicated when the point of obstruction is within the liver or between the liver and the point of entry of the splenic vein into the portal vein. If a splenorenal shunt is beyond present or future consideration, splenectomy *may* be helpful, since the blood contributed to the portal stream through the spleen is eliminated.

When the child reaches the age of eight to ten years, a portacaval shunt may be feasible. On occasion, however, if the child has not succumbed to hepatic failure or hemorrhage, the development of collateral circulation may have been adequate to have eliminated need for surgical intervention.

The course of this disease may be long and trying. The family must be aware of the signs and dangers of gastrointestinal hemorrhage. Temporary and sometimes lifesaving relief of esophageal bleeding may be obtained through emergency use of special balloons for tamponade which should be kept in readiness at home. The child is taught to swallow them; they are then inflated when at the point of probable hemorrhage. The procedure may control bleeding until transfusion therapy can be arranged.

Anemia from loss of blood may require iron therapy. Supportive measures for the relief of any hepatic disorder should be used.

## SPLENIC CYTOPENIA

### (HYPERSPLENISM)

Doan and his co-workers have described two blood dyscrasias often associated with some degree of splenomegaly in which they believe the basic disorder to be in the spleen. These are primary splenic neutropenia and splenic panhematopenia. It is postulated that in these diseases the spleen exercises a pathologic sequestration and destruction of formed elements of the blood, as it is presumed to do selectively in hereditary spherocytosis for erythrocytes and in primary thrombopenic purpura for platelets.

### PRIMARY SPLENIC NEUTROPENIA

This syndrome is an acute or chronic granulopenia presumed to be due to excessive de-



struction of neutrophils by the spleen (see also p. 965). The spleen may or may not be palpable. There is a myeloid hyperplasia in the bone marrow and active phagocytosis of large numbers of neutrophils in the spleen by macrophages. These factors, with the low white cell count in the peripheral blood, suggest that normal neutrophils are destroyed by an abnormally functioning spleen or that some abnormality in the granulocytes accounts for their destruction by the spleen. The course of splenic neutropenia may be characterized by exacerbations and remissions. During the active phase there may be fever, nausea, fatigue, and dull pain in the upper left abdominal quadrant. The total white blood cell count is usually 2000 to 3000 per cubic millimeter, but may be less than 1000, with almost complete absence of neutrophils. Splenectomy apparently controls the disease.

#### SPLENIC PANHEMATOPENIA

**Primary Type.** In this syndrome it is believed that there is an abnormal destruction of all cellular elements of the blood by the spleen. Dameshek has suggested that the abnormal action of the spleen may not be directly phagocytic, but that it may be due to an abnormal inhibiting effect of a splenic hormonal substance upon hematopoiesis in the bone marrow. The disease may apparently occur as a chronic relapsing or relatively acute condition.

Clinically, this syndrome simulates an aplastic anemia, owing to the reduction of the red and white cells and platelets in the blood. However, the marrow in primary splenic panhematopenia is hyperplastic in relation to all elements. Splenectomy may be effective.

**Secondary Type.** Splenic hematopenia may exist as a secondary factor in any condition in which there is extreme enlargement of the spleen, irrespective of the cause. Presumably the anemia, leukopenia and thrombopenia may result because the bone marrow, in spite of hyperactivity, is unable to compensate.

**Treatment.** Splenectomy is often effective in the treatment of the various splenic cytopenias. Failures have been attributed to (1) the presence of one or more remaining accessory spleens; (2) the presence of generalized reticuloendothelial hyperplasia (in such a case splenectomy would result in removal of only a small part of the offending reticuloendothelial system); or (3) failure to ascertain that the bone marrow is not primarily

at fault. Evidence of myelophthisis, hypoplasia, or toxic depression of the bone marrow must be excluded by study of the marrow before splenectomy.

Splenectomy may be considered in hypersplenism associated with thalassemia major, chronic myelocytic leukemia, Gaucher's disease and chronic lymphomas; it may be responsible for sufficient clinical improvement and prolongation of life to be justified even in a condition which is eventually fatal.

#### INFARCTION OF THE SPLEEN

Infarction of the spleen in children is rare. It has been encountered in such generalized, primarily vascular disorders as polyarteritis nodosa, thrombotic thrombocytopenia, and the like, and is a possibility in persons with sickle cell trait who travel by air. The onset is sudden, with abdominal pain in the left upper quadrant. Splenectomy has been the usual treatment; more conservative management has been suggested.

NATHAN J. SMITH

#### REFERENCES

- Anderson, N. A.: Traumatic Rupture of the Spleen in Children. *J. Pediat.*, 15:535, 1939.
- Atkinson, M., and Sherlock, S.: Intrasplenic Pressure as an Index of Portal Venous Pressure. *Lancet*, 2: 1325, 1954.
- Barcroft, J.: Features in the Architecture of Physiological Function. London, Cambridge University Press, 1934.
- Bostick, W. L.: Primary Splenic Neoplasms. *Am. J. Path.*, 21:1143, 1945.
- Bush, J. A., and Ainger, L. E.: Congenital Absence of the Spleen with Congenital Heart Disease. *Pediatrics*, 15:93, 1955.
- Parpart, A. K., Whipple, A. O., and Chang, J. J.: The Microcirculation of the Spleen of the Mouse. *Angiology*, 6:350, 1955.
- Philipsborn, H. F., Jr., Trausman, H. S., and Greer, D., Jr.: Rupture of the Spleen: A Complication of Erythroblastosis Fetalis. *New Eng. J. Med.*, 252: 159-162, 1955.
- Scott, H. W., Jr., and Bowman, J. R.: Traumatic Rupture of the Spleen in Childhood. *J.A.M.A.*, 130:270, 1946.
- Symposium: Hypersplenism. *Am. J. Med.*, 11:494, 1951.

#### *Primary Splenic Neutropenia*

- Wiseman, B. K., and Doan, C. A.: A Newly Recognized Granulopenic Syndrome Caused by Excessive Splenic Leukolysis and Successfully Treated by Splenectomy. *J. Clin. Investigation*, 18:473, 1939.

#### *Splenic Panhematopenia*

- Doan, C. A., and Wright, C.: Primary Congenital and Secondary Acquired Splenic Panhematopenia. *Blood*, 1:10, 1946.

# The Lymphatic System

The lymph vessels begin as small capillaries in the intercellular spaces of the body. These capillaries unite to form larger vessels, which join in turn to form the large lymphatic ducts which enter the subclavian veins. Tissue masses (lymph nodes and lymph nodules) are associated with this system of vessels and interrupt it in many regions. The lymph which the vessels contain is a clear, colorless fluid similar in composition to intercellular fluid except for protein content, which is about midway between that of blood serum and of interstitial fluid. As a result of the valvular construction and contractile activity of lymph vessels, lymph flows through the vessels to the lymph nodes, where it is filtered through extensive channels of reticuloendothelial tissue and again enters lymph vessels to end in the venous return to the heart.

Lymph nodes are important elements in defenses of the body against infection; they immobilize toxins of large molecular weight as well as infectious organisms. Damage by entrapped bacteria may occur, but must be extensive before the efficiency of the filter becomes so reduced that organisms pass the barrier. Lymph nodes are widely distributed, but are abundant about the large joints (popliteal spaces, inguinal areas, axillas, epitrochlear regions), in the mediastinum, retroperitoneal area and mesentery, and in the cervical region, where they filter the lymph from the upper respiratory tract and scalp.

In addition to the encapsulated lymph nodes, there are less sharply delineated and smaller collections of lymphoid tissue known as lymph nodules. These are found in the bone marrow, underlying the epithelium of

the gastrointestinal tract and in submucosal regions of the upper respiratory tract, particularly in the nasopharynx.

Besides their filtering and phagocytic actions, the lymph tissues serve as important sites of antibody production. The active germinal centers of both nodes and nodules are the chief site of production of the lymphocytes of the peripheral blood and, to a less degree, of the monocytes.

The growth of lymphoid tissue follows a pattern unlike that of other tissues. Small in amount at birth and in early life, lymphoid tissue increases rapidly during early childhood, reaches adult size by about six years and exceeds adult size from that time until puberty, when striking atrophy occurs. The actual number of nodes increases about three times in this same period. It is suggested that changes in endocrine activity are primarily responsible for the lympholysis that occurs with puberty, particularly maturation of adrenal cortical function.

During infancy and early childhood, lymphoid tissue characteristically responds to infection by rapid and excessive swelling and hyperplasia, which may last long after the primary infection which caused it has disappeared. Lymph nodes around the respiratory tract, from the tonsillar region to the mediastinum, are more frequently involved than those in other areas. Involvement of the mesenteric lymph nodes is also common. Occasionally a node or a group of nodes may harbor infection long after the original site has been cleared. Thus lymph nodes, when diseased, may be a hazard rather than a safeguard.

## DISEASES OF THE LYMPH VESSELS

*Acute lymphangitis* is a part of the local lesion of acute cellulitis; involvement of the lymph vessels and the regional lymph nodes draining an infected area is also a common accompaniment of other infectious lesions.

The inflamed superficial lymph vessels can often be seen in the skin radiating toward the regional lymph nodes.

Diffuse chronic or persistent *lymphedema* (elephantiasis) is a rare condition except in



tropical countries, where it is mainly due to the lymphangitis of filariasis (p. 588). Persistent lymphedema resulting from lymphangitis of nonparasitic origin is extremely infrequent in childhood. Localized lymphedema may result from obstruction by lymphangiomas (p. 1359) or other tumors, from surgical removal of lymph nodes or the effects of irradiation.

*Congenital lymphedema*, or elephantiasis, known as *Milroy's disease*, is limited to one or both lower extremities and apparently is usually genetically determined. The lymphedema is permanent, pits on pressure, and the limb is painless (Fig. 306). Milroy's disease may be manifest at birth or may appear later in childhood. Some cases of hemihypertrophy have been attributed to congenital lymphedema.

Chylous ascites and chylothorax are discussed on pages 686 and 818, respectively.

**Tumors of Lymph Vessels.** See page 1359.

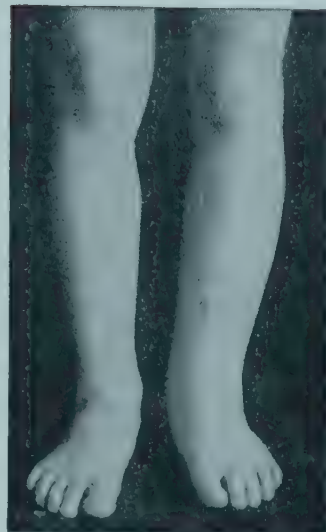


FIG. 306. Milroy's disease in a boy 8 years of age, the swelling of the left leg having been present for at least 4 years.

## DISEASES OF THE LYMPH NODES

Generalized enlargement of lymph nodes encountered in the neonatal period suggests congenital syphilis, generalized cytomegalic inclusion disease, toxoplasmosis or widespread bacterial sepsis. Subsequently generalized enlargement points most likely to infectious mononucleosis, leukemia, Hodgkin's disease or metastatic tumor. Mild degrees of generalized enlargement occur with many infectious processes, such as measles, German measles, mumps, scarlet fever, tularemia, typhoid fever and infectious lymphocytosis. A mild degree of generalized adenopathy is occasionally encountered as an adventitious finding in a child who has no apparent illness.

Enlargement of a single node or a group of nodes is much more common than generalized adenopathy. Most often it results from an infection in its drainage area. Thus a scalp infection or nasopharyngitis will be responsible for involvement of cervical nodes, and intestinal infections of mesenteric ones. However, generalized diseases such as those mentioned above may initially or even throughout their course involve only a few nodes of one or more regions.

### LYMPHADENITIS

#### ACUTE LYMPHADENITIS

**Etiology.** An acute inflammation of the lymph nodes is produced by pathogenic or-

ganisms brought generally by the lymph stream from some focus of infection, or less commonly by the blood in septicemia. If the infection is localized, only a regional group of lymph nodes is inflamed, whereas in general sepsis there may be generalized lymphadenopathy. Bacterial toxins may also be a cause of lymphadenitis, as in the cervical swelling associated with diphtheria. Lymphadenopathy may also be associated with absorption of broken down tissue from an area of trauma, particularly with extensive subcutaneous or deep hemorrhage.

**Clinical Manifestations.** The amount of swelling of the lymph nodes tends to parallel the severity of the infection in the primary focus. Common examples are the cervical lymphadenitis associated with acute tonsillitis, the mediastinal involvement in bronchitis and bronchopneumonia, and the inguinal lymphadenitis in infections about the genitals and in the lower extremities. Occasionally the lymph nodes show greater involvement than the primary site; suppuration may then take place, and an abscess may develop. If the nodes are in a small space surrounded by structures which restrict enlargement, the pain may be excruciating. The skin overlying the affected nodes may be red, and cellulitis may be present. Spasm of adjacent muscles may cause pain on movements.

Swelling of the deeper nodes in the neck may displace the lateral pharyngeal wall and simulate peritonsillar abscess.

Acute lymphadenitis of the mediastinal nodes may be sufficiently severe to encroach upon adjacent structures and cause respiratory difficulty with dyspnea, stridor, cyanosis, difficulty in swallowing, and a harsh, brassy cough. Suppuration of these lymph nodes may lead to extensive mediastinitis. Mesenteric lymph nodes are commonly involved in acute gastrointestinal disturbances in infants and children and may cause abdominal pain, at times simulating appendicitis (p. 678), as well as vomiting and occasionally diarrhea.

**Course and Treatment.** When therapy with a sulfonamide or an antibiotic is instituted early, and proper attention is given to the primary site of infection, acute lymphadenitis of the superficial nodes usually subsides relatively rapidly. Either hot or cold applications may be used, depending upon which is more comfortable for the child. When suppuration with obvious abscess formation becomes apparent, aspiration by needle or incision and drainage is necessary.

#### CHRONIC LYMPHADENITIS

As a result of persistent or recurrent tuberculous or nontuberculous infection in any local area or in any system, the lymph nodes draining these sites may become chronically enlarged because of hyperplasia and chronic fibrosis. Such nodes are generally found in the cervical region as the result of chronic tonsillitis; in the cervical, axillary, epitrochlear and inguinal regions as the result of chronic eczema with secondary skin infections. Occasionally, chronic lymphadenitis of the mediastinal nodes results from recurrent bronchitis and bronchiectasis, and chronic mesenteric adenitis from infection in the gastrointestinal tract, not necessarily tuberculous. Protracted systemic infections such as syphilis, brucellosis or tularemia may produce chronic lymphadenopathy, which may be widely distributed. Neoplasms and metabolic diseases, such as Gaucher's disease and the related disturbances of lipid metabolism, may also produce chronic changes in the lymph nodes, which should be differentiated from chronic inflammatory processes. Biopsy is urgently needed if a diagnosis is in doubt after other appropriate diagnostic studies.

In conditions associated with chronic lymphadenitis the lymph nodes are only occasionally tender and are rarely painful. Local

treatment is usually not necessary. Treatment of the underlying condition is the most important factor. In subacute and chronic lymphadenitis of bacterial origin the systemic administration of an antibiotic agent must be prolonged for as much as two to three weeks. Resolution of the inflammatory process is slow, and relapses are common when antibiotic therapy is inadequate as to specificity, dose or duration.

#### NEOPLASMS OF LYMPH NODES

Primary neoplastic disturbances of lymph nodes appear to originate in their lymphoid or reticuloendothelial elements. Those which seem confined to a single cell type are classified as sarcomas: *lymphosarcoma*, if the predominant cell is a relatively mature large or small lymphocyte; *lymphoblastoma*, if a more primitive lymphocyte predominates; and *reticulum cell sarcoma*, when this cell is the one involved. Less readily differentiated morphologic types of cells are occasionally encountered, and the tumors have been given the names of *clasmatocytoma* or *monocytoma*. In other instances there is a multiplicity of abnormal cells, and no single cell seems to characterize the proliferative process. In *Hodgkin's disease*, for example, reticulum cells, eosinophils, granulocytes, multinucleated giant cells and abundant fibrous tissue occur in abnormal amounts and destroy the normal architecture of involved nodes. In *giant follicular lymphoma* a similar but less complicated picture is encountered: large follicle-like overgrowths of immature lymphoid tissue occur which compress normal tissue, destroy the reticular pattern of the node, and are associated with masses of abnormal multinucleated cells.

All these entities are sufficiently distinct clinically so that as accurate a diagnosis as possible should be made on a histologic basis to guide treatment and prognosis.

#### LYMPHOSARCOMA

Lymphosarcoma is a malignant neoplasia of lymphoid tissues. The similarities of lymphosarcoma and lymphatic leukemia, except for their sites of predilection, have become increasingly evident: leukemia involves bone marrow and produces striking alterations in the peripheral blood, whereas lymphosarcoma may be confined for varying periods of time to the lymph nodes. Patients with lymphosarcoma frequently have classic anatomic and clinical manifestations of acute lymphatic



leukemia in the late stages of their disease.

Lymphosarcoma may be found at any age; Berghinz observed it in the newborn infant of a mother suffering from the disease. In one series of 583 patients under fourteen years of age with malignant tumors, including leukemia, twenty-seven, or 5 per cent, were diagnosed as lymphosarcoma; the incidence is twice as high in boys as in girls.

**Pathology.** The normal architecture of the node is destroyed, and rarely there are areas of hemorrhage and necrosis. Microscopically, there is an overgrowth of large or small lymphocytes which infiltrate the fibrous tissue, invade the capsule and extend beyond its borders into neighboring tissues. Extension from lymph nodes into adjacent organs occurs late in the disease and may account for splenomegaly, hepatomegaly, pulmonary infiltrations and cardiac and renal involvement. Ultimately the bone marrow is involved in many patients, and it becomes impossible to establish whether the primary disease is lymphosarcoma or lymphatic leukemia.

**Clinical Manifestations.** The presenting symptom depends upon the site of involvement; it may be a visible mass when superficial nodes are primarily involved. Such masses are rarely painful, grow with varying degrees of rapidity, and are most frequent in the cervical, axillary and inguinal regions. The mediastinum is a relatively common site of lymphosarcoma, and cough may be the first complaint, followed by rapid development of tracheal or bronchial obstruction or by chylous pleural effusion. Occasionally, respiratory obstruction may constitute a medical emergency. Retroperitoneal lymphosarcoma may give rise to disturbed intestinal or urinary function, abdominal pain or abdominal enlargement due to chylous ascites. Involvement of the lymphoid nodules of the intestinal tract may cause intestinal obstruction.

As lymphosarcoma progresses there is widespread involvement of lymphoid tissue throughout the body, with symptoms indicative of interference with functions of the respiratory, gastrointestinal or urinary system. Fever, anorexia and cachexia become major clinical features; eventually, with involvement of the bone marrow, the picture is that of leukemia with hemorrhagic disturbances.

**Laboratory Findings.** Initially there are few if any distinctive laboratory findings. An acquired hemolytic anemia may occur early in lymphosarcoma, but is more common in adults than in children. The mechanism of

its production is not understood, but it may be related to the production of abnormal proteins by the neoplastic tissue (p. 954). These "antibodies" may create difficulty in cross matching blood. The bilirubin level is elevated when a hemolytic process occurs, and a reticulocytosis of some degree is found.

When lymphosarcoma enters the "leukemic phase," the peripheral blood and marrow will reveal findings typical of lymphatic leukemia. If renal involvement occurs, there may be profuse hematuria and even renal failure.

Roentgenographic examination of the chest will usually reveal extensive mediastinal shadows, and there may be pleural effusion. Enlarged retroperitoneal lymph nodes compressing the kidney may be responsible for distortion of pyelographic shadows. Osseous lesions similar to those of leukemia may occur.

The *diagnosis* is based upon the demonstration of characteristic histologic alterations in an involved lymph node. Inasmuch as characteristic changes are often not present, even in involved nodes, several nodes suspected of being involved should be obtained for study. A definitive diagnosis should not be made on the basis of equivocal evidence, and antineoplastic therapy should not be instituted until an unequivocal diagnosis is established.

Although careful evaluation of the peripheral blood will often indicate whether the bone marrow is involved, it will usually be worth while to examine an aspirated specimen of marrow to evaluate the degree of involvement and to estimate probable tolerance to potentially depressant therapy.

**Course and Prognosis.** Although a number of agents are temporarily helpful, no recoveries from lymphosarcoma are known. With optimal management, periods of well-being may be obtained for months or years.

**Treatment.** Results of surgical removal of isolated lymphomatous masses have been disappointing, but the potentialities may need re-evaluation in combination with newer modes of therapy, especially when the process seems confined to a single readily accessible area.

Roentgen ray therapy is perhaps the most effective treatment. Local therapy usually leads to almost immediate reduction in the size of the tumor masses, often with amelioration of fever, weight loss and other symptoms of hypermetabolism. Radiation should be used with great caution, however, for mediastinal

lesions when symptoms of respiratory obstruction are present, since the treatment may cause temporary enlargement of the mass and increased respiratory obstruction. In such cases treatment should be initiated with nitrogen mustard or related substances or with cortisone.

Nitrogen mustards exert a cytotoxic effect similar to that of roentgen rays. Owing to their cytotoxic effect, toxic symptoms in susceptible patients or in those given an excessive dose may be severe. Nausea and vomiting are commonly encountered, and diarrhea occasionally, but the most serious toxic effect is depression of bone marrow, with leukopenia, thrombocytopenia and anemia. Hemorrhagic manifestations may be especially severe and are accentuated by toxic damage to the endothelium of capillaries and small vessels. The depression of bone marrow is usually most manifest three to five weeks after administration of the drug. During this period the blood should be carefully observed for signs indicating need for blood transfusion or antibiotic therapy. Nitrogen mustard is contraindicated when there is extensive involvement of the bone marrow.

Nitrogen mustard is ordinarily given in a dose not to exceed 0.1 mg. per kilogram of body weight per day on four consecutive days. Bis-beta-chloroethylmethyl amine hydrochloride is commonly used. The course of therapy must not be repeated until after an interval of four to five weeks; toxic effects may not be manifest before that time. Nitrogen mustard is given intravenously and must be administered with great care, since injection into perivascular tissue leads to severe local necrosis. It is best given by injection into the tubing of an infusion set through which physiologic saline solution is being administered. The skin of the physician handling nitrogen mustard should be well protected against accidental contamination, and he should wear protective glasses.

An extensive search has been made among compounds related to nitrogen mustards for more effective substances. Of the many ethyleneimine derivatives which have been investigated, triethylene melamine (TEM) has proved useful. It has the advantage over nitrogen mustard that it can be given orally and rarely leads to as striking evidences of gastrointestinal toxicity. Unfortunately, more severe depression of bone marrow results from overdosage of TEM than from nitrogen mustard. The dose of TEM is not well established for

children; from 1 to 5 mg. is given each day for a few days, depending upon the age and size of the patient.

The antagonists of folic acid, the purine analog 6-mercaptopurine, and ethyleneimines other than TEM may also effect temporary control of lymphosarcoma. ACTH and cortisone sometimes produce dramatic reductions in the size of tumor masses.

As lymphosarcoma progresses, supportive measures should include blood transfusion for anemia or hemorrhage and antibiotic drugs for infections. Other measures, particularly those which support the emotional comfort of the patient and family, are similar to those suggested for the child with leukemia.

### HODGKIN'S DISEASE

Hodgkin's disease is a fatal disease in which there is chronic, progressive and painless enlargement of the lymph nodes and lymphoid structures in one or more regions of the body. It is relatively rare in infants, but becomes increasingly frequent after eight years of age. Males seem to be more frequently affected than females in childhood.

**Etiology.** The cause is unknown. A variety of infectious agents have been thought responsible, but none has been established. Evidences of malignancy, such as extension of the tumor beyond the boundaries of the lymph nodes and invasion of other tissues such as the bone marrow and liver, are common.

**Pathology.** The microscopic changes of early Hodgkin's disease are diffuse hyperplasia and proliferation of large reticuloendothelial cells. Some of the latter assume giant forms, both mononucleated and multinucleated; these are the so-called Dorothy Reed or Sternberg cells. An abundant admixture of lymphocytes and eosinophils is usually present; eosinophils may be particularly prominent. The normal architecture of the lymph node disappears, and is supplanted by irregular fibrosis, particularly late in the disease. Grossly, the lymph nodes may assume a semitranslucent, pinkish-gray appearance.

These changes may be altered materially by radiation therapy, after which the nodes become denser and harder and are matted together, owing to increased fibrosis.

**Clinical Manifestations.** The first evidence is usually painless swelling of one or more groups of superficial lymph nodes, often in the cervical region. Progressive involvement



of other nodes may follow, though the rate of extension varies considerably. Involved nodes tend to be discrete, elastic and usually fairly firm. Tenderness is rare. Mechanical pressure of the enlarging nodes may produce local manifestations, such as engorgement of the vessels of the neck, or edema. Involvement of mediastinal nodes is common and may account for such symptoms as cough, hoarseness, dyspnea and dysphagia. Involvement of abdominal nodes may produce ascites, and jaundice if the biliary tract is obstructed. The spleen is commonly enlarged and may become hard; it may extend as low as the umbilicus.

Occasionally the first manifestations are fatigue, anorexia and loss of weight, with a fluctuating fever, or they may develop as the disease progresses. Periods of high fever lasting one or two weeks followed by remission may occur at regular intervals (*Pel-Ebstein syndrome*). Loss of weight and wasting may occur in such instances. Pain from pressure of an enlarged node on nerve trunks, particularly along the vertebral column, may become severe and require constant sedation. An acute variety with sudden onset of fever, anorexia, nausea, vomiting, prostration, severe anemia, leukopenia and thrombopenia, but with little or no generalized lymphadenopathy, is occasionally seen. This type resembles lymphosarcoma and leukemia, both in its course and in the systemic infiltration, which develops rapidly.

**Laboratory Data.** The blood may show little or no change early in the disease, but as the bone marrow is invaded, a progressive hypoplastic anemia occurs. The number of leukocytes may vary from 5000 to 25,000 per cubic millimeter. Before aplastic anemia develops, the blood platelets are occasionally increased in number, and there may be an increase in number of monocytes. The neutrophils may show evidence of increasing immaturity. Frequently in the terminal phase in children there are thrombopenia, leukopenia (particularly lymphopenia) and severe anemia.

**Diagnosis.** As a rule the diagnosis can be made only by exclusion of other causes of chronic lymphadenopathy and by microscopic examination of a biopsied node. In the differential diagnosis, tuberculosis, chronic infection of the nose, throat and sinuses, primary or metastatic malignancies of the lymphoid tissue, leukemia and benign granulomatous processes such as cat-scratch disease must be considered.

**Course and Prognosis.** The duration may vary from a few months to several years. In the chronic type the patient may be in relatively good health for many months. Periods of remission may be so complete that the diagnosis seems doubtful. Recurrence is invariable, however, and death results from pressure on important structures, particularly in the respiratory tract with secondary infection in the lungs, or from cachexia and extensive involvement of bone marrow.

**Treatment.** When the diagnosis is established early in the disease, surgical removal of involved tissue may be justified, provided that complete extirpation of all enlarged nodes appears to be possible. Roentgen therapy is then usually administered over the involved region to the limit of the patient's tolerance. Roentgen therapy alone often produces remarkable results when the nodes are greatly enlarged and particularly when they cause pressure on the mediastinal or intra-abdominal structures. The enlarged nodes may shrink surprisingly rapidly, with complete relief from symptoms, but the effect is temporary. After a few weeks to several months the nodes enlarge once more, and another course of roentgen therapy may be less successful. Eventually the patient develops a tolerance to such treatment.

When roentgen therapy no longer provides symptomatic relief, or if the disease is widespread when first seen, treatment with nitrogen mustard or related ethyleneimine derivatives is preferred. Their use is identical to that described for lymphosarcoma (p. 994), and the same precautions must be observed. Triethylene melamine (TEM) and the thio derivative of triethylene phosphoramidate are also used; they are relatively easy to handle and produce few toxic symptoms. Relief of pain, decrease in temperature and a feeling of well-being are often evident within a few days. These agents do not appear to increase the period of survival beyond that expected from roentgenotherapy. Other supportive measures in Hodgkin's disease are similar to those of lymphosarcoma and leukemia.

NATHAN J. SMITH  
VICTOR C. VAUGHAN, III  
LOUIS K. DIAMOND

#### REFERENCES

- Berman, L.: Malignant Lymphomas, Their Classification and Relation to Leukemia. *Blood*, 8:195. 1953.

Custer, R. P., and Bernhard, W. G.: The Inter-relationship of Hodgkin's Disease and Other Lymphatic Tumors. *Am. J. M. Sc.*, 216:625, 1948.

Desjardins, A. U.: Radiotherapy for Hodgkin's Disease and Lymphosarcoma. *J.A.M.A.*, 99:1231, 1932.

Gall, E. A., and Mallory, T. B.: Malignant Lym-

phoma: Clinico-pathologic Survey of 618 Cases. *Am. J. Path.*, 18:381, 1942.

Rundles, R. W., and Barton, W. B.: Triethylene Melamine in the Treatment of Neoplastic Disease. *Blood*, 7:483, 1952.

Shimkin, M. B., Appermann, K. C., Bostick, W. L., and Low-Beer, B. V. A.: Hodgkin's Disease, *Ann. Int. Med.*, 42:136, 1955.



# The Thymus Gland

The recognized clinical disturbances of the thymus gland are not many; they include infrequent instances of thymic tumors and abscesses, and the possible relationship of the thymic gland to myasthenia gravis. The thymus gland has occupied a uniquely important but incorrect place as a frequent cause of *respiratory obstruction* and of *sudden death*; in neither instance are there substantial data to justify a significant causative role.

**Anatomy.** The thymus is derived from the third and, at times, the fourth branchial pouch and normally descends to its position in the lower anterior part of the neck and upper part of the chest, where it resides just beneath the upper part of the sternum. Rarely the gland is entirely absent; somewhat more often there are failure of descent, unilateral or bilateral hypoplasia and fetal rests of thymic tissue in other organs, as, for example, in the thyroid and in the lungs.

The thymus has three distinct tissues: a medulla which contains the Hassall's corpuscles (transformed from the original epithelial cells), a cortex which is principally a lymphoid structure containing small round lymphocytic cells (*thymocytes*), and the supporting connective tissue. There are differences in the proportions of these various elements at different age periods. A decrease in parenchymal tissue begins about the time of puberty, with an increase in connective tissue and fat. The significance of the decrease in total size of the gland and especially in its parenchymal tissue with increasing age is not known.

For a number of years it was generally thought that a large thymus gland was a factor in respiratory obstruction and in sudden death. The data of Hammar and Boyd, however, indicate that the weights which had been considered to be those of normal glands were, in actuality, those of glands reduced in size by inanition and disease. Thymic tissue is extremely sensitive to the general nutritional status of the body. According to Boyd, severe undernutrition or disease (hyperthy-

roidism and leukemia are exceptions) will reduce the weight of the thymus by one third within three days. The range in weight of the normal thymus is indicated in Table 105. When the weights of the thymus in well nourished infants dying suddenly from adequately explained causes as automobile accidents are compared with those in well nourished infants dying suddenly from unexplained causes, there are no significant differences.

**Functions.** It is generally agreed that the thymus serves a lymphopoietic function, but there is no agreement on the many other functions which have at times been attributed to it. The principal controversy centers on whether or not the gland has any endocrine activity. The principal reported relationships are as follows: (1) Thymectomy results in genital hypoplasia, enlargement of the adrenal cortex, compensatory hypertrophy of the thyroid, and retardation of growth in the successive generation. (2) Castration, adrenalectomy or thyroidectomy prevents thymic involution or causes hyperplasia of the thymus. (3) Hypophysectomy in the prepuberal period delays involution of the thymus. The apparent relationship between the thymus and the adrenal has been responsible for an assumption that an adrenal factor rather than a thymic one may be responsible for the cases of sudden death attributed to status thymicolymphaticus. Park and McClure, after removing the gland from puppies, concluded that the organ served no essential need.

Thymectomy has been credited with improvement of some patients with myasthenia gravis. The postoperative studies of Harvey,

Table 105. Weight of Normal Thymus in Grams

	Average	Range
Birth.....	10	3-31
2 months.....	20	4-31
6 to 11 years.....	30	13-55
20 years.....	20	7-50
Old age.....	10	3-30

Lilienthal and Talbot indicate an increase in the amount of transmitter substance at the neuromuscular junction.

**Respiratory Obstruction.** Whether the thymus is ever responsible for significant respiratory obstruction is a controversial point. Although the thymus was once considered the most frequent cause of laryngeal and tracheal stridor, many clinicians of wide experience now think that it is never a factor. Laryngeal stridor and attacks of apnea and cyanosis can be explained otherwise in practically all instances if a careful study is made. The strongest arguments that thymic enlargement may be responsible for respiratory obstruction are bronchoscopic and roentgenographic observations of compression of the trachea. However, there may be some doubt whether the thymus was the cause of the compression, and in those instances credited to it some other factor may have been responsible.

There is no doubt that the thymus may cause a widening of the upper mediastinal shadow, which may be eliminated by shrinkage of the thymic tissue by roentgen therapy. There is no substantial evidence, however, that the size of this shadow bears any relation to respiratory obstruction or sudden death. Roentgenographic studies have also demonstrated that the size of the upper mediastinal shadow may be influenced by factors such as anomalous positions of the larger blood vessels, mediastinal lymph nodes, tumors, and pleural accumulations of fluid in the anterior-superior mediastinal area. Furthermore, the size and shape of the upper mediastinal shadow can be altered by a change from the horizontal to the upright position and by inspiration and expiration, the shadow being definitely larger during expiration. Roentgenographic studies for evidences of thymic enlargement should include a posteroanterior film taken in the upright position at the end of inspiration, as well as lateral films. No exact criteria are available for the range of normal measurements of the upper mediastinal shadow.

Whenever there are symptoms of laryngeal stridor, apnea or cyanosis, a complete examination with laryngoscopy, bronchoscopy and a roentgenologic study of the chest, including

visualization of the esophagus by means of barium, should be obtained (p. 877). In the majority of instances some condition such as a laryngeal or tracheal lesion, congenital heart lesion, vascular ring, chronic pneumonic infection, or tetany will be found to be the causative mechanism. Though one cannot say that there are *no* instances in which an enlarged thymus is the causative factor of respiratory obstruction, it must be extremely rare. The instances in which roentgen treatment is indicated are for practical purposes nonexistent. Routine roentgenographic examination of infants and small children for evidence of an enlarged thymus as a preliminary to a surgical procedure is now rarely practiced and is not indicated.

**Status Thymicolymphaticus (Lymphatism).** Lymphatism as a cause of sudden unexpected death is discussed on page 351. It may be stated here that the evidence available does not justify incrimination of the thymus as a cause of unexpected sudden and otherwise unexplained death. The term "status thymicolymphaticus" and its implication as a cause of thymic death should be abandoned because its use tends to inhibit an adequate search for the real cause of death.

**Neoplasms.** See page 1349.

WALDO E. NELSON

## REFERENCES

- Gilmour, J. R.: Some Developmental Abnormalities of the Thymus and Parathyroids. *J. Path. & Bact.*, 52:213, 1941.
- Glaser, J., Aponte, J. L., and Barsky, P.: Widened Roentgenographic Mediastinal Shadow (Thymus?) and Allergy in Childhood. *J. Pediat.*, 52:267, 1958.
- Harvey, A. M., Lilienthal, J. L., Jr., and Talbot, S. A.: Observations on the Nature of Myasthenia Gravis; The Effect of Thymectomy on Neuromuscular Transmission. *J. Clin. Investigation*, 21:579, 1942.
- Harvey, R. A.: Mediastinal Pleurisy in Infants. *Am. J. Roentgenol.*, 49:145, 1943.
- Panel Discussion on the Thymus Gland. Eighth Annual Meeting of the American Academy of Pediatrics. *J. Pediat.*, 14:534, 1939.
- Shapiro, A. V., and Bell, L.: Study of the "Widened" Mediastinum in Children and Pitfalls in Diagnosis. *Am. J. Roentgenol.*, 49:159, 1943.



# Disturbances of Cellular Lipid Metabolism and Related Conditions

## DISTURBANCES OF LIPID METABOLISM: THE LIPIDOSES

The term "lipid" is generic and includes all fats and substances compounded with fats. Disturbances of lipid metabolism are responsible for a number of clinical entities for which the term "lipidoses" has been proposed. Clinical interest is centered chiefly in xanthomatoses, xanthomatous tissue changes, Gaucher's disease, Niemann-Pick disease, Tay-Sachs disease, lipochondrodystrophy.

The common characteristic of these clinical disturbances is an accumulation of large, poorly staining, lipid-containing cells (histiocytes) which arise primarily from reticulo-endothelial cells in all parts of the body. Most of these diseases appear sufficiently different clinically, chemically and pathologically to be defined as clinical entities. However, occasional instances of organic involvement with cells containing poorly classifiable lipid material do occur. The specific lipid in most of the aforementioned diseases has been chemically identified and serves as one of the criteria for diagnosis and classification. Cholesterol and its esters accumulate in xanthomatous cells, cerebroside (kerasin) in Gaucher's disease and sphingomyelin in Niemann-Pick disease. In all instances a particular lipid predominates, but other lipids are also present abnormally in cells of patients with such disturbances.

Three mechanisms could be responsible for the lipidoses: (a) excessive production of a normal lipid and saturation of the tissues involved in its removal; (b) normal rate of production of an essentially normal lipid, but with an abnormality of the end organ tissues resulting in local accumulation (Unzmann's Gaucher lipoprotein hypothesis); (c) production of an abnormal lipid.

In Gaucher's and Niemann-Pick disease the lipid changes in the cells are well de-

veloped when clinical symptoms first become manifest. In the Hand-Schüller-Christian syndrome, on the other hand, the earliest lesion is a granuloma, and cholesterolization and xanthoma cell formation occur only with progression of the disease, if at all. Thus in this disease the intracellular lipid disturbance appears to be a secondary and not a primary manifestation, and for this reason the disease has been included in the reticuloendothelioses. Secondary xanthomatous tissue changes occur in other conditions when the reticular and histiocytic cells have an excessive amount of lipid material made available to them systemically as in hyperlipemic states, or locally as in chronic inflammatory reactions and neoplastic growths.

### GAUCHER'S DISEASE

Gaucher's disease may occur in two forms—the acute infantile type and the chronic type, which occurs in older children and adults. In both types the underlying disturbance is the accumulation of abnormal amounts of cerebroside in cells, primarily of the reticulo-endothelial system.

**Etiology.** The familial incidence is relatively high, but the simultaneous occurrence of infantile and chronic types is not seen within a single family. Gaucher cells may be found in the bone marrow of a parent or siblings of a patient in the absence of signs of the disease. The incidence is greater among Jewish people than in the general population.

**Acute Infantile Form.** The infant usually appears normal at birth, but soon exhibits apathy and progressive physical and developmental retardation. The abdomen becomes enlarged as first the spleen and then the liver increase in size. Subsequently neurologic

symptoms occur which progress and may include hypertonia and opisthotonos. Dysphagia and choking spells, severe cough and intermittent cyanosis are frequently present and are aggravated by increasing pulmonary infiltration with Gaucher cells. Cachexia becomes marked, and death usually occurs during the first year of life, the average duration of illness being six months after its recognition. The infantile form is rare as compared to the chronic form.

**Chronic Form.** The chronic form of Gaucher's disease is insidious in onset. More than 50 per cent of reported cases have their onset during the first decade of life. Neurologic symptoms are absent, and the disease is characterized by progressive enlargement of the spleen with resulting prominence of the abdomen. Anemia or joint pain secondary to bone involvement may also be initial symptoms. Hepatomegaly occurs early or late and is not as striking as the splenic enlargement. The patchy brownish pigmentation of the face, neck, hands and legs and pale yellow deposits in the conjunctivas described in adult cases are not ordinarily seen in pediatric patients. The disease may progress slowly or rapidly; anemia is usually prominent. Thrombocytopenia may result in hemorrhagic manifestations and often occurs early in the disease.

The bone changes, which are frequent, may give rise to pain and swelling in adjacent joints and produce a characteristic roentgenographic appearance consisting in flaring of the ends of the long bones (so-called Erlenmeyer flask appearance) with thinning and flaring of the cortex; these are most evident in the lower portion of the femur. In addition, widening of medullary cavities may occur in other bones such as the vertebrae, pelvis, tibiae and humeri, leading to pathologic fractures and severe deformities. The prognosis of the chronic form of Gaucher's disease is favorable as to life, but anemia and orthopedic problems may cause considerable handicap.

**Diagnosis.** A positive diagnosis may be established by demonstrating the characteristic Gaucher cell in the bone marrow. The enlargement of the spleen and liver and the bone changes are due to accumulations of these large, pale, round cells in the reticulo-endothelial system and diffusely in other cells as the disease progresses. The cytoplasm has a characteristic fibrillar appearance, and the nuclei are eccentrically located and frequently multiple. Gaucher cells are filled with kera-

sin, which was originally thought to differ from normal kersin in that it contains glucose rather than galactose. Why the acute infantile type of the disease has such striking neurologic involvement, which is absent in the chronic type, is unknown. Postmortem examination of the brain in the infantile type reveals a glial reaction and ganglion cell destruction with occasional foam cells.

**Treatment.** Splenectomy is indicated for symptomatic relief of pressure or thrombocytopenia, but no form of treatment has any curative effect upon the disease process. Transfusions may be indicated for anemia.

### NIEMANN-PICK DISEASE

This heredofamilial disease occurs predominantly in Jewish infants, and is usually fatal before the third year of life. The infant appears normal at birth, but soon begins to show physical and mental retardation. In spite of the general emaciation, the abdomen enlarges, and the spleen and liver usually become enormous. When the disease is fully developed, the infant appears apathetic and dull, the skin has a yellowish-brown appearance, especially on exposed parts, and anemia is usually present. The clinical picture is that of progressive emaciation and retardation (idiocy) with enlargement of the abdomen due to the massive size of the liver and spleen. Occasionally on fundal examination a cherry-red spot may be found identical to that of Tay-Sachs disease. Platelets are reduced in number late in the disease, in contrast to Gaucher's disease. Vacuolated cytoplasmic changes (lipid) in the monocytes and lymphocytes may be found in the peripheral blood. This finding is not present in other lipidoses, and thus is an important diagnostic feature.

Lipemia is not a constant feature of the disease, but rarely, and late, the fatty acids, cholesterol and lecithin, are increased in the blood. Sphingomyelin, which is increased in the tissues, is not increased in the blood. The Niemann-Pick cell with its waxy, highly refractile lipid droplets is usually readily identifiable in pathologic material obtained from bone marrow, splenic puncture or a biopsied lymph node. The cells stain characteristically with Smith-Dietrich stain (Fig. 307, A).

No treatment is successful, and death occurs in most cases before three years of age. Occasional cases are seen in which the course is relatively slow and mental deficiency may be minimal or absent.

A relationship between amaurotic idiocy



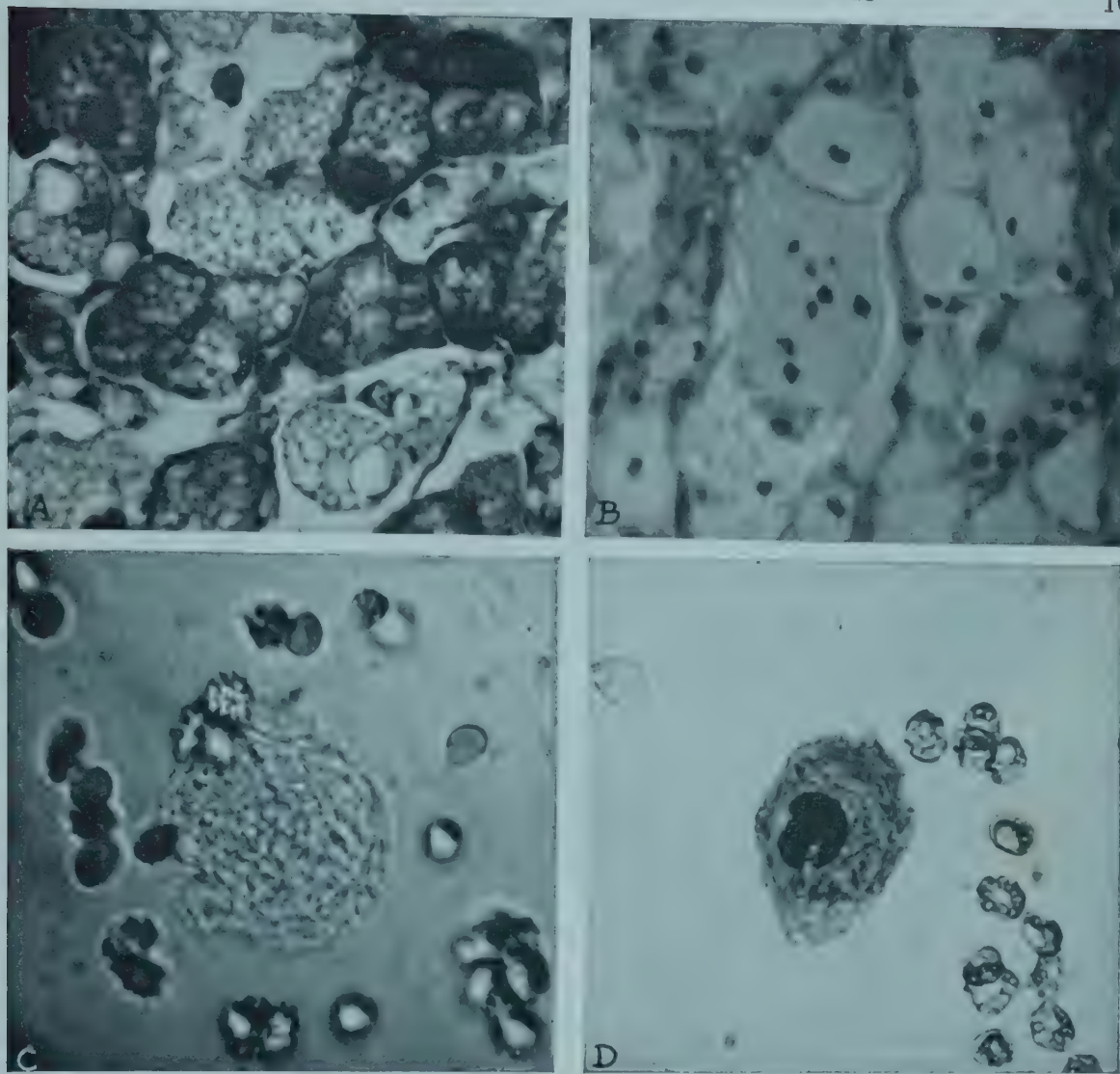


FIG. 307. Photomicrograph of characteristic cells (histiocytes) found in the various types of disturbed cellular lipid metabolism (lipidosis). A, Nests of histiocytes infiltrated with highly refractive lipid droplets characteristic of Niemann-Pick disease. B, Collection of "foam cells" typical of xanthomatosis. C, Unstained characteristic cell of Gaucher's disease obtained by splenic puncture, showing fibrillar appearance of the cytoplasm. D, Same cell stained, demonstrating the nucleus.

(Tay-Sachs type) and Niemann-Pick disease has been suggested, but at present they are regarded as separate clinical entities.

## XANTHOMAS OF THE SKIN

### (XANTHOMATOSIS)

The term "skin xanthoma" is applied to lesions which are yellow or orange, containing accumulations of fat, predominantly cholesterol. The inclusion of lipid diseases such as Gaucher's into a group called "xanthomatosis" is inappropriate.

Dermal xanthomas are classified on the basis of a normal or elevated serum cholesterol.

**Xanthomas with Normal Serum Cholesterol.** Xanthomas which exist in association

with a normal level of serum cholesterol either belong in the clinical category of xanthoma disseminatum (juvenile xanthoma) or are associated with one of the reticulo-endothelioses.

In *xanthoma disseminatum* the lesions are benign, appear in infancy, are usually multiple, are accompanied by no visceral involvement, and the patient grows normally. The cause of these lesions is unknown; they tend to disappear spontaneously, though slowly, and no treatment is necessary. The patient should be seen regularly and carefully checked with roentgenograms of the chest and long bones to rule out possible reticuloendotheliosis (Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma).

**Xanthomas with Elevated Serum Cholesterol.** Dermal xanthomas accompanied by elevated serum cholesterol are a part of the syndrome known as *xanthoma tuberosum* and are secondary to diseases which may produce chronic hyperlipemia. In *xanthoma tuberosum* the dermal lesions consist of soft yellow-brown nodules of variable size on the elbows, knees, buttocks and heels in contrast to the involvement of face and trunk in patients with *xanthoma disseminatum*. Xanthomatous swellings of the tendons may also be noted. The patient usually has relatives who have high serum cholesterol levels with or without skin xanthomas. The prognosis in this condition should be guarded, owing to the danger of involvement of the coronary arteries and

heart valves which may cause sudden death. Avoidance of excess dietary fat is recommended, but this yields no dramatic effect, since the body is able to manufacture cholesterol.

Finally, dermal xanthomas may be secondary to any chronic disease giving rise to high serum cholesterol levels such as diabetes mellitus, the nephrotic syndrome, idiopathic familial hyperlipemia, chronic obstructive hepatic disease, hypothyroidism and the hepatic form of glycogen storage disease. The prognosis for this type of dermal xanthomas is dependent entirely on that of the underlying disease.

SYDNEY S. GELLIS

## DISEASES OF THE RETICULOENDOTHELIAL SYSTEM: THE RETICULOENDOTHELIOSSES

This group of diseases includes the Hand-Schüller-Christian syndrome, Letterer-Siwe disease and eosinophilic granuloma. These syndromes are considered to be variants of the same underlying disease process, the etiology of which is unknown. The basic disorder consists in formation of granulomatous lesions of the reticuloendothelial system. Formerly the Hand-Schüller-Christian syndrome was included in the lipidoses because of accumulations of lipid in the form of cholesterol and cholesterol esters. Such accumulations may also be found in eosinophilic granuloma or Letterer-Siwe disease. Lipid deposits are most likely to occur in the slowly progressive forms of the disease and are considered secondary and not primary manifestations.

### HAND-SCHÜLLER-CHRISTIAN SYNDROME

Classically, but almost never observed, the Hand-Schüller-Christian syndrome consists in the triad of defects in membranous bones, exophthalmos and diabetes insipidus. More commonly the osseous lesions occur alone or in combination with other characteristic lesions such as *xanthoma disseminatum*, mild hepatomegaly, seborrhea of the scalp, pulmonary infiltrations and stomatitis.

The onset is insidious and usually occurs before the age of six years. Swelling and necrosis of the gums with sore mouth and re-

sorption of the alveolar bone with the extrusion of teeth (involvement of maxilla and mandible), aural discharge including involvement of the mastoid, and soft tissue swellings over osseous lesions may be the earliest signs of the disorder. Cutaneous manifestations are common and include papular rashes, seborrhea of the scalp, and petechial eruptions. Pinhead-sized nodules of *xanthoma disseminatum* may occur diffusely over the entire body or more often within the axillas and antecubital fossas or on the neck as isolated or grouped, yellow to mahogany colored, raised lesions. At this stage of the disease a roentgenogram of the skull usually discloses sharply defined defects or areas of bone rarefaction (Fig. 308). Other bones of the skeleton such as the long bones, pelvis, ribs and spine may be involved or may be the primary site of the disturbance. A biopsy taken during the early stage will show the histologic picture of a granuloma with a few scattered foam cells.

Later, growth and sexual development may be retarded, and diabetes insipidus may develop. Exophthalmos may result from accumulation of xanthomatous tissue in the retro-orbital region. Diffuse infiltration of the lungs with reticuloendothelial proliferation may result in extensive pulmonary fibrosis, and the roentgenographic appearance may superficially resemble that found in miliary tuberculosis or pneumoconiosis.



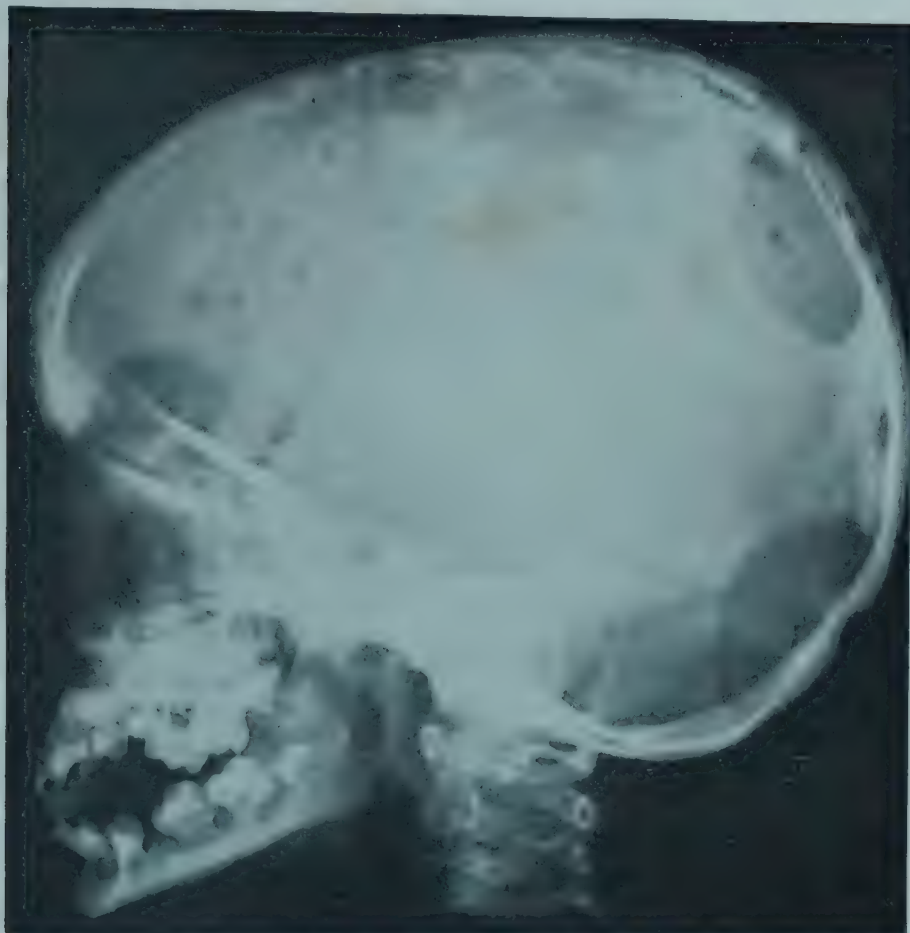


FIG. 308. Roentgenogram of skull of a child with Hand-Schüller-Christian syndrome, showing typical punched-out osteolytic lesions.

The lipid substances in the blood are not characteristically altered, and the total cholesterol is invariably within the normal range. There are no characteristic hematologic changes, although anemia is common in advanced stages of the disease. The osseous lesions, when not accompanied by other classic symptoms, may be confused with isolated bone cysts, osteitis fibrosa cystica, multiple myeloma, metastases of neuroblastoma, and osseous lesions of the lymphoma group. Diagnosis by sternal marrow aspiration is seldom successful.

The course is chronic, and spontaneous remissions may occur. The ultimate prognosis is uncertain and must be guarded even when patients are seen early and treated promptly. Intercurrent infection is not well tolerated.

The osseous lesions and the symptoms of diabetes insipidus are favorably influenced by roentgen therapy, but in many instances this effect is only temporary, and new lesions appear. Pituitrin substitution therapy by subcutaneous, nasal or rectal routes is effective in allaying the symptoms of diabetes insipidus.

### LETTERER-SIWE DISEASE

This is a disease of infancy and early childhood whose course is rapidly progressive and fatal. Apparently owing to the rapid course, xanthoma formation is minimal. The rapid progression accounts for the strikingly different clinical pattern from that of the Hand-Schüller-Christian syndrome, despite the similar basic pathologic process.

The clinical findings consist in moderate to extensive enlargement of the liver and spleen, generalized lymph node enlargement, anemia, leukopenia and thrombocytopenia with hemorrhagic manifestations, skin eruptions and skeletal changes, not unlike those seen in the Hand-Schüller-Christian syndrome. The infants fail to thrive and may have fever.

Eruptions of the skin usually appear early; they consist of petechiae, occasionally small macules and seborrhea of the trunk and scalp.

Biopsy of dermal lesions or lymph nodes permits the diagnosis of reticuloendotheliosis. In some areas foam cells containing cholest-

terol and cholesterol esters may be found in addition to the small reticuloendothelial cells. The recent procedure described by Moore of examining touch preparations from the skin for the presence of histiocytes is a valuable diagnostic aid.

The course of the disease has been affected little by radiation. At present corticosteroid therapy offers the only hope for these patients, and further experience with it is indicated.

### EOSINOPHILIC GRANULOMA

Eosinophilic granuloma is characterized by the presence of localized rarefactions involving one or more bones. Single lesions occur chiefly in older children and young adults; multiple lesions are common in younger children.

The onset is insidious, and the patient may be symptom-free, the lesion being detected on an incidental roentgenographic examination or because of the development of a spontaneous fracture. Symptoms, when present, usually are localized pain and tenderness with swelling of the adjacent soft tissues. Elevation of the white blood cell count occurs occasionally. Rarely a moderate eosinophilia may be present. Practically any bone may be involved, favorite sites being the cranial bones, the extremities and pelvis. On roentgenographic examination the lesion is clear cut and usually round or oval. The overlying cortex is not expanded, but may be destroyed by the process. Biopsy reveals a granulomatous inflammatory lesion containing mononuclear cells, polymorphonuclear leukocytes and varying numbers of eosinophils.

*Treatment* consists in surgical excision or roentgen therapy, either method resulting in rapid cure of the local lesion. The *prognosis* should be guarded, however, because of the

possibility of lesions elsewhere in the skeleton. The danger of lesions appearing later in the viscera or the skin must also be kept in mind, as well as the possible transition of the disease to the Hand-Schüller-Christian syndrome or to Letterer-Siwe disease. With increasing age the prognosis improves greatly.

SYDNEY S. GELLIS

### REFERENCES

- Avery, M. E., McAfee, J. G., and Guild, H. G.: The Course and Prognosis of Reticuloendotheliosis (Eosinophilic Granuloma, Hand-Schüller-Christian Disease and Letterer-Siwe Disease). *Am. J. Med.*, 22:636, 1957.
- Cox, P. J. N.: A Case of Letterer-Siwe Disease Treated with Cortisone. *Great Ormond St. J.*, 10: 104, 1955-56.
- Crocker, A. C.: Skin Xanthomas in Childhood. *Pediatrics*, 8:573, 1951.
- Crocker, A. C., and Farber, S.: Niemann-Pick Disease: A Review of Eighteen Patients. *Medicine*, 37:1, 1958.
- Groen, J.: The Hereditary Mechanism of Gaucher's Disease. *Blood*, 3:1238, 1948.
- Mermann, A. C., and Dargeon, H. W.: The Management of Certain Non-lipid Reticuloendothelioses; 28 Cases Treated over a 22 Year Period. *Cancer*, 8:112, 1955.
- Moore, T. D.: A Simple Technique for the Diagnosis of Non-lipid Histiocytosis. *Pediatrics*, 19:438, 1957.
- Morrison, R. W., and Hack, M. H.: Histochemical Studies in Gaucher's Disease. *Am. J. Path.*, 25: 597, 1949.
- Siwe, S. A.: The Reticuloendothelioses in Children; in *Advances in Pediatrics*, New York, Interscience Publishers, Inc., 1949, Vol. 4.
- Thannhauser, S. J.: Eosinophilic Granuloma of Bone. *J.A.M.A.*, 134:1437, 1947.
- Uzman, L. L.: The Lipoprotein of Gaucher's Disease. *Arch. Path.*, 51:329, 1951.
- Van Creveld, S.: The Lipoidoses; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1953, Vol. 6.



# The Genitourinary System

## CLINICAL ASPECTS OF RENAL PHYSIOLOGY

The initial step in the formation of urine is the passage of all filtrable constituents of the plasma from the capillaries of the glomeruli into the capsular space. The amount of filtration or capsular fluid formed is influenced mainly by the hydrostatic pressure in the capillaries, which must be greater than the combined counterforces of the osmotic pressure of the plasma proteins and the intracapsular tissue pressure. The capsular fluid supposedly contains all filtrable constituents of the plasma in the same concentration except for variations in the ionic concentrations resulting from the absence of proteins in the filtrate (Donnan effect).

During the passage of the glomerular filtrate (ultrafiltrate of plasma) through the tubules certain "threshold" substances are, under usual conditions, completely reabsorbed in the proximal segment (glucose, amino acids), and others, such as creatinine, are not reabsorbed at all. The waste products which are not reabsorbed, irrespective of the plasma concentration, are called "nonthreshold" substances. It is thought that reabsorption of water, sodium, potassium, and the like, is accomplished by independent processes. The distal tubule regulates the acid-base balance of the body by selective reabsorption of bicarbonate and alkaline phosphate, ionic exchange with hydrogen ions and by synthesis of ammonia. The tubules also have an excretory capacity and clear such substances as Diodrast, para-aminohippuric acid, phenol red, penicillin and creatinine. Potassium can also be excreted by the tubules. Water is reabsorbed in the proximal segment and in the distal tubule, largely influenced by antidiuretic hormone.

Renal excretion of a substance may be accomplished by filtration, filtration with tubular reabsorption or filtration plus tubular excretion. If a substance is completely fil-

tered from the blood by the glomeruli and then completely reabsorbed by the tubules, the clearance of this substance will be zero (e.g., glucose). If a substance were to be completely filtered and not reabsorbed at all, then the clearance of this substance would be equal to the glomerular filtration rate (e.g., inulin). Obviously a substance being completely filtered and then partially reabsorbed (e.g., urea) would have a clearance value less than the rate of glomerular filtration. Other substances (para-aminohippuric acid and Diodrast) are excreted by the tubules as well as by glomerular filtration. The tubular clearance of these substances can be obtained by subtracting the amount filtered from the total quantity of the substance found in the urine. At low concentrations of para-aminohippurate or Diodrast in the plasma, the clearance of para-aminohippurate provides a measure of the quantity of plasma which perfuses the renal excretory tissues. However, since only 92 per cent of the para-aminohippurate in arterial blood is removed by one circulation through the kidney, it is better to speak of "effective" rather than absolute renal plasma flow. The renal blood flow is computed from the renal plasma flow and the hematocrit value. The ratio of the glomerular filtration rate to the renal plasma flow is known as the filtration fraction. In the kidney 20 per cent of the plasma perfusing renal excretory tissue is filtered by the glomeruli. Blood flow through the kidney is controlled by vascular resistance, largely the arteriolar glomerular bed, which is subject to chemical and nervous control. With emotional excitement and such conditions as shock and dehydration, which decrease blood volume, blood is diverted from the kidney by vasoconstriction. Vasodilatation, as, for example, during fever, results in a greater flow of blood through the kidneys. Denervation of

a kidney does not significantly disturb its blood flow, pointing up the autonomous control of its circulation.

### GLOMERULAR FILTRATION

The formula,  $UV/P$ , is used to express the plasma clearance for a particular substance;  $U$  is the concentration of the substance in milligrams in a milliliter of urine, and  $V$  is the rate of urine formation in milliliters per minute, so that  $U$  times  $V$  is the rate of excretion of a substance in milligrams per minute. If this value is divided by the plasma concentration of this substance ( $P$  equals milligrams of the substance per milliliter of plasma), then  $UV/P$  is the volume of plasma necessary to produce that quantity of substance excreted in the urine in one minute. The clearance of a substance is thus defined as the volume of plasma from which a substance is completely removed in one minute. In man, inulin, mannitol and many other substances which are completely filtered from plasma are used to measure the glomerular filtration rate.

In man the rate of glomerular filtration is relatively constant and independent of urine flow under ordinary circumstances. During deep sleep a significant fall in the filtration rate with no change in renal plasma flow has been noted. However, the decrease in urine volume at night is thought to be due to increased tubular reabsorption of water.

The glomerular filtration rate can be altered under certain circumstances. With extreme dehydration the rate tends to decrease, and with expansion of the extracellular fluid compartment it may increase. The average rate of filtration in man is 127 ml. per minute corrected to a standard surface area (1.73 square meters). About 85 per cent of the water is reabsorbed as a passive process in the proximal tubules and about 14 per cent through antidiuretic hormonal control in the distal tubules, leaving about 1 per cent for excretion as urine. It has been proposed that the function of the loop of Henle is to establish an isotonic urine prior to its entry into the distal tubule by means of passive diffusion of water through the thin loop. Hypertonicity of the urine is thought to be accomplished in the distal portion of the nephron.

The capacity of the normal person to form a concentrated urine is dependent upon the integrity of the hypophyseal system and upon the capacity of the tubular cells to respond

to the antidiuretic hormone. It is believed that the rate of hormone release under usual circumstances is approximately 0.1 to 0.3 milliunit per kilogram per hour. Adequate quantities of administered antidiuretic hormone will prevent or blunt water diuresis.

Administration of hypertonic solutions such as mannitol results in an increased urine flow with a urinary osmotic pressure approximating the osmotic pressure of the plasma (osmotic diuresis). Under these circumstances the distal water reabsorption may be limited to a maximal rate of 5 to 7 ml. per minute per 1.73 square meters.

The maintenance of a constant osmotic pressure is important to physiologic functions; the kidneys play a large part in maintaining this homeostasis. Excretion of sodium, a main cation of the circulating fluid, is controlled by such factors as glomerular filtration rate, plasma sodium concentration, actions of the adrenal cortical hormones, the natriuretic action of the antidiuretic hormone, the activity of the tubule cell and possibly by other influences. The amount of sodium excreted in the urine under normal circumstances is less than 0.5 per cent of that which is filtered. The reabsorption of sodium is supposed to occur in two active processes: first, proximal reabsorption, which is independent of passive water diffusion and accounts for about 80 per cent of the sodium filtered; second, distal reabsorption, which accounts for about 19 to 20 per cent of it. The maximal effect of mercurial diuretics is inhibition of sodium reabsorption in the distal tubules. A small fraction (about 1 per cent) may be involved in ionic exchange for hydrogen, ammonia or potassium.

Adrenal cortical hormonal control regulating excretion of sodium is demonstrated in patients with adrenal cortical insufficiency, in whom the output of sodium is greatly increased. This increase involves failure of tubular reabsorption, since it occurs in the face of a low glomerular filtration rate. The antidiuretic hormone, with certain reservations, can prevent tubular reabsorption of sodium. The effect of the antidiuretic hormone on reabsorption of chloride is more striking, since increased excretion of chloride is observed with small doses of Pitressin in which contamination with the oxytocic factor is not usually present.

Since reabsorption of chloride usually follows that of sodium, generalizations concerning reabsorption of sodium also apply to reabsorption of chloride. It is incorrect, how-



ever, to assume a similar mechanism for excretion of sodium and chloride under all circumstances.

Potassium, unlike sodium, chloride and bicarbonate, is excreted by the renal tubules as well as reabsorbed. The reabsorption of potassium is thought to occur in the proximal tubule, with excretion of it in the distal segment. Although the mechanism of potassium excretion is unknown, it is believed that it is exchanged for sodium. Adrenal steroids and antidiuretic hormones augment the excretion of potassium.

## TUBULAR REABSORPTION

The discussion so far has emphasized the specific role of the kidneys in regulating the electrolyte composition and fluid volume of the body. The following consideration will emphasize the role of the kidneys in the excretion of waste products or foreign substances, the conservation of other products and the maintenance of acid-base equilibrium.

**Diffusion.** Urea, the end product of protein metabolism, forms a large part of the urinary solutes (osmotic load). The plasma urea clearance represents the volume of plasma completely cleared of urea per minute. The urea clearance ranges from 30 to 60 per cent of the inulin clearance and is influenced by the urine flow. Urea is completely filtered by the glomerulus, but a large portion diffuses back through the tubular cells. Since urea excretion is influenced by many variables, it cannot be assumed that its clearance bears a direct relation to the filtration rate. However, the urea clearance is of value as a guide to appraise renal function.

**Active Reabsorption.** Substances which are not present in the urine or which appear in lower concentration than in the plasma cannot be reabsorbed by diffusion, but require the expenditure of energy. In such instances there is a limit on the quantity which can be reabsorbed in a given time (tubular maxima— $T_m$ ). Tubular maxima may be explained on the basis of the law of mass action, the transfer of a substance (glucose) from the tubular lumen through the cell being dependent upon a fixed quantity of cellular constituents which handle the transport substance (glucose), and the rate at which these constituents liberate the transfer substance to the blood. Another explanation may be the competition for available free energy. Since these systems are activated by enzymes, the possibility of the presence of enzyme inhibi-

tors which limit active transport of tubular substances must be considered. Several such transport systems have been described.

**Glucose.** Glucose is completely filtered from the plasma. The rate of tubular reabsorption of glucose is estimated by the difference between the quantities filtered and excreted per minute. As the plasma concentration of glucose is elevated, a level is reached at which the tubular reabsorption of glucose occurs at a maximal and constant rate. This maximal rate is designated by the symbol  $T_m$ , and a suffix is attached to indicate the substance ( $T_{mG}$ ). With further increases in the plasma glucose concentration no additional glucose can be reabsorbed; consequently glycosuria results. In man the average  $T_{mG}$  is 375 mg. per minute. Xylose appears to compete with the glucose transport system.

**Phosphate.** A large portion of the urinary phosphate is in inorganic form (acid and alkaline phosphate). Phosphate, the main buffer in urine, is utilized by the kidney in the excretion of acid and the conservation of base. Plasma inorganic phosphate is filtrable through the glomerulus and, since the urine may be free of phosphate, must be reabsorbed by the tubule. In dogs, when the plasma level is normal or below normal, all filtered phosphate is reabsorbed. Tubular reabsorption remains constant, so that when the plasma level exceeds this capacity, urinary spillage results.

Acidosis increases the excretion of phosphate, particularly during the first several days until the production of ammonia becomes significantly increased. Nevertheless the phosphate reabsorptive system is relatively stable and appears to maintain a constant plasma phosphate level.

**Amino acids.** Clearances are low. Extensive reabsorption of each amino acid must occur, and individual amino acids apparently are processed differently.

**Sulfate.** Sulfate is reabsorbed by an active process and is limited by a maximal rate of reabsorption. Sulfate reabsorption is independent of chloride and phosphate concentrations in the tubular urine.

**Uric acid.** Uric acid, an end product of purine base metabolism (nucleic acids), appears to have a maximal rate of reabsorption of about 15 mg. per minute. In man the uric acid clearance is about 6 per cent of the filtration rate.

**Vitamin C.** Vitamin C (not synthesized in man) is excreted when the plasma level is above 1.0 to 1.3 mg. per 100 ml. The rate

of reabsorption of vitamin C in man averages 2 mg. per minute.

## TUBULAR EXCRETION

A substance having a clearance greater than the glomerular filtration rate is either actively excreted by the renal tubules or synthesized by the kidneys. Many of these substances (para-aminohippurate, phenol red, Diodrast) are irreversibly bound to plasma protein albumin. The equilibrium between free and bound dye depends upon the amount of dye present and the protein concentration. The rate of excretion of a substance is limited by a maximal tubular rate characteristic for it. As the concentration of this substance is increased in the plasma, more will be excreted in the urine until the transport system reaches its limit. However, in tubular excretion, contrary to tubular reabsorption, all substances are apparently excreted by the same system. Competition occurs when two substances demanding excretion are present in the plasma.

**Creatinine.** Exogenous creatinine in man is excreted by the tubules. The ratio of creatinine to inulin clearance averages 1.4 to 1. Exogenous creatinine clearance is depressed by raising the plasma concentration of creatinine. Endogenous creatinine clearances are used as a measure of glomerular filtration rate; most methods measure endogenous chromogen materials. Since there are variations in the plasma endogenous chromogens throughout the day, serial plasma determinations are necessary. In renal disease the endogenous creatinine/inulin clearance ratio increases to as much as 2.6 to 1. The endogenous creatinine clearance may also vary from the inulin clearance under conditions of dehydration and with osmotic diuresis.

**Phenol Red (Phenolsulfonphthalein).** This dye is used to measure renal function because it is rapidly excreted under normal circumstances and its excretion is reduced in renal disease. This measurement is gross at best, however, when used in the customary way, because at low plasma concentrations the excretion of this dye approximates renal plasma flow and at high plasma concentrations measures tubular excretory capacity.

**Diodrast and Para-aminohippuric Acid.** At low plasma concentration para-aminohippurate and Diodrast are considered to measure renal plasma flow (about 640 ml. per minute). At high plasma concentration these substances are excreted by both the tubules

and the glomeruli. The maximal rate of excretion for Diodrast is about 53 mg. per minute, while that for para-aminohippurate is about 79 mg. per minute.

**Penicillin.** Penicillin is excreted by the tubules at a clearance rate of about 550 to 900 ml. per minute, a rate approximately equal to that of the renal plasma flow. A maximal rate for tubular excretion has not been found. Carinamide depresses tubular excretion of penicillin, resulting in a higher plasma concentration.

## SPECIAL CLEARANCES

**Sulfonamide Compounds.** The unconjugated sulfonamide compounds have clearances less than the glomerular filtration rate. These clearances are influenced by the rate of urine flow, the electrolyte excretion and the pH of the urine. The acetylated compounds are also excreted by the tubules, as evidenced by the fact that their clearance values are greater than the filtration rates. Clearances of the conjugated compounds are not constant, because these forms are bound to plasma albumin in variable amounts. Alkalinization of the urine diminishes the tubular reabsorption of certain sulfonamides. Sulfonamides are believed to inhibit enzyme systems of carbonic anhydrase and consequently to interfere with acidification of urine.

**Salicylic Acid.** The conjugated and unconjugated forms are excreted together. At low urinary pH the clearance is about 5; at higher urinary pH it may approach the glomerular filtration rate. Salicylic acid is conjugated with glycine to form salicyluric acid and possibly glucuronic acid. Plasma protein binding occurs with salicylic acid; conjugated forms appear to be excreted by the renal tubules. The unconjugated forms in an acid medium are reabsorbed by the tubules at a clearance ratio close to that of urea; in alkaline urine clearances tend to be increased.

## ACID-BASE REGULATION

Selective reabsorption of alkaline phosphate and bicarbonate by the tubules helps to restore the two main buffers to the plasma. Virtually all the plasma bicarbonate filtered through the glomeruli is reabsorbed at plasma bicarbonate levels of about 28 mEq. per liter or below; at higher plasma concentrations the excess is excreted in the urine. It is believed



that the proximal tubules reabsorb a large portion of the bicarbonate, and about one fifth of the total reabsorption occurs in the distal tubules. Since excretion of chloride depresses reabsorption of bicarbonate, an interdependent relationship is presumed between these two anions in the proximal tubules. The reabsorption of bicarbonate in the distal tubule is thought to be independent of water and chloride, being effected by the ion exchange mechanism. The mode of excretion and the mechanism of buffer action in the base-saving action of phosphate have been discussed earlier in this section. At a pH of 7.4 alkaline phosphate makes up about 80 per cent and acid phosphate about 20 per cent of the inorganic phosphate. At a pH of 4.8 nearly all the phosphate exists as acid phosphate, making available to the body almost one milliequivalent as base-saving equivalent per mol of phosphate excreted.

The tubular excretion of hydrogen ions results in replacement of base by an exchange mechanism. Bicarbonate is converted into carbonic acid, which eventually dissociates into carbon dioxide and water. The carbon dioxide remaining in the tubule passes into the blood and eventually is excreted by the lungs. The net result of this renal process is the saving of base. The average man excretes about 25 to 30 mEq. of free acid each day. The quantity of buffers within the tubular urine is a factor in determining the rate of excretion of titratable acid. During diabetic acidosis free acid excretion may reach values of 150 mEq. per day. In chronic glomerular nephritis, in which this mechanism of ion exchange is impaired, the excretion of titratable acid may fall to 2 mEq. per day.

The average excretion of ammonia in man is about 50 mEq. per day. This cation is excreted with fixed acids. With an excessive acid load as in diabetic acidosis, ammonia excretion may increase tenfold. Ammonia ions replace cations (sodium) and are excreted with phosphate and other fixed acids. The amide nitrogen of glutamine is believed to provide about 60 per cent of the ammonia excreted. The enzyme glutaminase, present in sufficient quantities in the kidney, is thought to catalyze the reaction of glutamine to ammonia. The remaining fraction (40 per cent) of ammonia excreted in the urine is believed to be derived from alpha amino nitrogen. Ammonia exchange is considered to occur in the lower portions of the nephron (lower distal segment).

## RENAL FUNCTION IN YOUNG INFANTS

Renal function in adults is used as a standard of reference in estimating renal functional capacity in the infant. Comparative body weight, height, surface area, renal weight and basal metabolic rate have been suggested as standards of reference. Most observers have used the adult surface area of 1.73 square meters as a reference, and, unless otherwise stated, the clearance values in this section are all corrected to 1.73 square meters. It might be more desirable to use one square meter as a unit, if only for simplification of calculations. Renal function in the young infant differs quantitatively rather than qualitatively from that in the adult. Adult values for glomerular filtration rate, renal plasma flow and maximal tubular excretion of para-aminohippurate may be reached in some infants by about six months of age and in most infants by two years. The glomerular filtration rate in the young infant is about 25 to 50 per cent of that of adult values. Factors contributing to the lowered filtration rate may include afferent arteriolar constriction, persistent fetal cuboidal glomerular membranes and small, underdeveloped glomerular capillaries.

Effective renal plasma flow, as measured by para-aminohippurate, averages about 20 to 40 per cent of adult values.\* Thus it would appear that more plasma (30 per cent) passes through the glomeruli of young infants than of adults (20 per cent). Clearance values for the maximal rate of tubular excretion (para-aminohippurate) are about 20 to 40 per cent of the adult values, indicating that glomerular function develops more rapidly than tubular excretory capacity at this age period. The maximal rate of tubular reabsorption for glucose is about 20 to 35 per cent of the adult range.

The young premature infant can concentrate urine to about half the capacity of the adult. Full maturity of this function can be attained as early as two months of age. The rate of solute excretion with osmotic diuresis is about half that in adults. This limitation of the infant's kidney must be considered when administering saline solution. With osmotic diuresis, water reabsorption in the distal tubule appears to be limited as in the adult, but this ceiling is not greater

\* Until extraction ratios for para-aminohippurate have been estimated in infants, these figures must be accepted as tentative values.

than 2 ml. a minute per 1.73 square meters (about one half of adult values). The response of the renal tubule of the young infant to intravenously administered Pitressin also appears to be less than that of the adult. Excretion of the major electrolytes is low in young premature infants, possibly 20 per cent of that in adults. Young infants excrete little inorganic phosphate, presumably owing to their lowered glomerular filtration rate. When additional phosphate is presented to the tubules of young infants, the proportion reabsorbed is less than that in adults. Since breast milk has a relatively low phosphate content, the excretion of phosphate by breast-fed infants is at a low level, resulting in less buffer substrate for base conservation.

The young infant seems to have no difficulty in diluting urine (water diuresis). As early as the fifteenth day of life he can excrete as dilute urine as the adult (as low as 50 milliosmols per liter).

With an acid load (chloride) premature infants excrete less urinary ammonia than do full term infants. However, some premature infants at thirty days of age studied in our laboratory were able to increase the urinary ammonia excretions by tenfold (136 mEq. per 1.73 square meters per day) in response to oral administration of 7 mEq. per kilogram of body weight per day of calcium

chloride. The young infant, per unit of surface area, can excrete hydrogen ions in response to an acid load comparable to the adult when sufficient phosphate buffer is made available in the tubular urine.

Bicarbonate excretion appears to follow the same pattern as it does in adults, and the mechanism for bicarbonate absorption and excretion may be fully developed early in life.

PHILIP L. CALCAGNO

## REFERENCES

- Barnett, H. L., and Vesterdal, J.: The Physiology and Clinical Significance of Immaturity of Kidney Function in Young Infants. *J. Pediat.*, 42:98, 1953.
- Calcagno, P. L., and Rubin, M. I.: Effect of Dehydration Produced by Water Deprivation, Diarrhea and Vomiting on Renal Function in Infants. *Pediatrics*, 7:328, 1951.
- McCance, R. A.: Renal Function in Early Life. *Physiol. Rev.*, 28:331, 1948.
- : Renal Physiology in Infancy. *Am. J. Med.*, 9:229, 1950.
- McCrory, W. W., Forman, C. W., McNamara, H., and Barnett, H. L.: Renal Excretion of Inorganic Phosphate in Newborn Infants. *J. Clin. Investigation*, 31:357, 1952.
- Rubin, M. I., Bruck, E., and Rapoport, M.: Maturation of Renal Function in Childhood. *J. Clin. Investigation*, 28:1144, 1949.
- Smith, H. W.: *The Kidney: Structure and Function in Health and Disease*. New York, Oxford University Press, 1951.

## URINE AND URINATION

The kidneys are distinctly lobulated and comparatively large at birth and generally extend below the crest of the ilium, especially on the right side. Their weight is about 23 gm. (0.8 ounce), or 0.75 per cent of the total body weight in contrast to 0.45 per cent in adult life.

The kidney is composed of a large number of individual units termed nephrons. The nephron consists of a capillary tuft or glomerulus and an unbranched tubule. There are about 1,000,000 nephrons in each kidney. The tubules drain into a series of collecting tubules, which in turn empty into the renal pelvis. In fetal and neonatal life Bowman's membrane is composed of cuboidal cells which later change into thin, flattened cells, and the glomerular tufts have fewer discrete loops. It is thought that these anatomic differences may account in part for the decreased

filtration rate (inulin, urea) of the very young infant.

In the kidney of the newborn infant, section often reveals reddish-yellow streaks in the apices of the papillae. These are deposits of urates (uric acid infarcts) chiefly in the straight portions of the tubules in the medulla. Sodium, calcium and phosphorus salts and oxalic acid may also be found.

The bladder of the infant is practically an abdominal organ, since the small pelvis is not capable of containing it.

## NORMAL URINE AND URINATION

Excretion in the human kidney begins about the ninth week of fetal life and is continuous. Dilute urine has been found in the bladder of the four-month fetus. At seven months' gestation uric acid has been found in the kidney, and urea has been detected in the



amniotic fluid as early as two and a half months of gestation.

**Amount.** Urine is usually present in the bladder at birth, but little is secreted during the first two or three days of life. Occasionally infants have considerable edema at birth, and much of this fluid may be excreted in the urine during the next forty-eight hours. As soon as the child begins to take fluid, the urinary secretion is increased and is proportionately greater throughout childhood than in adult life. The amount is exceedingly variable; it is influenced by many factors, such as the amount of liquid ingested, the environmental temperature and the states of the digestive and nervous systems.

**Frequency of Micturition.** The frequency varies from two to six times in the first and second days of life. Commonly the infant does not void until more than twelve hours after birth, and often not until the second or even the third day of life. Excretion after this is frequent during infancy, varying from five to thirty or forty times in twenty-four hours; the urine is often retained for several hours during sleep. After control of the bladder has been obtained, the frequency of urination varies from six to eight times in twenty-four hours.

**Physical and Chemical Characteristics of the Urine.** The specific gravity during the first few days of life is relatively high (1.012), but after the ingestion of milk begins it falls rapidly to 1.002 to 1.006. The infant's kidneys, however, are capable of concentrating during restriction of water. In the premature infant this concentrating capacity is limited. The full term infant attains the ability of the adult to concentrate urine by about three months of age. The loss of concentrating capacity is evidence of renal disturbance. When solid food is added to the diet, the specific gravity of the urine gradually increases.

The urine is at first highly colored and slightly turbid, owing to its concentration and to the presence of urates and mucus. Later, even during childhood, it is generally paler yellow than in adult life. Sometimes in infancy, particularly in the newborn, it stains the diaper faintly red through the decomposition of urates. The reaction of the initial urine of the newborn is decidedly acid, but after a few days approaches neutrality; that of the morning urine is less acid than that of the afternoon. The pH varies between 5 and 7. Odor is almost absent in freshly voided urine in infancy and even in childhood un-

less the urine is highly colored. The ammoniacal odor often noted in the nursery is due to delay in changing the diapers, the urine decomposing after it has been passed.

There is little *urea* in the urine at birth. The proportion is increased by the third day, but is still relatively low during infancy. Phosphates, chlorides and sulfates are present. The concentrations of these are increased when a mixed diet is started, but still are less than in adults. McCance showed that infants after the first few days of life reabsorb a greater percentage of their filtered sodium and chloride than do adults. The amount of urea is greater in childhood than in adult life, when compared on the basis of body weight, but forms a smaller percentage of the total nitrogen excreted than in adults. Approximately 80 per cent of the urinary nitrogen is excreted as urea, 5 to 15 per cent as ammonia, and the rest as uric acid, creatine and creatinine. (Approximately 2 per cent of the total urinary nitrogen is excreted as alpha amino nitrogen, and approximately 2 per cent of the milliequivalents of organic acids in the urine consists of amino acids.) The percentage of uric acid is especially high in the newborn period, after which it diminishes, but it remains higher in childhood than in adult life. The relation of uric acid to urea is 1:14 in the newborn and about 1:70 in the adult.

About 7 to 10 mg. of *creatinine* per kilogram of body weight are excreted daily by the newborn, about 20 mg. at two years of age, and 30 to 40 mg. in adult life. The quantity of creatinine excreted varies somewhat with the protein intake; nevertheless the daily output is relatively constant and is directly proportional to the amount of body musculature. Creatinuria has an important relation to thyroid activity, being low in the cretin and rising to normal levels with thyroid administration.

*Creatine* is excreted in variable and large

Table 106. Average Daily Excretion of Urine

Age	Fluidounces	Cubic Centimeters
First and second days.....	1-2	30-60
Third to tenth day.....	3-10	100-300
Tenth day to 2 months.....	9-15	250-450
2 months to 1 year.....	14-17	400-500
1-3 years.....	17-20	500-600
3-5 years.....	20-24	600-700
5-8 years.....	22-34	650-1000
8-14 years.....	27-47	800-1400

amounts by infants and to a less degree by children up to puberty; in the male excretion of it ceases a few years before this time. For some unexplained reason premature infants excrete almost no creatine.

*Indican* is not usually found in the urine of healthy breast-fed infants, but in those fed artificially indican is generally present in small quantity. Older children on mixed diets excrete indican to the same extent as do adults.

*Albumin* in small amounts may often be found in the urine of healthy newborn infants during the first ten days of life, and throughout childhood with very sensitive tests a small amount can usually be discovered (average, 35 mg. per twelve hours).

*Sugar*, detectable by ordinary clinical meth-

ods, is frequently found in the urine of the newborn and in early infancy, when relatively large amounts of sugar have been ingested. With tests more sensitive than the usual copper reduction one, carbohydrates, both fermentable and unfermentable, may be discovered in the urine of children (between 0.3 and 0.9 gm. per twenty-four hours).

*Glycocoll* is a normal constituent in the urine of the newborn, and *urobilinuria* is common in healthy infants. *Rennin* and *pepsin* (these being perhaps the same substance) are also discoverable in the urine of children.

Careful examination, as by the Addis count, will in normal children almost always reveal casts, red blood cells and white cells (see below).

## DIAGNOSTIC TESTS USED IN THE STUDY OF KIDNEYS

### TESTS MEASURING INFLAMMATORY AND ANATOMIC STATUS OF THE KIDNEYS

**Routine Urinalysis.** Special emphasis should be placed on tests for specific gravity, acid-base reaction, albumin, sugar, acetone and occult blood and on microscopic examination for white and red blood cells, epithelial cells, and casts.

**Addis Count.** This test, which determines the physical status of the nephron, is carried out as follows: A normal breakfast is served at 8 A.M. After this no fluids are permitted until the test is complete; the patient has a "dry" lunch and dinner. Before retiring at 8 P.M. the patient voids, and this specimen is discarded. All urine passed from this time, including a voiding at 8 A.M. the following morning, is combined as a single sample. In the normal child this twelve-hour collection of urine will contain up to 1,000,000 red blood cells, 1,000,000 white blood cells, 10,000 casts and 40 mg. of protein. This specimen also gives a good estimation of the concentrating power of the kidney. In the normal child, because of the limited intake of fluid, the specific gravity is usually over 1.022. In inflammatory renal disease there is a sharp rise in formed elements and in the quantity of albumin.

**Erythrocyte Sedimentation Rate.** This test is used to indicate the existence of inflammatory disease. Though it does not specifically indicate renal disease, it can be used to determine the continuation or cessation of known inflammatory renal disease.

**Intravenous and Retrograde Pyelograms** provide a means to detect gross anatomic abnormalities and a crude measure of renal excretory function.

### TESTS MEASURING FUNCTIONAL INTEGRITY OF THE NEPHRON

**Concentration Test.** This test measures the capacity of the kidney to excrete a concentrated urine,

which is largely a matter of distal tubular integrity. This is probably the most practical test of the functional status of the kidney; it may be used alone to follow the course of renal disease. As the disease progresses, the specific gravity falls and finally becomes fixed at low levels ( $>1.010$ ). When the specific gravity is fixed at a low level, large volumes of urine must be excreted in order to eliminate the waste products. When polyuria does not occur because of inadequate fluid intake, cardiac failure or renal inability to excrete water, the body wastes accumulate in the blood and tissue fluids, resulting in decompensated impairment of renal function. The inability of the kidney to concentrate in acute nephritis may be striking and persists long after the urea clearance test has returned to normal. If the diet is low in salt, the values may be falsely low.

When albuminuria is massive, the specific gravity should be corrected.

The concentration test can best be carried out as described under the Addis Count. Whenever there is

Table 107. Elevation of Specific Gravity of Urine\*

Quantities of Substances Needed to Elevate Specific Gravity of Urine 0.001 at 15° C.

Urea . . . . .	3.595 gm.
Glucose . . . . .	2.700 gm.
Sodium phosphate . . . . .	3.792 gm.
Disodium phosphate . . . . .	0.979 gm.
Sodium chloride . . . . .	1.473 gm.
Sodium sulfate . . . . .	1.405 gm.
Albumin . . . . .	3.892 gm.

\* From Albarran, in Fishberg, A. M.: Hypertension and Nephritis. 4th ed. Philadelphia, Lea & Febiger.



a low specific gravity, it is important to observe whether edema fluid is being evacuated, since this may simulate the inability to concentrate.

The urine in early infancy is dilute. The specific gravity seldom rises above 1.010. The infant's kidney is capable of concentrating, however, and does so during dehydration. Infants of one to two months of age can concentrate urine solutes to a level of 1.2 osmols per liter. This is almost at adult level, which is about 1.4 osmols per liter. The premature infant rarely concentrates urine above 0.7 osmol per liter.

**Acid-Base Regulation.** The capacity of the kidney (distal renal tubule) to adjust its base-saving mechanisms (hydrogen ion exchange and ammonia production) in the presence of acidosis can be tested by administration of an acid salt such as calcium chloride. Under normal conditions, and in the presence of adequate phosphate excretion, the metabolic acids are excreted to some extent in free titratable form, and the pH of the urine falls. During this time some fixed base is lost in the urine. Within a day or so after birth there is a significant rise in ammonia production, and the metabolic acids are excreted in combination with ammonia to save body base. In the normal adult the ratio of ammonia/acid (titratable) varies from 1 to 2.5. The most acid urine which the kidney can form is pH 4.5. This capacity to excrete an acid urine and to produce adequate amounts of ammonia may be lost in the presence of disease. The premature infant is thought to have a limited capacity for ammonia production in response to an acid load.

#### TESTS MEASURING ABILITY OF THE KIDNEYS TO CLEAR BLOOD OF VARIOUS SUBSTANCES

**Urea Clearance.** Breakfast is withheld, but the child is given  $\frac{1}{2}$  pint of water to ensure an adequate urinary output. At the start of the test period the bladder is emptied and the urine discarded. After this, urine is collected for two to four hours. It is imperative that the length of the collection period and the quantity of urine excreted be measured with extreme accuracy, since the results of the test are based on the volume per minute of urine excreted. The length of the period is otherwise unimportant, except that longer intervals permit more accurate readings than shorter ones. A blood sample is obtained at a point midway in the urine collection. The blood and urine are analyzed for urea. The value of the urea clearance when the urine flow is 1.5 cc. per minute or over (maximum clearance  $UV/B$ )\* is constant and does not vary with the urine volume. Under such circumstances an average of 75 ml. of whole blood per minute is cleared of urea. When the urine volume falls below 1.5 ml. per minute, the clearance is said to vary with the square root of the urine volume—

standard clearance  $\frac{U\sqrt{V}}{B}$ . This equals an average

\*  $U$  = Micrograms of urea or urea nitrogen per 100 cc. of urine.

$B$  = Micrograms of urea or urea nitrogen per 100 ml. of blood.

$V$  = Volume of urine in cubic centimeters per minute.

clearance of urea from 54 ml. of whole blood per minute. In order to place the two formulas on a mathematically equivalent basis, the urea clearance, whether maximum or standard, is commonly expressed as per cent of normal. In children the urinary volume ( $V$ ) is corrected for the difference in surface area between the child and the adult. Urea clearance values above 75 per cent of normal usually, though not always, indicate intact renal function. Those between 50 and 75 per cent are in the doubtful range, and those below 50 per cent indicate decreased renal efficiency. In the presence of cardiac failure, however, low clearance rates should be accepted with caution.

Urea is filtered through the glomerulus and partially reabsorbed through the tubule, so that its total clearance is a measure of the functional status of both structures. In health approximately 60 per cent of the urea filtered finally appears in the urine. This is not a constant figure, however, for the slower the urine flows down the tubule, the greater is the amount of tubular reabsorption. Because of this variability the urea clearance test is not an accurate guide to the rate of glomerular filtration. The amount of urea that diffuses back into the blood is closely related to tubular reabsorption of water. This test should not be performed when the urine volume is rapidly increasing, for falsely high values may be obtained.

**Other Clearance Tests. Glomerular filtration.** This can now be estimated by measuring the clearance of the polysaccharide, inulin and the hexitols, mannitol, sorbitol and others. In the normal adult kidney  $UV/B$  for these substances averages 125 cc. per minute. The glomerular filtration rate in the infant in the first few months of life is at a much lower level. In the newborn period values from 40 to 50 cc. per minute are obtained (corrected to the adult surface area of 1.73 square meters). McCance and Widdowson recommend that the volume of total body water be used as the standard of comparison between infants and adults when measuring the glomerular filtration rate. These values gradually rise; many of them, when corrected for surface area, are within adult values by six to eight months of age, and most by two to three years. These sugars are not reabsorbed by the tubule and therefore are a measure of glomerular filtration.

**Tubular excretion.** Tubular clearance is measured satisfactorily by the excretion of Diodrast and sodium para-aminohippurate and somewhat less accurately by the excretion of phenolsulfonphthalein. At high blood plasma levels of these substances maximal tubular excretory capacity can be determined (see p. 1008).

**THE PHENOLSULFONPHTHALEIN TEST** is a less accurate but simpler test for the measurement of tubular function than the ones just mentioned. About 94 per cent of the injected dye is removed from the blood by tubular excretion. Clearance values around 400 cc. per minute have been described. A decrease in phenolsulfonphthalein clearance indicates either a decrease in effective renal blood flow (early in disease) or the presence of impotent tubules (late in disease), or both. The test is not sensitive enough to detect minor degrees of renal impairment. The dye is obtained in sterile ampules, 1 cc. of the solution

containing 6 mg. The test is most accurate when the dye is injected intravenously. About ten minutes before the injection the child drinks a glass of water and empties his bladder. In the so-called *fractional test* the urine, after the injection of the dye, is collected at fifteen, thirty, sixty and 120 minutes, the approximate normal amounts of dye excreted being, respectively, 35, 20, 10 and 5 per cent. Since the normal kidney can remove a large part of the dye in fifteen to twenty minutes, the usual two-hour collection periods permit the diseased kidney too great an opportunity to clear the blood of this dye. Catheterization may be necessary to obtain specimens on scheduled time in infants.

**GLUCOSE REABSORPTION TEST.** This test has been used to measure the tubular capacity to absorb solutes. Enough glucose must be given intravenously to raise the blood glucose to 600 mg. per 100 ml. in order to test tubular reabsorption under maximal capacity. The maximal reabsorptive capacity for glucose given by Goldring and Chasis for the adult is about 300 to 375 mg. per minute. In immature infants these values are considerably lower.

### RETENTION TESTS

In the presence of faulty glomerular clearance there is an accumulation of the substances in the blood normally cleared by the kidney. The more commonly estimated retentions are those related to some of the nitrogenous products: nonprotein nitrogen, urea nitrogen and urea. If the nitrogen balance and water balance are constant, the blood urea concentration (this also applies to the other nitrogenous waste products) varies inversely with the urea clearance. The normal figures for the three substances are as follows: urea nitrogen, 6 to 15 mg.; urea, 12 to 40 mg.; and nonprotein nitrogen, 25 to 35 mg. per 100 ml. of whole blood. The blood urea varies greatly with protein intake and dehydration, and in liver disease there may be a failure of deamination, producing a lowering of the urea concentration in the blood. Because the level of blood urea may vary independently of renal disease, it is hazardous to use it as a precise evaluation of glomerular disease.

Other substances may also be retained under similar circumstances. *Creatinine* in severe renal failure may rise from a normal level of 2 mg. per 100 ml.

of blood to 10 mg. or more. *Uric acid* may also rise from a normal level of 2.5 to 3.5 mg. per 100 ml. of blood. It may rise before the blood urea rises. *Phosphate, sulfate* and *potassium* may also be retained in renal insufficiency. Various organic acids are also retained when renal insufficiency is advanced.

### BLOOD PRESSURE

Since many symptoms of renal disease depend on vasospasm brought about by the primary renal disease, estimation of the degree of vasospasm as reflected in the blood pressure is an important guide in following the course of the disease.

MITCHELL I. RUBIN

### REFERENCES

- Alving, A. S., and Van Slyke, D. D.: The Significance of Concentration and Dilution Tests in Bright's Disease. *J. Clin. Investigation*, 13:969, 1934.
- Berglund, H., and Medes, G.: *The Kidney in Health and Disease*. Philadelphia, Lea & Febiger, 1935.
- Calvin, J. K., Isaacs, B. L., and Meyer, J.: Albuminuria in Children. *J.A.M.A.*, 86:1821, 1926.
- Goldring, W., and Chasis, H.: *Hypertension and Hypertensive Disease*. New York, Commonwealth Fund, 1944.
- McCance, R. A.: The Physiology of the Kidney in Infancy and Its Importance in Pediatrics. *Schweiz. med. Wchnschr.*, 76:857, 1946.
- McCance, R. A., and Widdowson, E. M.: New Thoughts on Renal Function in the Early Days of Life. *Brit. M. Bull.*, 13:3, 1957.
- Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry. Interpretations*. Baltimore, Williams & Wilkins Company, 1931.
- Pitts, R. F.: Acid-Base Regulation by the Kidneys. *Seminars on Renal Physiology. Am. J. Med.*, 9: 356, 1950.
- Pratt, E. L., Bienvenue, B., and Whyte, M. M.: Concentration of Urine Solute by Young Infants. *Pediatrics*, 1:181, 1948.
- Rubin, M. I., Bruck, E., and Rapoport, M.: Maturation of Renal Function in Childhood: Clearance Studies. *J. Clin. Investigation*, 28:1144, 1949.
- Smith, H. W.: *Principles of Renal Physiology*. New York, Oxford University Press, 1956.

## DISORDERS OF URINARY SECRETION

### DISTURBANCES IN QUANTITY OR EXCRETION OF URINE

Decreased urinary output may result from decreased formation of urine or retention of it in the bladder.

#### OLIGURIA

Urine may be secreted in small amount (*oliguria*) or, temporarily, not at all (*anuria*). This situation may be normal in the first

twenty-four hours of life. Pathologic causes in the newborn infant include renal agenesis, anomalies such as polycystic formations and obstructions resulting in hydronephrosis, acquired lesions such as thrombosis of the renal vein and renal artery and renal infarction and, most often, dehydration with anhydremia of any cause. After the newborn period any of these factors may be causative,



anhydremia, as in diarrheal disease, being the most frequent one. Suppression of urine is characteristic of acute glomerulonephritis, in poisonings by various metals and drugs and in conditions productive of shock and so-called lower nephron nephrosis. Obstruction of the renal tubules by crystallization of sulfonamide drugs is an example of mechanical blockage.

## RETENTION OF URINE

Formation of urine is not necessarily impaired, but there is failure of the bladder to expel it. In the newborn this may be due to malformation of the urinary tract, such as marked phimosi or atresia of the labia, or to urethral obstruction by abnormal folds of mucous membrane, uric acid crystals or a calculus. A balanoposthitis, vulvovaginitis, or inflammation of the meatus may cause retention, owing to the pain (*dysuria*) which urination produces. Disturbances in the innervation of the bladder and various reflex or direct inhibitions are factors, as in myelomeningocele, meningitis, myelitis, rectal irritation, spasm of the vesical sphincter, hysteria, mental depression, and the debility associated with severe febrile diseases.

## POLYURIA

Polyuria is a large increase in the amount of urine. It occurs in a variety of conditions and situations, including diabetes mellitus, diabetes insipidus, chronic renal disease and the recovery phase of so-called lower nephron nephrosis. It is also observed when a large amount of fluid is imbibed and during the reduction of edema. Nervous excitement and chilling of the body surface may produce a temporary increase in urinary secretion.

## FREQUENT URINATION

(POLLAKIURIA)

This is normal in the first two years of life. It also occurs with polyuria, cystitis and nervous excitement and from reflex stimulation by renal calculi. A highly concentrated acid urine causes it by irritation of the bladder.

## INCONTINENCE OF URINE

Incontinence depends upon a variety of causes. It is observed with phimosi, cystitis, impaction of a calculus in the urethra, para-

lytic conditions of the bladder resulting from disease of the brain or spinal cord, including spina bifida, and in profound exhaustion or coma. The bladder becomes overdistended until there is persistent overflow, or sometimes an intermittent expulsion of urine without the patient's knowledge. Malformations such as exstrophy of the bladder, abnormal openings of the ureters into the vagina, persistent urachus and absence of the vesical sphincter allow the urine to flow constantly. With partial obstruction, as from a malformation in the posterior urethra, the overdistended bladder often produces a constant dribble of urine. Incontinence is a characteristic symptom in many idiots, being then a form of enuresis.

MITCHELL I. RUBIN

## ENURESIS

Enuresis is defined as involuntary discharge of urine, but is generally used to indicate bed-wetting (nocturnal enuresis) by children beyond the age when control of the urinary bladder should have been acquired. There is considerable variability in the age when children acquire voluntary control of urination. A few achieve it between nine months and one year of age. The majority do not begin to have voluntary control before fifteen to eighteen months of age, and it is usually between the ages of two and three years when nocturnal control is firmly established. Some, usually boys, may not be dry at night before four to six years of age. Neuromuscular control sufficient for walking indicates that the child is physiologically ready to inhibit the normal emptying reflex of the bladder. This control is a willed effort and is dependent upon other factors than neuromuscular maturation. Even in children who have acquired good control there may be, for several years, occasional lapses associated with fatigue or emotional turmoil. The child with enuresis may occasionally have an "accident" during the day because of excitement, extreme urgency or engrossment in play. When there is continual involuntary discharge of urine, however, it is likely that the child has some organic disturbance.

Enuresis is a common symptom; estimates of its incidence vary from 5 to 15 per cent of all children, about twice as many boys as girls being affected. Blomfield and Douglas, in a recent survey in England of a random sample of 4294 children, found that 12.2

per cent wet the bed at four years of age and 7.3 per cent at eight years of age. The rate was highest in the lower socio-economic group. In the older age group, particularly in the upper economic level, boys outnumbered girls. Enuresis is associated with all degrees of intellectual capacity and occurs in all strata of society.

**Etiology.** The cause is usually an emotional disturbance in the child, secondary to a disturbed parent-child relationship. Infrequently, enuresis may be a symptom of nocturnal epilepsy or of lesions of the lower spinal cord or the genitourinary system. It may be an early symptom of diabetes mellitus or diabetes insipidus. Campbell doubts the assumption that organic lesions are rare as the cause of enuresis. He feels that about 10 per cent of such children have some pathology of the genitourinary tract and stresses the need for thorough re-examination of children whose enuresis has been assumed to be on a psychogenic basis, when they are not cured within two or three months.

The most common cause of persistent bed-wetting from infancy is too vigorous attempts at toilet training, before the age of physiologic readiness (usually fifteen to eighteen months). This produces confusion in the child. If the infant cannot do what he is asked to do, he becomes frustrated and guilty or antagonistic toward his parents. All too often this antagonism influences other patterns of behavior, and the effects upon the developing personality of the child are of much greater consequence than achieving early urinary control. When there is a healthy, warm parent-child relationship, it may be doubted whether the absence of efforts to train the child will result in continued wetting; many a mother reports that "her child trained himself."

Enuresis which develops after control has been established is usually associated with a temporary lack of security within the child. The birth of a new sibling, moving to a new home, separation from parents by illness or entering school may precipitate enuresis. Tonsillectomy, circumcision and other operative procedures may also be followed by periods of enuresis. Rigorous efforts to eradicate thumb- and finger-sucking or masturbation may also bring it on. When such factors do cause enuresis, it is usually an indication that the child's ability to adjust is not well developed and that the relationship between child and parents needs strengthening. Frequently measures designed to foster the child's

sense of security in the family group are sufficient.

There is often a history of enuresis in parents, grandparents or other relatives. This is said by some to indicate a hereditary trait. Although one cannot rule out some hereditary predisposition, it seems more likely that unsatisfactory adjustment transmitted by parents who have not succeeded in working out their own emotional equilibrium is the precipitating cause.

Some children without evident lesions void small amounts of urine at frequent intervals with considerable urgency. Such children are said to have an "irritable bladder"; belladonna is helpful in some of these children, but not in all. Bed-wetting frequently causes concern when the child is about three years of age and is passing from the light sleep of infancy to the heavy sleep of childhood. If the habit of urinary control is not established before this time, it will inevitably be more difficult to establish. It seems doubtful, however, whether the depth of sleep plays more than a secondary role in the causation of enuresis.

At one time spina bifida occulta was thought to be a common cause of enuresis. Karlin has shown that this is so only in children with gross defects of the spinal cord. A variety of physical conditions, such as phimosis, adherent clitoris and infected tonsils, have been suggested as the cause of enuresis. Though treatment directed against these conditions often has been associated with cessation of enuresis, a causal relationship is not necessarily established. Treatment which is dramatic or painful, as, for example, by instrumentation or injection, may stop bed-wetting, but it does not get at the underlying emotional factors and may actually increase them.

**Clinical Manifestations.** From the mild cases in which the bed is wet only occasionally there are all grades of severity up to those in which the bed is wet one or more times each night. Sometimes children dream that they are passing urine and may be awakened by the accident, but as a rule they are not aroused by the involuntary micturition. Bed-wetting may occur at any hour of the night, but frequently it occurs before midnight and may occur in spite of drastic restriction of the child's fluid intake.

Diurnal enuresis at times develops after nocturnal enuresis has continued for some time. The child has a frequent urgent desire to evacuate the bladder, which may come on so suddenly that the clothing is wet before



he can reach the toilet. In severe cases the patient is constantly wet with offensive, decomposing urine; in such instances some organic cause or a severe emotional disturbance is likely to be present. In some children play, exercise, sudden laughing, fright or other emotion is followed immediately by evacuation of the bladder.

**Diagnosis.** The diagnosis is made on the basis of a history of persistent bed-wetting with or without occasional "accidents" during the day hours and in the absence of evidence of neurologic or genitourinary disease, nocturnal epilepsy, diabetes mellitus or diabetes insipidus. When incontinence of urine is due to malformations or paralysis of the bladder, there is constant dribbling. In enuresis of the type discussed here the urine is always passed in a stream.

Every child with enuresis should have a careful physical examination and urinalysis, and he should be observed to see whether urine is passed in a stream; special studies should be limited to those clearly indicated by the history and physical examination. Indiscriminate instrumentation may cause the enuresis to disappear, only to have the child manifest other evidence of his disturbed feelings. Careful inquiry usually reveals evidence of other emotional disturbance, such as eating difficulties, overdependence on parents, thumb-sucking, nail-biting and other signs of immaturity. Despert found that enuretic children have difficulty in giving outward expression to their aggressive impulses.

*The diagnosis of an emotional disturbance in a child is not made by first excluding physical disease; the two conditions are not mutually exclusive. Difficulties in the emotional area are diagnosed by history, observation of the child's behavior and an evaluation of the parent-child relationship.*

**Prognosis.** The prognosis is determined by the underlying causes and the ability to cope with them. Most children stop wetting the bed before or during puberty. Enuresis, however, indicates that the child is having difficulties in growing up. The pressures which may have been used to force the child to acquire urinary control may have and may continue to have pronounced effects on his personality structure and adjustment. They frequently set the stage for the child to have continued difficulty in relating to authority. This may be the authority of learning in school or of the rules of society. Frequently the guilt of his own behavior interferes with the confidence and effectiveness of his ap-

proach to life. Enuresis sets him apart from others, exaggerates his feeling of difference and may make him uncertain of himself. Prognosis should be measured in terms of the child's total adjustment and not merely in terms of his ability to control urination.

**Prevention.** If parents could be guided in the institution of bladder training at appropriate times, if the element of struggle could be eliminated from the training process and from other areas of the parent-child relationship, enuresis would not be a significant problem. If parents, particularly mothers, could uniformly have the opportunity of friendly and informed consideration of their problems in child rearing by a competent physician, many factors which insidiously distort the parent-child relationship would be eliminated. In other words, if parents can be helped to be intelligently aware of and emotionally responsive to their child's needs, enuresis and many other manifestations of disturbed emotional growth would rarely appear.

**Treatment.** In children who have persistent enuresis, treatment is often slow and difficult. Attitudes developed during early training and the succeeding years affect the parent-child relationship so that it is difficult to modify it. The initial open struggle often has subsided, leaving partially concealed irritations and disgust in the parent and a discouraged, antagonistic attitude in the child. The effect of such feelings on the happiness and general adjustment of the child is apparent. The emotional growth of children has little chance of being healthy if the relationships with parents are not warm and unencumbered by chronic open or hidden antagonistic or critical feelings.

An approach which aims at helping the parents in understanding and improving their relationship with the child and at the same time offers to the child some aid to complement his own efforts is most likely to succeed. The parents should understand that scolding, punishing and shaming only make it more difficult for the child to control urination, and that encouragement, patience and acceptance build up his self-confidence and his desire to be dry.

There is a variety of approaches to the control of the bed-wetting itself. Their principal purpose is to give the child the feeling that he has support in his efforts to control his bed-wetting. Limitations of fluids, getting the child up one or more times during the night and various medical preparations may

be useful. Recently an old method has been revived and is being commercially exploited. It is a conditioning type of treatment with a pad in which urine completes a circuit which sets off a bell. A basically similar method was described by Pfaundler in 1904. Such conditioning methods may occasionally have their place if one is first sure that the parent-child relationships are not seriously awry and the child not seriously disturbed. Their indiscriminate use is contraindicated.

There are differences of opinion about the benefit derived from restriction of fluids in the latter part of the day. At least an excessive intake should be avoided. Such moderate restriction as a half-glass of milk at the evening meal and no fluids thereafter until morning, except during extremely hot weather, may be recommended.

The child should empty the bladder just before going to bed. In the child three to five years of age all that may be required for the control of enuresis is to take him from bed, awaken him and place him on the toilet three or four hours after his retirement. Some clinicians have advised a similar plan for older children, except that the child is responsible for his own awakening and for going to the toilet. An alarm clock is set for an arbitrary hour, as, for example, 1 A.M.; if the bed is not wet at this time, the period before awakening is gradually prolonged.

Tincture of belladonna is a useful adjunct; it has some effect in relaxing a hypertonic bladder and allowing it temporarily to retain more urine. The child should be encouraged to believe that it will help, but that it will not completely replace his own efforts to stay

dry. It may be started at a dose of 5 drops three times a day and increased a drop per dose per day until there are signs of atropism; a maintenance dosage just below this level is then desirable until it is apparent that the enuresis is not being controlled or, if it is controlled, for an additional two or three weeks. During this period the dose may be tapered off.

Many physicians have found that a direct relationship through frequent visits by the child without a parent is helpful. There need be little discussion beyond a brief report from the child and an occasional simple suggestion by the physician. There should be an attitude of both working together to solve a common problem.

Unfortunately there is a significant number of children with enuresis whose relationships with their parents are complicated by severely disturbed feelings. Efforts at straightening out such situations are often unsuccessful without direct psychiatric treatment of the child and help to the parents. Such treatment can best be accomplished in a child guidance clinic or by a child psychiatrist. Recognition of such cases depends upon experience in evaluating the degree of the disturbance. If psychiatric treatment is not available, an attempt at understanding and modifying the situation is worth while by the pediatrician or family physician.

SHERMAN LITTLE

#### REFERENCE

- Blomfield, J. M., and Douglas, J. W. B.: Enuresis: Prevalence among Children Aged 4-7 Years. *Lancet*, 1:850, 1956.

## ALTERATIONS IN COMPOSITION OF URINE

For Alcaptonuria and Cystinuria, see pages 259 and 262.

### ALBUMINURIA

#### PHYSIOLOGIC OR BENIGN ALBUMINURIA

Delicate tests show albumin in the urine of most persons; the average normal excretion in twelve hours is between 30 and 50 mg. More marked albuminuria may occur transiently during the newborn period. Small amounts of albumin may be found after violent exercise, overeating and cold bathing. Albuminuria is not infrequent during acute

infections, states of dehydration, and in diarrheal diseases and cardiac failure. These forms of albuminuria depend primarily on the extrarenal disturbance.

#### ORTHOSTATIC ALBUMINURIA

(POSTURAL, CYCLIC, LORDOTIC ALBUMINURIA)

In this entity, albumin, which is derived from the serum proteins, appears in the urine after the child has been standing or sitting and disappears when he lies down.

**Etiology.** The mechanism of this disturb-



ance is not clear. In some instances anatomic renal defects seem to be a factor. One theory ascribes the albuminuria to a diminished pulse pressure. The most widely accepted view is that in the erect position the child develops an exaggerated lumbar lordosis which by pressure interferes with renal circulation, resulting in a rise in renal venous pressure. Compression of the inferior vena cava is also thought to be a factor. Faulty posture, however, is not present in many of these patients; conversely, not all children with lumbar lordosis exhibit albuminuria. Evidences of vasomotor instability in some of these patients suggest that alterations in vascular control of the kidney may also be responsible. Orthostatic albuminuria occurs most often in late childhood, with equal frequency in males and females; a familial tendency has been noted.

**Clinical Manifestations.** The quantity of protein in the urine varies from a trace to 8 to 10 gm. a day. The protein is composed chiefly of albumin, although occasionally large amounts of globulin are found. A substance considered to be a mucoprotein (precipitated by acetic acid in the cold) is often found in small amounts. In some instances a posture which will increase the lordosis will increase the amount of proteinuria. Casts are rarely found, but when present, they disappear when the child is lying down. In rare instances children with orthostatic albuminuria have greatly diminished but persistent albuminuria when lying down. In such instances nephritis must be differentiated.

The patient's general health may be good, or more often there may be faulty nutrition, anemia, fatigability, headaches or various nervous symptoms. Digestive complaints and constipation are common, but are probably not related to the albuminuria. The patient is often lordotic and slender, and tends to be tall and asthenic. There may be intermissions when the albuminuria disappears for weeks or months. There is no evidence that the protein stores of the body are depleted. The disorder, which is benign, tends to disappear after adolescence, but may persist into adult life.

**Differential Diagnosis.** Orthostatic albuminuria should be carefully differentiated from nephritis. The persistence of albuminuria in the night specimens and the presence of red blood cells and casts in the routine urinalysis are evidences in favor of nephritis,

as is a demonstrated decrease in renal function. Occasionally in chronic nephritis albuminuria may increase while the patient is in the upright position.

**Treatment.** Treatment consists in improvement of the general health. Protein should not be restricted, but should be given in amounts adequate to take care of the regular needs and to replace that lost in the urine. Attention should be paid to improvement of muscle tone and correction of any faulty posture. The child should be allowed a normally active life, since there is no evidence that restricted activity will speed the disappearance of the condition.

#### *FEBRILE ALBUMINURIA*

Albuminuria occurs commonly in association with high continued fever from any cause, but disappears on cessation of the fever. The urine is highly colored and concentrated, and contains a small amount of albumin and occasionally a few hyaline or epithelial casts.

#### *ADVENTITIOUS ALBUMINURIA*

The presence in the urine of blood or purulent material in sufficient quantity will produce an albuminuria. Bence-Jones type of protein is found in the urine of patients with multiple myeloma.

#### *GLYCOSURIA*

Glucose is usually present in the urine of normal persons in amounts not detectable by commonly used tests (p. 1012). The presence of readily detectable glycosuria indicates either a high level of blood glucose (hyperglycemia) or faulty tubular reabsorption of glucose. Hyperglycemia may result from excessive ingestion or parenteral administration of sugar or from some metabolic disease such as diabetes mellitus. Deficient tubular reabsorption may result from a congenital defect (renal glycosuria and such entities as the de Toni-Fanconi syndrome and cystinosis and other defects of renal tubular function associated with amino-aciduria and phosphaturia), from cellular infiltration (glycogen disease), from cellular damage (mercury, lead or opium poisoning) or from altered tubular cell function (phlorhizin and disturbances in the hypothalamic area of the brain). Feeding large amounts of saccharose to normal infants may produce saccharosuria, sometimes with elimination of glucose and

levulose as well. The term *alimentary glycosuria* is used when glucose is excreted by healthy children after excessive ingestion of it. Transient glycosuria may also result from emotional disturbances, excessive physical activity, febrile diseases, convulsions, meningitis, brain tumors or brain injury, and in hyperthyroidism.

*Renal glycosuria* is the term used for a genetic defect in the reabsorption of glucose by the renal tubules which results in an abnormally low renal threshold for glucose. The fasting blood sugar level is within the usual range or below it, and the glucose tolerance curve is normal or low. The glycosuria per se is not handicapping, except that affected children may suffer ketosis more readily than normal ones, especially during febrile episodes, with vomiting or when the dietary intake is low. It must, of course, be differentiated from diabetes mellitus.

### PENTOSURIA

Pentose will reduce copper slowly, but is not fermentable. It is said to occur sometimes after ingestion of fruits such as pears, plums, cherries and strawberries. In most instances pentosuria is a rare, benign, congenital metabolic disorder, most common in Jewish males (see p. 277).

### GALACTOSURIA

Galactosuria may occur in normal infants after ingestion of large amounts of lactose and in those with chronic galactosemia, a congenital metabolic defect (p. 274).

### LITHURIA

Some uric acid is always excreted in the urine, even during complete starvation. The amount is increased during states of indigestion; in increased destruction of tissue, as in leukemia, anemia, lead poisoning, pneumonia; and by increased ingestion of purine bases. In the urine of the newborn infant it may be precipitated and form a whitish or reddish deposit upon the diaper. Uric acid may be precipitated in the bladder when the urine is highly acid, and give rise to pain on micturition. In the newborn infant there may be uric acid infarctions of the kidney, producing attacks of abdominal pain, which otherwise are without importance. When treat-

ment is deemed necessary, water should be given freely and the urine alkalinized.

### INDICANURIA

Indican is usually present in small amounts in the urine of artificially fed infants. It is increased in digestive disturbances, being frequently associated with constipation.

### LIPURIA

Fat in the urine may depend upon an excess of it in the food or upon fatty degeneration of the kidneys. Fat in the urine is found frequently in small amounts during uncontrolled diabetes mellitus, in nephrosis and in the nephrotic stage of chronic nephritis.

In *chyluria* there is sufficient fat to give the urine a milky appearance, and there may be albuminuria and red blood cells as well. Chyluria results from blockage of the lymphatic system, with leakage of chyle into the urinary system; some cases are due to filaria.

### ACETONURIA

The ketone bodies (acetone, aceto-acetic acid and beta-oxybutyric acid) may occur in small amounts in the urine of healthy infants and small children. An excess indicates inadequate carbohydrate metabolism, but not necessarily an acidosis. The ketones are normal metabolic products of fat combustion within the liver and are oxidized by the muscles. Only when ketones are produced at a rate which exceeds the capacity of the muscles to oxidize them are they excreted in the urine. Acetonuria occurs much more readily in young children, except in early infancy, than in older ones and adults and is a common finding in association with persistent vomiting, starvation, acute digestive diseases and acute febrile disorders, as well as with diabetes mellitus.

### HEMATURIA

The amount of blood present may be sufficient to produce a blood-red urine or may be so small that it is detected only on microscopic examination. Since blood cells disintegrate in an alkaline and dilute urine, the specimen should be examined soon after voiding. Hematuria must be distinguished



from hemoglobinuria, in which only blood pigment is present, and from bright red urine containing beet pigment sometimes seen after ingestion of this vegetable. In the newborn, hematuria must be distinguished from the brick-red staining caused by urates.

**Etiology.** Large hemorrhages are most often renal in origin, whereas blood appearing only at the onset or termination of micturition is likely to be from the lower urinary tract. The two-glass test may help determine whether hematuria occurs only during a phase of micturition or throughout the voiding. Blood casts are proof that hematuria is of renal origin. Cystoscopic examination and ureteral catheterization may be necessary to determine the origin.

Among the local causes are glomerulonephritis; pyelonephritis; neoplasms, usually of the kidney; renal tuberculosis; calculus; trauma; renal angioma; hemorrhagic cystitis; chronic infection, with dilatation of ureters which bleed; and chemical and toxic irritants, such as urotropin, turpentine, carbolic acid and the sulfonamides. Thrombosis of the renal and intrarenal veins and bilateral cortical necrosis may produce hematuria, often in association with renal failure. In the newborn uric acid infarction in the kidney can be a cause. A common cause for slight bleeding is ulceration at the meatal opening of the penis produced by irritation of ammoniacal urine; the blood is bright red and appears only in the first few drops of urine passed.

There are numerous systemic causes for hematuria, of which sepsis, especially in the newborn, is a common one. Leukemia, purpura, aplastic anemia and hemophilia are among the blood dyscrasias which may produce hematuria. Scurvy is often manifested early by the presence of a few red blood cells in the urine. Vitamin K deficiency may result in hematuria. Congestive cardiac failure may be a cause. Strenuous physical exercise and exposure to cold may cause a temporary, slight hematuria. In some cases varicosities of the renal vessels have been found. Spontaneous bleeding is sometimes seen in allergic persons, but whether it is an allergic manifestation is not clear.

### AMMONIACAL URINE

In most instances ammonia appears in the urine only after exposure to the air. In some instances, however, the conversion of urea to ammonia is produced almost immediately on passage of the urine. In many infants the ammonia is highly irritating to the skin and often results in varying degrees of dermatitis as well as meatal ulcers.

In long-standing urinary tract infections, including cystitis, the breakdown of urea to ammonia may occur in the bladder. Increased ammonia excretion may also result from increased production of it in the kidney during metabolic acidosis. In the latter instance the urine does not have an ammoniacal odor.

## ABNORMAL PIGMENTS IN THE URINE

For Porphyrinuria and Tyrosinuria, see pages 279 and 258.

### ABNORMALLY COLORED URINE

A red tint may be due to blood, hemoglobin, porphyrinuria or ingestion of beets (*anthrocyaninuria*) or certain dyes. Urates produce a reddish precipitate. Bile may produce a reddish-yellow color. A green or blue urine may be caused by ingestion of methylene blue; purple by fuchsin; magenta by phenolphthalein; red with a greenish fluorescence by eosin; black by ingestion of carbolic acid, in alcaptonuria, or by the presence of melanin; bright yellow by ingestion of carotene-containing foods. Some of these colorations may follow ingestion of certain artificially colored candies.

### HEMOGLOBINURIA

Hemoglobin appears in the urine when blood destruction is too rapid for the reticuloendothelial cells to dispose of it. A positive benzidine test in the absence of red blood cells is diagnostic of hemoglobinuria, but spectroscopic examination offers the most conclusive evidence. In severe hemoglobinuria renal tubular function may be disturbed. Albumin is present in small amount, and hyaline and granular casts are usually found. In some instances the so-called lower nephron nephrosis syndrome develops with rapidly occurring oliguria and renal failure. The urine is light or dark red or reddish-brown, at times almost black. Hemoglobinuria may be caused by hemolytic blood dyscrasias; severe infections; burns; parasitic diseases, such as

malaria; poisoning, as with carbolic acid, potassium chlorate, oxalic acid, arsenic, phosphorus, carbon monoxide, chloroform, quinine, naphthol, aspidium, snake venom and mushrooms; favism; and by transfusion with incompatible blood. Sulfonamides may also cause hemoglobinuria.

Besides removal of the primary cause of the hemoglobinuria, immediate therapy consists in hydration and alkalization.

### PAROXYSMAL HEMOGLOBINURIA

This rare disturbance, a manifestation of late congenital or acquired syphilis, occasionally occurs in childhood. The hemoglobinuria is transient, recurring after exposure to cold and occasionally after exertion. It results from the presence of an autohemolysin in the blood which unites with the red blood cells at low temperatures, leading to rapid hemolysis. The titer of the autohemolysin may show variation from day to day and may persist after the patient has ceased to have paroxysms upon exposure to cold (the *Donath-Landsteiner test*). The attack can be reproduced by immersing an extremity in iced water ( $18^{\circ}\text{C}.$ ). Venous blood withdrawn from the extremity at such a time will contain free hemoglobin. In the spontaneous attack, blood which has been chilled in the peripheral capillaries becomes hemolyzed when it passes to the higher temperature of the internal vessels. Hemoglobinuria occurs when the kidney threshold for hemoglobin is exceeded. With hemoglobinuria there may be chills and fever, prostration, slight jaundice, pain in the lumbar region and such vasomotor symptoms as cyanosis, pallor, urticaria, and coldness of the extremities. There may be no symptoms except the urinary ones. The urine has a dark red or burgundy color. In the freshly voided specimen red blood cells may be found in

addition to the hemoglobin. The erythrocytes in the blood diminish in number during the attack, but rapidly return to normal. There may be a slight polymorphonuclear leukocytosis, a diminished coagulation time and an indirect van den Bergh reaction. The discharge of hemoglobin may last from a few hours to (rarely) one or two days.

The paroxysmal type of hemoglobinuria is not dangerous. *Treatment* consists in rest, warmth, perhaps residence in a warm climate, and antisiphilitic treatment.

*Paroxysmal nocturnal hemoglobinuria* is rarely seen in children.

### MELANURIA

Excretion of melanogen is rare, occurring in some cases of melanotic neoplasms, and has been reported, perhaps incorrectly, in other conditions such as cachexia, pneumonia, intestinal obstruction, and after exposure to roentgen and sun's rays.

### BILE PIGMENTS IN THE URINE

Both urochrome and urobilin are found in normal urine. Urochrome is the chief pigment of normal urine. Under normal circumstances urobilin is taken up by the liver. When the capacity of the liver is reduced or when this pigment is produced in the intestine in amounts the liver cannot handle, the blood level of this pigment rises. It is then excreted in the urine in abnormal amounts. Thus its presence in large amounts in the urine is a sign of liver damage or excessive blood destruction (the primary source of the urobilin). Bilirubin in the urine usually indicates the existence of obstructive jaundice. It may be found in small amounts during various types of hemolytic icterus.

## MALFORMATIONS OF THE URINARY TRACT

Single and multiple malformations of the urinary tract are common in children, being found in 5 to 12 per cent of autopsies. Many of them produce no symptoms or disturbances of function.

The kidneys may be absent, hypoplastic, hypertrophic, duplicated, ectopic, polycystic or fused (*horseshoe*). There may be absence

of one or both ureters; they may be hypoplastic, duplicated, dilated or ectopic; or they may be obstructed by strictures, valves, kinks or abnormally placed blood vessels which cross them at a right angle. The bladder may be absent or hypoplastic, or there may be hemiatrophy of the trigone, exstrophy, a ureterocele or diverticulum. The urachus



may remain patent, or there may be a cyst of it. Fistulas may extend from the bladder to the rectum or the vagina. The urethra may be absent, hypoplastic or obstructed by a stric-

ture, or there may be a hypospadias or epispadias. The urethra may be connected with the rectum by a fistula. These are the most common malformations of the urinary tract.

## MALFORMATIONS OF THE KIDNEY, URETERS AND BLADDER

Malformations which obstruct the flow of urine are the most common types and have the gravest clinical significance. Aside from these, the more important malformations are congenital cystic kidneys, hypoplastic and aplastic kidneys, exstrophy of the bladder and persistent urachal tract.

### RENAL AGENESIS AND HYPOPLASIA

*Bilateral renal agenesis* is a rare condition encountered more frequently in males than in females. The infant is usually stillborn or lives only a few hours, although one infant is reported to have survived for eleven days. The anomaly may be an isolated one or may be associated with other malformations, as with fusion of the lower extremities. The diagnosis may be suspected during life by the peculiar facies, first described by Potter. The distance between the eyes is increased, the palpebral fissures are flattened or even mongoloid in their configuration, and there are prominent epicanthi. The ears are large and low set, and the chin is receding.

*Unilateral renal agenesis* is usually associated with complete absence of the ureter on the affected side, although rarely a patent ureter may be present with a normal trigonal orifice. The single kidney may be pelvic in location and its ureteral orifice open into the midline of the bladder. Malformations of the genital tract are present in over half of the patients, but anomalies involving systems other than the genitourinary tract are less frequent than in patients with bilateral renal agenesis.

*Bilateral renal hypoplasia* may be compatible with life for months to a few years. The manifestations are those of chronic renal insufficiency: stunting of growth, anemia, polyuria with a urine of low, fixed specific gravity, azotemia, hyperphosphatemia, and the osseous changes of so-called renal rickets. The morphologic changes in the kidneys are similar to those in unilateral renal hypoplasia.

Unilateral renal hypoplasia may differ only quantitatively from normal, in which case

the diagnosis is dependent upon the demonstration of decreased numbers of pyramids. Pyelography reveals a small, triangular-shaped pelvis from which emerges only one or two calyces; the appearance may simulate that of the upper portion of a duplicated renal pelvis. The opposite kidney and its pelvis are enlarged. Urine that is apparently normal may pass from the ureter on the affected side, yet death from renal insufficiency follows removal of the larger kidney.

In other instances not only is the hypoplastic kidney decreased in size, but also its histologic appearance is greatly altered. The renal pelvis may be relatively large. Scattered small cysts are present in the affected kidney, which consists of islands of normal or hypertrophic renal parenchyma alternating with areas of fibrous tissue containing small cysts, a few glomeruli and scattered islands of hyaline cartilage. With more advanced degrees of renal hypoplasia the affected kidney may consist entirely of a mass of fibrous tissue containing cysts. The renal pelvis is absent, and the affected ureter is hypoplastic or imperforate; a ureteral orifice, however, is usually present in the trigone.

The *unilateral multicystic kidney* is probably a variant of renal hypoplasia, although the lesion has been referred to as unilateral polycystic disease of the kidney. The presenting complaint is usually that of an abdominal mass which may be thought to represent a Wilms' tumor or a hydronephrotic kidney. The kidney is a large misshapen mass composed of multiple cysts of varying sizes united to each other by loose fibrous tissue. The renal pelvis is usually absent, and the ureter is imperforate.

Pyelonephritis may be the initial manifestation associated with renal hypoplasia, and hypertension is common. Relief of the hypertension has been reported following removal of a unilateral hypoplastic kidney. Although the hypertension may recur after nephrectomy, removal of a unilateral hypoplastic kidney appears to be justified if the opposite kidney is shown to be functioning adequately.

## POLYCYSTIC DISEASE OF THE KIDNEYS

The term "polycystic disease of the kidneys" is frequently applied to any kidney containing multiple cysts. It is preferable, however, to differentiate true polycystic disease of the kidneys from such other lesions as renal hypoplasia with cysts and multicystic kidney. True polycystic kidneys are almost always bilateral; whether unilateral forms ever occur is uncertain, but many which have been reported as such probably represent instances of unilateral renal hypoplasia with cysts or multicystic kidneys. The kidneys are enlarged, but retain their usual reniform shape; rarely the enlargement may be so great as to interfere with delivery of the infant. Myriads of minute cysts are present in the cortex and medulla with a resultant spongy appearance; the cysts may be so minute, however, as to be overlooked on superficial examination of the surfaces of the kidneys. The renal pelvis and calyces are present but distorted because of the increased bulk of the surrounding tissue.

The pathogenesis of polycystic disease is still unknown. Many believe that polycystic disease as encountered in adults is essentially the same as that encountered in infants, but there is suggestive clinical and morphologic evidence that they represent different entities. Tubular cysts encountered in adults communicate with the renal pelvis, whereas those in infants do not; glomerular cysts do not communicate with the pelvis in either infants or adults. Moreover, genetic studies suggest that the infantile form probably is transmitted as a mendelian recessive trait, whereas the adult type occurs as a dominant character.

Other anomalies may occur in infants with polycystic disease of the kidneys, e.g., polydactylism, hydrocephalus and cardiac malformations. Polycystic disease of the liver occurs in 20 to 30 per cent of affected infants; cysts in other viscera such as the pancreas, spleen and lungs occur less frequently.

The clinical manifestations vary with the severity of the process. In severe types death occurs in utero or shortly after delivery and is associated with massive abdominal enlargement. Less severe renal involvement is associated with evidences of chronic renal insufficiency and the presence of bilateral palpable abdominal masses. Severe hypertension may be present even in the first few months of life and may be associated with cardiomegaly and signs of congestive cardiac



FIG. 309. Polycystic kidney disease. Pyelogram shows "spider pelvis" characteristic of this disease.

failure. Hepatomegaly may be present in association with polycystic disease of the liver, and secondary infection may occur both in the renal and in the hepatic cysts. Pyelography characteristically reveals elongation of the renal pelvis and major calyces with flattening of the minor calyces; a variety of patterns may be produced, however, and the roentgenographic findings are not pathognomonic of the disease.

## SOLITARY RENAL CYST

Simple renal cysts are usually solitary and unilateral, but several cysts involving one kidney or bilateral solitary cysts may occur. The presenting complaint is usually that of an abdominal mass. The cysts are usually unilocular and do not as a rule communicate with the renal pelvis. They should be differentiated from polycystic disease of the kidneys, multicystic kidneys, hydronephrosis and Wilms' tumor.

## EXSTROPHY OF THE BLADDER

Exstrophy of the bladder occurs chiefly in boys. When the defect is complete, the entire lower urinary tract from the apex of the bladder to the external urethral meatus is exposed and everted on the abdominal wall. The trigone and the ureteral orifices can be seen in the center of the mass. There is an associated complete epispadias of a short penis; in girls the clitoris may be fissured and the labia separated. In some instances the



exstrophy is not complete, and only a part of the bladder is exposed. The exposed bladder mucosa is bright red, has numerous folds, and is extremely sensitive to touch. With advancing years this sensitivity decreases, and portions of the bladder mucosa are replaced by squamous epithelium. There is a wide diastasis of the rectus muscles below the umbilicus; the pubic rami are widely separated, causing the child to walk with a waddling gait. The testes are usually in the abdomen, and bilateral inguinal hernias may be present. In girls the vagina may be absent or replaced by a cloaca including vagina and rectum. At times there are defects of the lower bowel. These patients are quite uncomfortable. It is difficult to prevent seepage of urine, and there is usually a constant odor of it. The surrounding skin is often badly excoriated, and ulcerations of the bladder mucosa are common. Rarely there are malignant lesions. It is surprising how few of these children acquire infections or obstructions of the urinary tract. Exstrophy of the bladder is not incompatible with a full life span.

When the exstrophy is not complete, a satisfactory plastic closure of the abdominal and bladder walls may be obtained. In a complete exstrophy Ladd recommends implantation of both ureters into the sigmoid, obtaining valvelike ureteral orifices by embedding the ureters for some distance in the intestinal wall before an opening is made into the bowel lumen. The operation is performed in one stage, but not until the child

has attained good anal sphincter control at three to five years of age. In addition, a plastic repair is performed on the bladder and external genitals. The results of this operation have been relatively good. Mild degrees of hydroureter and hydronephrosis are common, but usually tend to decrease after a time; occasionally there is a severe degree of persistent hydronephrosis. Pyelonephritis is not infrequent, but can usually be controlled by antimicrobial therapy. The colon bacillus is the most common infecting organism. Adequate renal function can usually be maintained for many years. The ultimate prognosis depends in great measure on the extent of renal damage from back pressure and infection. The gait usually can be improved by a brace designed to correct the deformity of the pelvic girdle which is associated with this condition.

#### PATENT URACHUS AND URACHAL CYST

In the early embryonic stage the bladder extends to the umbilical region, subsequently descending along the anterior abdominal wall. During this descent the upper portion becomes attenuated to form the narrow tube-like urachus, which later is obliterated. On rare occasions an open lumen persists, permitting discharge of urine into the umbilicus in postnatal life. This type of urachal defect is usually associated with obstruction of the urinary tract below the bladder. In some instances there is only an external communication at the umbilicus, and the rest of the



FIG. 310 Exstrophy of the bladder in a boy 10 years of age. Below the bladder is shown the atrophic penis and, below it, the empty scrotum. There is also a right inguinal hernia.

urachal tract is closed off; in others there is only an internal communication to the bladder, with the remaining tract obliterated. The most common urachal lesion is a blind cyst occurring usually at the upper end of the tract just under the umbilicus and extra-peritoneally.

When the entire urachus is patent, there is a constant flow of urine from the umbilical region. The *diagnosis* can be established by means of dyes excreted through the urine, by chemical analysis of the discharge, and by roentgenography after injection of contrast material into the bladder or into the umbilical opening. The urachal cyst exists as a deep midline swelling below the umbilicus attached to the internal part of the abdominal wall.

Urachal cysts may become infected, and at such times the *symptoms* are those of a midline abscess. The abscess may rupture internally into the bladder or the peritoneum, or externally through the umbilicus.

Urachal cysts should be removed when diagnosed and before infection has occurred. If infection has already occurred, surgical drainage is indicated with subsequent removal of the cyst. Tracts which drain urine should be obliterated by surgical means.

## MALFORMATIONS PRODUCING

### OBSTRUCTION TO THE URINARY FLOW

Though urinary obstruction leading to the production of hydronephrosis is usually caused by a congenital defect within the urinary tract, obstruction is also caused by external pressure as by an aberrant blood vessel on the kidney pelvis or ureter or by a neoplasm (usually of the kidney). Urinary calculi, kinking of a ureter secondary to a prolapsed kidney, inflammatory strictures, neuromuscular lesions of the bladder and/or ureter and extreme phimosis are other causes of obstructions.

Care must be exercised in deciding whether a kidney pelvis is slightly enlarged because of back pressure or is simply within the upper range of normal in size. The absence of evident obstruction below the pelvis and of blunting of the calyces would favor the latter probability. However, when the obstruction is at the pelvic-ureteral junction, there will be no ureteral dilatation below this point. In some instances the pelvis is extrarenal and therefore appears enlarged; or there may be congenital absence of a major calyx, or one calyx may be larger or smaller than the others without having any special significance.

It is advisable to divide obstructive lesions into two groups: (1) those below the bladder and (2) those above it. Since there is dilatation of the structures proximal to the obstruction, the bladder will become dilated and its walls hypertrophied when the obstruction is distal to it, but will be uninvolved when the obstruction is above it. Thus involvement of the bladder is a valuable diagnostic guide.

### OBSTRUCTIVE LESIONS INVOLVING THE BLADDER NECK OR URETHRA

Although a tight phimosis may obstruct the urinary flow, it is rarely a cause of serious trouble. When obstructive uropathy and phimosis coexist, a careful search for another obstruction should always be made. Meatal strictures, inflammatory and otherwise, may rarely cause obstruction.

*Congenital obstructions* in the urethra occur almost solely in boys. Congenital narrowing or partial absence of the urethra rarely occurs. The common anomaly consists of one or two membranous folds with one end attached to the verumontanum and the other usually to the lateral urethral walls. As the urine flows from the bladder, these folds acting as valves are ballooned out, causing a diminution in the urethral orifice. At times an obstruction resembling an iris diaphragm may partially or completely encircle the posterior urethra below the verumontanum. There may be some difficulty in establishing the presence of urethral valves, since often there is no obstruction to the passage of a urethral catheter into the bladder. A less common obstruction of the neck of the bladder results from a shelf or bar of hypertrophied muscle on the floor of the bladder at its junction with the posterior urethra. There is some evidence that this lesion is progressive and may not produce serious obstruction during infancy. Prostatic hypertrophy is an infrequent cause of urinary obstruction; transient prostatic hypertrophy causing urinary obstruction has been noted after hormonal therapy for cryptorchism.

In some instances of bladder and ureteral dilatation with hydronephrosis *no obstructive lesion can be found*. Probably these cases belong to the group of neuromuscular dysfunctions. In some of them there are demonstrable lesions of the spinal cord with or without an associated spina bifida. In approximately half of sixty children with megaloureters and megalobladder Swenson and Fisher found a diminution in ganglion cells in the bladder wall and have termed the condition aparasympathetic bladder. These patients



seem to have a loss of sensation in the bladder, but are not incontinent. In contrast to the sex differences in the incidence of obstructive lesion within the lower urinary tract, these cases occur as often in girls as in boys. Slight enlargement of the renal pelvis and widening of the ureters are occasionally seen in infections of the urinary tract without evident obstruction below.

When infravesicular obstruction is of long standing, the bladder may become greatly enlarged, the muscular wall extremely hypertrophied, and the bladder mucosa thrown into innumerable folds. At times diverticula are present. An irregular appearance of the bladder contour may be seen at cystoscopic examination or roentgenographically when no diverticula can be demonstrated; normal bladders may occasionally show some distortion of contour. At times distortion of the bladder contour may result from pressure of an overdistended bowel or an abnormally placed uterus. The persistence of an enlarged bladder after the patient has just voided is suggestive of residual urine in a hypertrophied bladder, indicating obstruction to the urinary flow; this supposition should be tested by a postvoiding catheterization.

#### OBSTRUCTIVE LESIONS INVOLVING THE URETEROVESICAL JUNCTION, URETER, PELVIS OR KIDNEY

Anomalies involving the ureters are the most common ones of the urinary tract. Complete or partial absence of one or both ureters may occur. Duplication, complete or partial, of one or both ureters is fairly common; the duplication may be limited to the renal pelvis. Partial obstruction of the ureter, usually due to a narrowing of the lumen, occurs most often at the pelvic-ureteral and the vesico-ureteral regions; it may occur where the ureter crosses the iliac vessels. In any of these locations the narrowing of the lumen may be due to an inflammatory stricture, a congenital anomaly or compression of the ureter from without, as, for example, by an aberrant blood vessel near the pelvic-ureteral junction.

The obstruction may be a fold in the mucosa at the vesical orifice or an extreme narrowing at the orifice so that there may be ballooning of the ureteral wall into the bladder, producing a *ureterocele* or intravesical cyst of the ureter. This anomaly, which is really a prolapse of the ureter, may be unilateral or bilateral. When the intra-

vesical portion is large, it may result in complete blockage of ureteral urine flow and secondary hydronephrosis. In the early stages correction can often be obtained by endoscopic incision or amputation; when there is significant renal damage, partial or complete nephrectomy and ureterectomy are indicated for the unilateral lesions.

*Diverticula* of the ureters are rare; they may be responsible for obstruction and may be difficult to demonstrate. Retrograde urography would appear to offer the best chance of detection.

The mechanism producing the so-called *megaloureter* (great lengthening and tortuosity of the ureter with greatly thickened walls and hydronephrosis, but without an obstructive or apparent neurologic lesion) is not understood. Occasionally megaloureters occur in association with congenital aganglionic megacolon. Swenson and Fisher noted some defect in bladder function in approximately 50 per cent of their patients with megacolon. In about 3 per cent of them they could demonstrate a megalobladder and megaloureter with evidences of urinary retention. They have attributed these anomalies to a defect in parasympathetic innervation.

Hydroperitoneum has been observed in the newborn in association with congenital obstructive lesions of the urinary tract. Obstruction of the urethra has been the lesion most commonly found.

#### HYDRONEPHROSIS

Dilatation of the kidney pelvis and calyces is due to obstruction in their drainage mechanism. Rarely obstruction of the renal pelvis results from displacement of a movable kidney. If the obstruction is infravesicular, then the hydronephrosis is bilateral (Fig. 311) and develops somewhat more slowly than when the obstruction is supravesicular. Several years may elapse before maximal dilatation is obtained. If there are obstructive lesions in both ureters, the hydronephrosis is also bilateral. If only one side is obstructed, then the hydronephrosis is unilateral (Fig. 312). If the obstruction produces back pressure in the ureters, they become dilated, at times thickened, and, often, increased in length with great tortuosities. In long-standing lesions the renal substance is greatly atrophied as a result of the pressure on the tissues and their blood supply, and the kidney

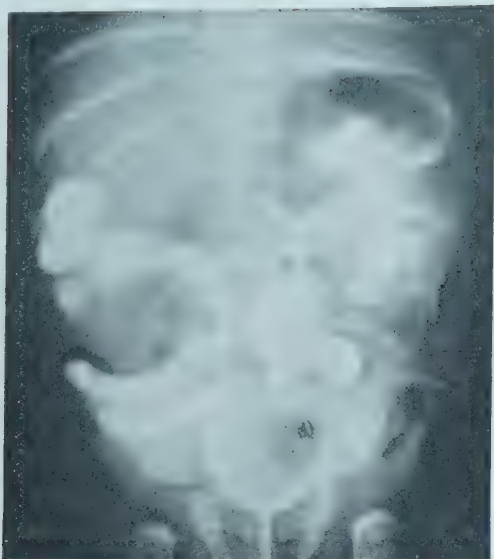


FIG. 311. Hydronephrosis. Reflux pyelogram showing bilateral hydronephrosis and hydroureters and enlargement of the bladder secondary to obstruction produced by a congenital valve anomaly in the posterior urethra.

may ultimately consist of a thin-walled cystic mass with little functioning renal tissue. The calyces appear on the urogram as large balls, and there may be little or no renal tissue separating them. At times the combined mass of a unilateral hydronephrotic kidney and dilated ureter will produce a large cystic tumor filling half or more of the abdominal cavity. A history of an abdominal mass fluctuating in size and associated with changes in urinary volume is suggestive of hydronephrosis secondary to obstructive uropathy.

**Clinical Manifestations.** The symptoms resulting from obstructive uropathy can, in general, be divided into three categories: (1) interference with the flow of urine, (2) infection, and (3) renal insufficiency.

**Symptoms resulting from interference with the flow of urine.** In *infravesicular obstruction* or with *primary bladder dysfunction* these symptoms are more striking than when the obstruction is above the bladder. The presenting symptom is often an abdominal tumor (distended bladder) noted by the mother. There is a thin, weak urinary stream, which is projected for only a small distance, or a continuous dribble. There may be some hesitation or difficulty in starting the urine flow and even periodic inability to void at all. It is important to question the mother about the voiding habits of the child and especially to watch the child void. Residual bladder urine can be demonstrated by catheterization,

but only immediately after a voluntary voiding.

In the so-called *cord bladder* there may be complete paralysis with overflow incontinence. Reflex automatic voidings usually develop with associated dribbling. In supralumbar lesions this type of voiding may be reasonably efficient, but residual urine still remains in the bladder. Relaxation of the rectal sphincter is usually an associated lesion. In so-called *aparasymphetic megalobladders* the defect in function is said to be less pronounced than with cord bladders, and incontinence does not occur.

In *supravesicular obstruction* symptoms referable to the urinary tract may be entirely lacking. In some instances there may be intermittent periods in which large quantities of urine are voided, owing to the release of an obstructed and greatly distended ureter and/or a hydronephrosis. Many of these children complain of vague or even severe colicky abdominal pains variously referred to the renal region or midanterior area of the abdomen. The pain may also radiate to the groin or thigh and resemble a Dietl's crisis. Large masses which may give the impression of being cystic are often palpated in either or both flanks. The distended bladder can be palpated above the symphysis even after urination.

In very young infants with relaxed abdominal walls the kidneys can normally be palpated. This examination is best conducted bimanually with one hand pressing upward in the flank and the other downward over the anterior abdominal wall. When the kidneys are easily palpable or appear at all enlarged, a thorough urologic study is indicated (see below).

**Symptoms resulting from infection.** (See p. 1032.) Irregular bouts of fever, with or without chills, or convulsions in the young infant are commonly present. Intermittent or persistent pyuria, microscopic hematuria and rarely gross hematuria occur. In some long-standing cases, even though the renal substance is infiltrated with small round cells (old infection), the urine finally becomes free of pus cells and bacteria. There may be malaise and, in long-standing cases, cachexia. Children whose malnutrition is not readily explainable on other grounds should have a thorough examination of their urinary systems.

**Symptoms of renal insufficiency.** The third category of symptomatology is manifest



by progressive renal dysfunction, death resulting from renal failure. Pyuria may or may not persist, casts and red cells are often present, and the urine, which is increased in volume, has a fixed, low specific gravity. The nonprotein nitrogen of the blood is increased, the blood pressure is elevated, and there is a state of acidosis with which there may be a relatively alkaline urine (pH above 6). All phases of renal function are reduced. The blood inorganic phosphorus may be elevated and the calcium reduced, resulting in tetany, renal hyperparathyroidism and dwarfism with the characteristic bony deformities of renal rickets.

The suspicion that a congenital malformation of the urinary tract exists should lead to immediate urologic study. The simplest methods are urinalysis, measurement of the blood urea nitrogen, cystography and intravenous urography. Cystography will often

demonstrate an infravesicular obstruction with reflux into the dilated ureters, either by hydrostatic pressure or during voiding. The child should be tested for sensitivity to the contrast material to be used for intravenous urography before it is injected intravenously. In some instances intravenous urography will fail to demonstrate a congenital defect, and retrograde urography is required. When it is desired to determine whether the renal involvement is unilateral or bilateral, renal function tests of each kidney should be performed. Cystometric studies and studies of ureteral peristaltic activity may be helpful in evaluating the lesion and gauging prognosis.

**Treatment.** The treatment of obstructive uropathy is that of renal insufficiency and infection, when they exist, and relief of the obstruction. Since the sudden release of urine from a greatly distended bladder may result

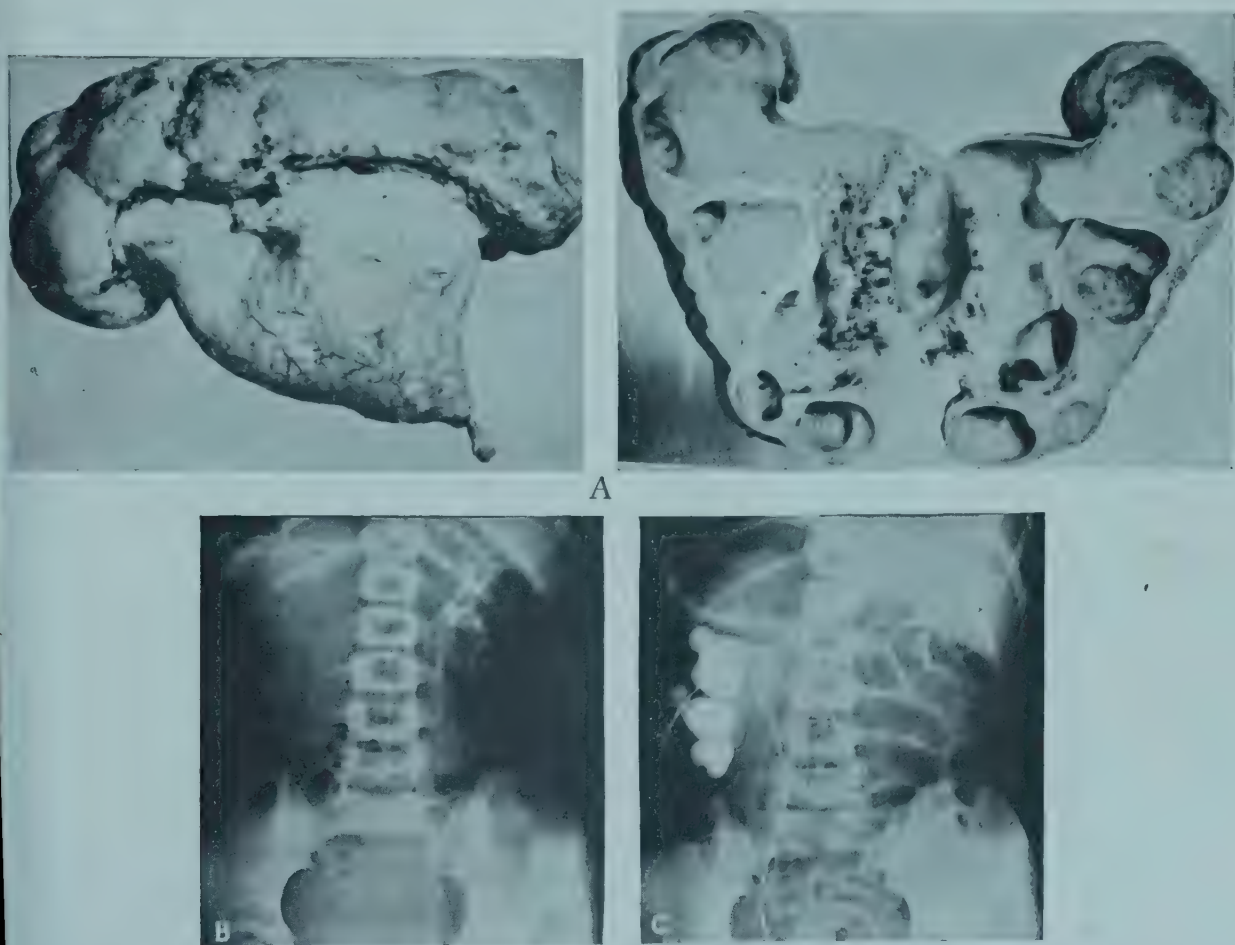


FIG. 312. Congenital obstruction at the ureteropelvic junction due to fibrosis of the ureteral wall. An anomalous renal artery crossed the ureter at this point and may have precipitated these fibrotic changes. A, Kidney removed at operation. Note the stricture at the ureteropelvic junction and the greatly dilated renal pelvis and calyces. B, Intravenous urogram showing normal right renal pelvis. The left renal pelvis is not visualized, probably because of poor renal function and great dilution of the Diodrast. C, Retrograde pyelogram showing greatly dilated calyces on the left side which were not visualized at all in the intravenous urogram (B).

in shock and even fatal anuria, the bladder should be emptied by gradual decompression through an indwelling catheter. A rapid improvement in renal function often follows this drainage, even in cases of long-standing obstruction. In the so-called aparasympathetic bladders the patient must be taught to make sustained effort to empty his bladder completely; the aid of manual suprapubic pressure is often necessary. A schedule of four or five voidings a day and one or two at night can be recommended. Resection of the bladder neck may be necessary to relieve urinary retention.

Other obstructive lesions are also amenable to surgery, but before operation is attempted the patient's general condition should be improved as much as possible and the urinary tract infection brought under control. Even though considerable renal function has been lost, with the present means of controlling infection surgical relief should be attempted. Useful life is compatible with a considerably lowered renal function, and it is often surprising to what extent the renal function will improve after an obstruction is relieved. In the mild cases there may be an almost complete restoration of the urinary tract to normal size and a complete recovery of renal function. In more advanced cases less anatomic and functional recovery occurs, but even in those cases in which there is extensive renal destruction little is to be lost in trying surgical treatment.

### DISPLACEMENT OF THE KIDNEY

**Dystopia.** Accompanying or independent of some of the malformations described, the kidney, especially the left, may occupy a position lower and nearer the midline of the body than normal. On palpation this may cause confusion with such conditions as intussusception, fecal accumulation and ap-

pendicitis. There may be no symptoms, or the kinking of the ureter may cause pain and dysuria, and lead to hydronephrosis.

**Movable Kidney.** This relatively uncommon condition may be congenital or acquired. The acquired form is seen oftener in girls than in boys during late childhood and may result from pressure by tumors or from trauma. *Symptoms*, if present, are a sensation of pressure or dragging in the abdomen or lumbar region, attacks of renal colic (Dietl's crisis) and perhaps chronic urinary tract infection. General splanchnoptosis may also be present. Hydronephrosis may develop from kinking or twisting of the ureter. In establishing a *diagnosis* it should be remembered that it is often possible to palpate the lower pole of the kidney in normal children. Intravenous pyelography in the supine and upright positions will usually establish the diagnosis, but retrograde pyelography is necessary at times. *Treatment* consists in efforts to retain the kidney in position by a pad or bandage. Surgical measures are seldom required.

MITCHELL I. RUBIN

### REFERENCES

- Bell, E. T.: Cystic Disease of the Kidneys. *Am. J. Path.*, 11:373, 1935.  
 Campbell, M. F.: *Clinical Pediatric Urology*. Philadelphia, W. B. Saunders Company, 1951.  
 Donath, J., and Landsteiner, K.: Ueber paroxysmale Hämoglobinurie. *Münch. med. Wchnschr.*, 51: 1590, 1904.  
 Drabkin, D. L.: The Normal Pigment of the Urine. *J. Biol. Chem.* 75:443, 481, 1927.  
 Eagle, J. F., and Barrett, G. S.: Congenital Deficiency of Abdominal Musculature with Associated Genitourinary Abnormalities. *Pediatrics*, 6:721, 1950.  
 Swenson, O., and Fisher, J. H.: New Techniques in the Diagnosis and Treatment of Megaloureters. *Pediatrics*, 18:304, 1956.  
 Zuelzer, W. F., and others: Circulatory Diseases of the Kidneys in Infancy and Childhood. *Am. J. Dis. Child.*, 81:1, 1951.

## INFECTIONS OF THE URINARY TRACT

### PYELONEPHRITIS, PYELITIS

Acute infections of the urinary tract are relatively common in pediatric practice. Such infections are rarely limited to a single portion of the urinary tract, and for this reason the term "pyelitis," commonly applied, is scarcely applicable. Infections of the renal pelvis usually extend into the renal paren-

chyma, producing a pyelonephritis, and there is usually some associated inflammation of the ureters and bladder.

Acute infection of the urinary tract may be suspected from the clinical symptoms (often there is none related directly to the urinary tract), but the diagnosis is established only by demonstration of pus cells and bacteria in the urine, whose origin is not



from an extraurinary source such as a vaginitis or "container contamination."

**Etiology.** The incidence of acute pyelonephritis is highest during the diaper age, being somewhat less during the first few weeks of life than during the remainder of infancy. Pyelonephritis represents the most common renal disease of childhood, and in its chronic forms is the most common cause of chronic renal failure. It occurs about six times as frequently in the female as in the male, except during the neonatal period, when there is about an equal incidence. There is some experimental and clinical evidence that a lowered tissue resistance of the urinary tract predisposes to infection. Many different bacteria infect the urinary tract, but the colon bacillus group is responsible for about 80 per cent of all cases. Less frequently the *Staphylococcus*, hemolytic *Streptococcus*, *Streptococcus faecalis* and still less commonly other organisms such as those of the *Proteus*, *Pseudomonas*, typhoid, *Salmonella* and dysentery groups and tubercle bacilli are etiologic.

In chronic pyelonephritis the colon bacillus accounts for relatively few infections, and multiple bacterial infections are common. *Proteus* and pyocyaneus are common infecting bacteria in chronic infections associated with urinary obstruction and in patients who have had many recurrent infections and considerable antibiotic therapy. Though some of the infections, especially the coccal forms, reach the kidney by way of the blood stream from a distant focus, there is evidence to suggest that the larger number of infections ascend by way of the urinary tract to the kidney through the urinary stream by regurgitation or through the lymphatic channels, and that infection from the renal pelvis spreads throughout the kidney by way of the perivascular or vascular routes. The observations that the colon bacillus is an unusual blood stream invader, that the incidence of pyelonephritis is highest in the diaper age, that it is more frequent in girls whose urethra is short and more often infected from fecal contamination add support to the belief that infections of the urinary tract most commonly occur by the ascending route rather than by the hematogenous one.

Stasis from congenital malformations is the most common cause of chronic urinary tract infections, being present in about 75 per cent of them. Rarely the tract may be obstructed by a calculus or foreign body or by a neoplasm of, or adjacent to, the urinary tract.

The presence of a neurologic bladder may impede the flow of urine. Once infection is established it is difficult to eradicate it unless adequate urinary drainage is obtained. Hence there is danger from infection after the catheterization of patients with obstruction of the bladder neck. Occasionally pyuria results from rupture of an abscess into the urinary tract. The proximity of an inflamed appendix to the right ureter has also resulted in pyuria.

**Pathology.** Infection and inflammation are rarely limited to the renal pelvis (pyelitis); most often there are also inflammatory changes irregularly distributed throughout the kidney mass. The majority of cases which come to autopsy are associated with obstructive lesions of the urinary tract.

In the mild cases there are congestion and leukocytic infiltration in the renal pelvis, and small hemorrhages may be present. In the interstitial spaces and in the tubules are collections of polymorphonuclear cells and, in the chronic form, lymphocytes. The capillaries are dilated, and hemorrhage may be seen throughout the interstitial tissue as well as in the tubules. In the more severe, acute forms miliary abscesses occur throughout the parenchyma; the kidney may be greatly swollen, and clumps of bacteria may be present.

When the infection has been prolonged, there are often extensive areas of scarring with loss of functional renal parenchyma. The end result may be a small, shrunken kidney. In such long-standing cases active infection may have ceased, and bacteria and pus may have disappeared from the urine. Many of the nephrons undergo complete degeneration and finally disappear; the remaining tubules are dilated and filled with coagulated protein. Calcium deposits may be present in lesions of long standing. Arteriosclerosis and arteriolosclerosis may be present in association with chronic pyelonephritis.

In most instances some degree of inflammatory reaction is seen in the submucosa of the ureters and bladder. In long-standing infection secondary to infravesicular obstructive anomalies the bladder and ureters may be dilated and their walls greatly thickened. Infection itself is said to produce some dilatation of the kidney pelvis and ureter. Whether the dilatation is caused by blockage or by weakening of the walls from infection is not known. Occasionally inflammatory thickening of the ureter is responsible for urinary obstruction with proximal dilatation of the ureter and pelvis. With subsidence of infec-

tion in such cases it is possible that the ureter and pelvis may return to their normal size. With long-standing obstruction of the urinary tract the renal tissue may be compressed into a thin shell surrounding the greatly dilated calyces (Fig. 312). With increasing destruction of renal tissue, renal function progressively fails.

**Clinical Manifestations.** Typically in *acute pyelonephritis* the onset is abrupt with fever, the child appearing acutely ill. The temperature not infrequently reaches  $103^{\circ}$  to  $105^{\circ}$  F., but is rarely sustained at such levels for over a day or two; characteristically there are wide fluctuations. On occasion there may be little or no fever.

In the infant there are usually no localizing signs to indicate that the infection is in the urinary tract, except perhaps for urinary frequency, which is difficult to evaluate at this age. During the period of high temperature the infant is likely to be irritable, and other central nervous symptoms such as convulsions and meningismus may be manifest. Prostration may be great. Gastrointestinal manifestations are common, vomiting often being a striking symptom. It may be projectile, associated with exaggerated gastric peristaltic waves and persistent enough to simulate pyloric stenosis. Diarrhea occurs occasionally, as it may with other infections during early life, and may result in dehydration. Anorexia is usually marked.

In older children there may be localizing symptoms. When there is an associated cystitis, frequency of urination, urgency and dysuria may be present. Not infrequently there is pain, sharp or dull, over the renal area with muscular spasm and tenderness on palpation. It cannot be overemphasized that at any age all symptoms may be lacking or none may be related to the urinary system, and the diagnosis is established, if at all, by urinalysis and culture.

In most untreated cases the fever lasts seven to ten days and the urinary changes about three weeks. The acute clinical manifestations usually last for only the first few days of the disease. Pallor, anorexia and failure to thrive, however, may persist for weeks after the urine has returned to normal if the kidney lesion remains active. In the unusual, severe form when large areas of the kidney are abscessed, there is great intoxication; in such infections death may occur within a week or two after the onset of the illness. The fatality rate, however, is low among the ordinary acute cases.

*Chronic infections* present the more serious problems. Instead of subsiding after two or three weeks, as most often happens, the infection may persist for months or years with intermittent fever, pyuria and progressive involvement of the renal parenchyma leading to interference of renal function and to hypertension. The principal symptoms are inanition, anemia and failure to grow, but acute exacerbations are common. During early childhood a not too restricted life is compatible with a greatly reduced renal function, which finally fails, producing uremic symptoms, often during periods of rapid growth, as in puberty. In many instances, although the infection becomes quiescent or is "burnt out" and pus and bacteria no longer appear in the urine, the kidney is chronically scarred and contracted and there is a persistent decrease in renal function. Since the manifestations of the renal insufficiency are not unlike those of chronic nephritis, the true etiology of the renal lesion may be overlooked unless a past history of pyuria is obtained or a congenital malformation of the urinary tract is demonstrated. In unilateral chronic pyelonephritis renal function may not be significantly reduced, owing to hypertrophy of the nonaffected nephrons in the diseased kidney and in the uninfected kidney. Loss of renal concentrating capacity, however, is a common feature of persistent pyelonephritis and may occur early. Secondary hyperparathyroidism may be a complication. Hypertension may be marked and may be responsible for cardiac failure or cerebral hemorrhage. Since chronic infection is commonly associated with obstructive lesions of the urinary tract, persisting symptoms may be referable to urinary obstruction and renal failure (see p. 1028).

**Diagnosis.** The diagnosis is based upon demonstration of pus and bacteria in the urine. Urine is normally sterile, but is readily contaminated during and after voiding. Urine contains a small number of white blood cells under normal circumstances. Addis counts of healthy children (voided in boys, catheterized in girls) demonstrate between 1,000,000 and two million white blood cells in the urine excreted in a twelve-hour period. In a fresh, uncentrifuged specimen obtained by similar means there should not be more than one or two white blood cells per low power microscopic field, or a freshly shaken specimen should contain not more than one cell per 10 high power fields. The most common source of pus in the urine is from vaginal secretions, and many girls are treated for



months for a so-called pyelitis when the origin of the pus cells is in the vagina. Thus when pus cells are found in the urine, a "clean" specimen should be obtained after thorough bathing of the genitals with soap and water. In boys the foreskin should be retracted and the glans cleansed. If possible, only the latter portion of the voiding should be collected. If this specimen also contains pus cells, then a catheterized specimen should be obtained. Only catheterized specimens are suitable for bacterial culture, and even here the first few drops should be discarded.

It is important to recognize that bacteria may be present in abundance in the urine in the absence of pyuria; bacterial culture in the absence of pyuria may identify a focus of infection. However, isolation of a few bacteria in a catheterized specimen from girls or a mid-stream voided specimen from boys is not diagnostic of urinary infection. Infected urine usually contains more than 100,000 bacteria per milliliter; counts lower than this may represent contamination, suppressive therapy, rapid excretion (not permitting sufficient time for bacterial multiplication in bladder), acid urine with pH below 5.5 or an alkaline urine above 8.5. Certain organisms as group A streptococci, some strains of staphylococci and enterococci may grow poorly in urine and thus produce few bacteria.

The direct examination of a cleanly voided specimen of urine, even in girls, gives a reasonably reliable indication of urinary infection. The absence of bacteria in a fresh drop of urine stained with Gram's stain is strong evidence against the existence of urinary infection. The presence of bacteria in such preparations is usually associated with bacterial counts of 100,000 per milliliter or more.

The external vaginal orifice and the surrounding perineum must be thoroughly cleansed before collecting urine for slide examination or culture; pHiso-hex or Zephiran 1:1000 is used for this purpose.

During the first two or three days of the disease while the fever and associated symptoms are most severe the urine may be normal. Pyuria may be intermittent, especially in chronic infections, but also in acute ones. Initially the absence of pyuria may be due to failure of the interstitial pyogenic collections to rupture into the renal tubules; subsequently temporary absence of pyuria may be due to ureteral obstruction in a unilateral infection. In some instances the urine may be

grossly cloudy, but usually is clear. If the child's dietary intake has been restricted or if there has been persistent vomiting, there may be acetonuria. The urine most often contains a few red blood cells and on rare occasions may be grossly bloody. In the more severe cases granular and hyaline casts may be present. There is a mild anemia, more severe in the graver cases, and a varying degree of polymorphonuclear leukocytosis.

In every instance of persistent or recurring pyuria of urinary tract origin the child should be examined by intravenous and, if necessary, retrograde urography in search of structural or neurologic abnormalities which might be responsible for stasis and thus for persistence of an infection. The use of the cystogram provides a relatively simple method to examine the child for ureteral dilatation, which is not disclosed by intravenous urography. When there is no spontaneous reflux into the ureters with the upper half of the body lowered, there may be reflux during voiding, the so-called voiding cystogram.

**Treatment.** Though most acute urinary tract infections heal spontaneously, it is advisable to treat them with an antibacterial agent in order to shorten the course and to attempt to avoid the infrequent instances of progressive renal damage. Other aspects of therapy include bed rest during the febrile stage and sedative and/or analgesic drugs only when necessary to secure rest or relief of pain. In acute cases the intake of fluids should not be restricted, since the chance of renal infection is increased when urinary output is diminished. In all instances of persistent urinary tract infection urographic studies are indicated to determine whether there is an obstructing anatomic lesion; an intravenous pyelogram may be the only procedure necessary.

The selection of the antibacterial agent in the acute cases should be based whenever possible on the establishment of its effectiveness against the invading organism. Such information is essential in all chronic infections when antibacterial therapy is used as an adjunct to measures designed to eliminate any anatomic variants or neurologic dysfunction which may contribute to persistence of infection.

The sulfonamides are perhaps the antibacterial drugs most widely used for urinary tract infections. They are effective against many of the common pathogens of the urinary tract, and bacterial drug resistance is not rapidly established. Sulfadiazine, sulfa-

merazine and sulfisoxazole (Gantrisin) are all effective. Gantrisin has the advantage of being more soluble and hence is somewhat less likely to produce crystalluria. Combination of two or more sulfonamides in total doses equal to that for a single agent is another means for decreasing the production of crystalluria. Effective doses of the sulfonamides are in the range of 0.1 to 0.2 gm. per kilogram of body weight per day in four to six divided doses. In a few instances the dose may need to be increased, and often in the case of drug-resistant bacteria better results can be obtained by the combination of a sulfonamide and an antibiotic chosen on the basis of effectiveness demonstrated *in vitro* against the bacterium in question. In the treatment of chronic or complicated infections the sensitive organisms may be eliminated and be replaced by resistant bacteria.

Nitrofurantoin (Furadantin) is bacteriostatic and bactericidal against most of the pathogens of the urinary tract; strains of *Proteus* and *Pseudomonas* are relatively resistant. It is contraindicated during oliguria or with severe renal damage. Blood cell counts should be made periodically during prolonged therapy to watch for possible hematopoietic suppression. (See p. 217 for dosage.)

Mandelic acid (calcium mandelate or mandelamine, p. 219) has been of limited usefulness in the control of chronic urinary infection because it is effective only in the presence of an acid urine, which was difficult to maintain by available methods. Recently Kass has been able to maintain the urine at a pH 5 over a period of months by oral administration of methionine. At this pH he has found mandelic acid an effective antibacterial agent for such organisms as *Proteus*, *Pseudomonas*, the coli group and staphylococci even when the commonly used antibiotics have failed. In cases in which complete sterilization has not resulted there has been a decrease in the bacterial count. Kass uses the urinary pH (nitrazine paper, pH of 5) as an indication of the amount of methionine needed. In general a sufficiently low pH has been obtained with 1 gm. of methionine per 5 kg. of body weight per day. Voided bacterial counts less than 100,000 colonies per cubic centimeter are used as an indication of the effectiveness of mandelic acid and the amount of it to be prescribed. Kass has also used hippuric acid as an antibacterial agent in a similar manner with gratifying results.

Antibacterial therapy should be continued until the patient is afebrile and two sterile

urine cultures are obtained at an interval of three days. After the therapy has been discontinued the child should be re-examined (including a urinalysis) at intervals of a week and a month to detect any recurrence.

## PERINEPHRITIS

### (PERINEPHRIC ABSCESS)

Perinephritis is an inflammatory reaction in the soft tissues surrounding the kidney. The infection is usually unilateral and usually proceeds to suppuration unless checked by therapy. Pus accumulates below the kidney and may extend in any direction, usually along the lumbar muscles toward the pelvis. It may rupture into the iliocostal space, above Poupart's ligament, or into the peritoneum, intestines, kidney, bladder or pleura.

**Etiology.** Perinephritis may follow trauma over the renal area, it may be blood-borne from suppurative infections elsewhere, or it may be a direct extension from a neighboring focus. Staphylococcal infections of the skin frequently antedate the renal infection. In the majority of instances infection of the perinephric space results from rupture of an embolic renal cortical abscess.

**Clinical Manifestations.** The symptoms come on abruptly with fever, chills and other signs of acute infection. The fever is usually remittent. Signs localizing the disease to the renal region appear early with pain in the lumbar region of the affected side which may be referred to the groin, hip, thigh or knee. Movement of the spine causes discomfort, so that the patient walks with difficulty or prefers to lie on his back and, because of the spasm of the iliopsoas muscle, keeps his thigh flexed. Extension of the flexed leg is resisted, owing to the induced pain, but movement of the hip and knee joint in other directions is unhampered. Locally, there is tenderness with muscle spasm over the renal area and eventually an indefinite swelling, at times with demonstrable fluctuation. The overlying skin and subcutaneous tissues may become reddened and edematous.

Urinary symptoms are usually lacking, although in about half of the cases there is pyuria during the course. Often a bulging psoas shadow can be seen on the roentgenogram, and elevation and decreased excursion of the diaphragm are evident during fluoroscopy. Acute cases may terminate within several weeks with gradual subsidence of all symptoms and signs; or the infection may become chronic and persist for months with



final resolution or with rupture of the pus into one of the areas mentioned.

**Prognosis and Treatment.** The prognosis is influenced by the primary disease. Treatment consists in rest in bed, local application of heat during the early stages, administration of an appropriate antibiotic, and, if suppuration occurs, surgical drainage. Blood and urine cultures may aid in establishing an etiologic diagnosis and thus permit a more effective selection of the antibacterial agent.

MITCHELL I. RUBIN

## REFERENCES

Farrell, J. I., and Young, R. H.: Hypertension Caused by Unilateral Renal Compression. *J.A.M.A.*, 118:711, 1942.

- Guild, H. G., Kindell, F. B., and Gibson, T. A.: Arteriosclerosis in Childhood. *Bull. Johns Hopkins Hosp.*, 62:159, 1938.
- Kass, E. H.: Chemotherapeutic and Antibiotic Drugs in the Management of Infections of the Urinary Tract. *Am. J. Med.*, 18:764, 1955.
- Kass, E. H.: Bacteriuria and the Diagnosis of Infections of the Urinary Tract. *A.M.A. Arch. Int. Med.*, 100:709, 1957.
- Kass, E. H., and Ziai, M.: Methionine as a Urinary Tract Antiseptic. *Antibiotics Ann.*, 1957-1958, New York. Medical Encyclopedia, Inc.
- Stanfeld, J. M., and Webb, J. K. G.: Observations on Pyuria in Children. *Arch. Dis. Child.*, 28:386, 1953.
- Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension. *Medicine*, 18:221, 1939.
- Wilson, J. R., and Schloss, O. M.: Pathology of So-Called "Acute Pyelitis" in Infants. *Am. J. Dis. Child.*, 38:227, 1929.

## DISTURBANCES OF THE KIDNEY

### NEPHRITIS

(BRIGHT'S DISEASE)

#### ACUTE GLOMERULONEPHRITIS

(ACUTE HEMORRHAGIC NEPHRITIS)

Glomerulonephritis is largely a disease of childhood and is the most common form of nephritis in children. Its true incidence is not known, since many of the milder cases are unrecognized clinically; it accounts for about 0.5 per cent of hospital admissions. About two thirds of the cases occur in children under seven years of age. It is uncommon under three years of age, but it has been observed in the newborn period and as a congenital lesion. It seems to be more common in boys than in girls. In contrast to the chronic vascular forms of nephritis, there is little familial susceptibility.

**Etiology.** Acute glomerulonephritis apparently is an antigen-antibody reaction secondary to an infection elsewhere in the body. Like rheumatic fever, this infection is most often in the upper respiratory tract (occasionally on the skin) and most often is caused by a group A beta hemolytic *Streptococcus*. Not all strains are nephritogenic. Type 12 appears to be the most common of the nephritogenic strains, and types 4 and 25 somewhat less common. The rate of renal involvement in infections with the so-called nephritogenic strains also appears to vary in different epidemics. Nephritis occurs in about

1 per cent of cases of scarlet fever. The onset of nephritic symptoms occurs one to three weeks after the onset of the streptococcal infection. Other organisms such as the *Pneumococcus*, *Staphylococcus* and viridans strains of the *Streptococcus* have also been thought to be infrequent etiologic agents.

Focal nonsuppurative glomerulonephritis may occur at the height of a variety of infections and may be associated with sulfonamide reactions. The proteinuria and hematuria in these conditions are usually transient.

Climate plays little part. The incidence of glomerulonephritis, unlike that of rheumatic fever, is the same in both the northern and southern parts of the United States. The rarity of second attacks is probably dependent on the type-specific immunity induced by the infecting *Streptococcus* and the relatively few nephritogenic strains.

See also Nephritis in Schönlein-Henoch purpura (p. 921).

**Pathology.** In acute glomerulonephritis the kidneys are slightly enlarged, pale and dotted with small punctate hemorrhages on the cortical and cut surfaces. Histologically, the endothelial cells of the glomerular capillaries show swelling and proliferation, which obstructs the flow of blood. The epithelial cells of the capsules and of the tufts are also proliferated, and polymorphonuclear cells and monocytes may have infiltrated the glomeruli. The usual appearance is that of large, dark-staining, relatively avascular

glomeruli. Albuminous fluid, red blood cells and white blood cells escape into the capsular space and into the tubules. Fibrin is deposited in the capsular space, leading to adhesions between the capillary tuft and capsular wall. The cells of the tubules are swollen and granular, and contain hyaline and fatty deposits. The interstitial tissues tend to be edematous and congested with a minimal amount of inflammatory cellular reaction. When acute glomerulonephritis heals, there may be no residual evidence of the disease.

In subacute glomerulonephritis the kidney is large and pale. Histologically, there is disappearance of some nephrons, whereas others have undergone a compensatory hypertrophy. The remaining glomeruli reveal changes similar to those described, but often with more numerous capsular adhesions; proliferation of the epithelial cells of the capsule leads to the formation of epithelial crescents. Although some of the glomeruli have become completely hyalinized and their associated tubules have undergone atrophy or have disappeared, the hypertrophy and dilatation of the remaining nephrons prevent actual shrinkage of the renal mass. Focal areas of lymphocytic infiltrate are present in the areas of atrophic renal parenchyma.

It is not always possible to correlate the clinical picture with postmortem renal changes. Electron microscopic studies of renal tissue obtained during life by needle biopsy give promise of providing correlative information.

Though it is postulated that capillary damage in glomerulonephritis is not limited to the kidney, there is little anatomic evidence of it. In some organs other than the kidney small extravascular collections of red cells appear. The occasional finding of petechiae in the skin, the early generalized edema (before cardiac failure occurs, while the serum albumin is at good levels, and in the presence of a good urinary output) and the high protein content of this edema fluid are suggestive evidences of the presence of widespread capillary damage. Cerebral edema is present in some cases; its exact cause is not clear. It may depend on vascular injury, as does the edema elsewhere. In some instances its presence is correlated with a high venous pressure associated with cardiac failure.

Cardiac involvement, as demonstrated by the electrocardiogram, by enlargement on physical and roentgenographic examination or by signs of congestive failure, occurs in

many of these patients and may be an early finding. Little is known about the pathologic lesions in the heart.

**Clinical Manifestations.** There is great variability in the clinical patterns of glomerulonephritis. The attack may be so mild as to go unnoticed or to be detected only by continued clinical observation with recording of temperature and by urinalyses after a streptococcal infection such as scarlet fever. At the other extreme the onset may be abrupt and severe, and there may be some or all of the following: high fever, severe headache, malaise, oliguria to anuria, hypertension with encephalopathy, and cardiac decompensation. Death may occur during such acute episodes. The clinical pattern of the average case is sufficiently characteristic to permit its description.

As a rule the child is not very ill. The most frequent presenting symptom is hematuria. The parents have usually forgotten the preceding acute respiratory infection, and the history of it is elicited only by direct questioning; at times, however, the respiratory infection is still present when the hematuria appears. In some cases puffiness about the eyes antedates the onset of the hematuria or appears coincidentally with it. For the first few days the urine is grossly bloody (at times there is only microscopic hematuria), then acquires a smoky, dirty, brownish hue. Edema may be generalized, but severe edema is usually not seen in acute glomerulonephritis except when fluids have been forced in the presence of oliguria and during cardiac failure. The temperature may be as high as 103° to 104° F. for three to five days, then gradually falls to about 100°, fluctuating at this level for weeks or until the renal lesion has healed entirely. At times there are such gastrointestinal symptoms as loss of appetite, vomiting and constipation; less often, diarrhea. Some patients complain of headache. When the child does not appear acutely ill, it is difficult to impress upon the parents the seriousness of the illness.

On examination little may be found other than a residual upper respiratory tract infection or slight puffiness about the eyes. Varying degrees of hypertension may be present. When the blood pressure is elevated, the pulse rate is slow if the cardiac action is good. The urine is usually decreased in amount, of a high specific gravity, and contains albumin, varying amounts of red blood cells, some white blood cells, and hyaline, granular and cellular casts. The level of blood urea nitrogen is



usually elevated. There is an inverse relationship between the urinary volume and the elevation of the blood urea nitrogen. There is a similar relationship between the urinary volume and the acid-base balance, the severity of the acidosis being directly related to the degree of oliguria. Such a relationship holds for all the waste products excreted by way of the kidney. A slight decrease in the serum albumin, however, is usual. Anemia tends to develop quickly, and the corrected erythrocyte sedimentation rate is rapid.

Some abnormality can be detected on serial electrocardiograms in about 75 to 80 per cent of the cases. In about 50 per cent the heart will be enlarged, and there is evidence of failure in about 20 per cent.

Improvement, manifest by abatement of the constitutional symptoms, usually begins within one to two weeks after the onset, and grossly visible blood disappears from the urine about this time. As a rule the blood pressure returns to normal after about a week, and the blood chemical findings during the second week. Diuresis usually commences after three or four days, and the patient may lose 5 to 7 pounds even though no clinical edema is evident.

Microscopically, the urine returns to normal in an average of about six weeks. Several urinalyses are necessary to establish the cessation of the disease, since red blood cells may be absent and reappear subsequently. Occasionally gross hematuria returns after having temporarily subsided for a few days. When a more delicate test, such as the Addis count, is used, abnormal numbers of red blood cells appear in the urine for about four months in the average case. Thus, though the average patient is usually well clinically within about two weeks, he still has diseased kidneys for about four months. In rare instances complete clearing of the urine may not occur for a year or more.

The erythrocyte sedimentation rate can be used as a measure of the progress of the disease. It remains rapid in the average case for about three months. The prognostic value of the sedimentation rate depends on the fact that it remains rapid in all cases going on to chronicity even though the Addis count may temporarily be normal. Occasionally the sedimentation rate returns to normal at the usual time and the Addis count remains abnormal for several months longer. In such an instance the sedimentation rate is a good prog-

nostic guide, indicating eventual recovery in the face of an abnormal Addis count.

**Urinary findings.** The specific gravity of the urine during the acute phase is usually high even when correction is made for the albumin content. Rarely the ability of the kidney to excrete a concentrated urine is lost early in the disease, and the specific gravity of the urine is low. Retention of nitrogenous wastes is usually associated with this low specific gravity. The volume of urine may be normal, but in most instances it is reduced; in about 5 per cent of cases there is oliguria approximating anuria. It is surprising that these severe states of oliguria are not responsible for extensive generalized edema. Vomiting, which is a striking feature of uremia, probably is a factor limiting water retention. There is no correlation between generalized vasospasm or arterial hypertension and volume of urine or its specific gravity.

Though a definite diagnosis of glomerulonephritis cannot be made in the absence of hematuria, infrequently only a few red blood cells can be detected microscopically at any time in the course of the disease. Gross hematuria occurs in about half of the cases. Freshly passed urine should be examined for both red blood cells and casts, since both may disappear when alkaline or dilute urine is allowed to stand. White blood cells are also found in increased numbers; occasionally so many are present as to suggest pyelonephritis.

The amount of albumin in the urine varies greatly and is not correlated with the severity of the disease. The amount decreases as the renal process heals, and usually parallels the disappearance of red blood cells. In cases going on to latent or chronic stages albuminuria and irregularly recurring hematuria persist; they are more regularly detected by the Addis count than by routine urinalysis. Children with these urinary abnormalities for more than a year after the acute phase should be regarded as having entered the chronic phase, in which the prognosis is grave, though recovery is possible. During convalescence, but not subsequent to recovery, exacerbations are to be expected after an acute respiratory infection (or after tonsillectomy) and are not in themselves a bad prognostic sign.

**Hypertension.** Hypertension is present in about 60 to 70 per cent of the cases. It may appear at any time during the acute phase; systolic pressures may be as high as

200 mm. of mercury, with diastolic pressures of 100 to 120. The rise may be sudden: for example, from a normal level in the morning to high levels by afternoon. The drop may be just as precipitous. In most instances the hypertension is present during the first four or five days of the illness, slowly returning to normal levels by the end of the first week. In some cases, usually those with more extensive renal damage, the hypertension may persist for weeks; in persistent cases it may be permanent.

The mechanism of hypertension in acute glomerulonephritis is considered to be dependent on generalized vasospasm, possibly resulting from renal ischemia, rather than on cerebral edema. Hypertension is associated and directly correlated with cerebral symptoms (hypertensive encephalopathy) and cardiac disturbances.

**Cerebral symptoms.** Cerebral symptoms appear after an acute rise in blood pressure and are probably due to cerebral ischemia resulting from the vasospasm. Symptoms persist during hypertension and consist chiefly in headache, drowsiness, convulsions and vomiting. Restlessness, dimness of vision and diplopia may be associated. The pulse is slow. When the blood pressure is reduced (relaxation of the vasospasm), the cerebral symptoms disappear. There is no correlation between these episodes and the degree of renal impairment or water retention.

Cerebral edema may occur, but certainly it is not the total or the usual explanation for hypertensive encephalopathy. In the majority of cases the cerebrospinal fluid pressure is within normal limits and there is no papilledema. In cases with cerebral edema, papilledema may be present. Furthermore, measures designed to reduce the vasospasm result in a disappearance of the cerebral symptoms, whereas diuretics which induce cerebral dehydration usually fail to control the symptoms. When there is cerebral edema, dehydrating measures may be of aid. Constriction of the retinal arteries is usually the only fundal finding in the acute phase; retinal hemorrhages and exudation are observed only in the chronic phase.

Episodes of hypertensive encephalopathy usually last a day or two and spontaneously end with the fall in blood pressure, although death may occur during the cerebral attack. Recovery under appropriate treatment is usually complete and rapid. It is possible that residual disturbance may occasionally result from prolonged anoxia.

**Cardiac symptoms.** Cardiac involvement is present in about 75 to 80 per cent of the cases. Usually evidence of it is limited to electrocardiographic changes. Signs of cardiac failure are occasionally the presenting symptoms, and the basic disturbance may be detected only by urinalysis or the finding of hypertension. When the hematuria is not marked and other evidences of severe renal damage are lacking, the diagnosis is difficult. Acute glomerulonephritis is second only to rheumatic fever as a cause of acute cardiac failure in children beyond the age of infancy. Hypertension, though not invariably present, is strong evidence in favor of a nephritic origin of cardiac failure. The increased peripheral load incident to the vasospasm apparently overburdens the weakened myocardium, producing failure, and it is also possible that the generalized vasospasm may result in hypoxia of the myocardial cells. Hypervolemia secondary to retention of sodium and water has been suggested as an etiologic factor in the cardiac failure of nephritis. Others believe that the symptoms ascribed to cardiac failure may occur as a result of hypervolemia in the absence of cardiac failure. The pulse rate during the acute phase of the disease tends to be relatively slow; a rapid rate suggests myocardial damage.

The most striking changes in the electrocardiogram are observed in the T wave, consisting chiefly in flattening or inversion in one or more leads, although a transient increased amplitude of the T wave is occasionally observed. Inversion of the T wave occurs late in the cycle and is not infrequently preceded, especially in leads I and II, by a slightly depressed, upward bowed segment. Transient inversion of the T wave occurs as frequently in lead III as in lead I, but cardiac failure is commoner with inversion of the T wave in lead I.

Cardiac signs usually subside rapidly with the fall in blood pressure, and even the child in cardiac failure will show rapid improvement within a day or two. Usually all evidence of cardiac involvement except that of enlargement will disappear within a week to ten days. The enlargement usually disappears more slowly, requiring about six to eight weeks. The systolic apical murmur is usually the last evidence to disappear. Cardiac failure is a cause of death in acute glomerulonephritis and usually occurs early in the disease. Patients who recover have complete restoration of cardiac function.

**Renal function.** Renal function is im-



paired in most patients early in the disease. The glomerular filtration rate is generally reduced to some extent, and it may be greatly reduced. There is lack of correlation with the extent of the reduction and recovery. The fall in urine volume is in part at least related to reduced filtration; there is, however, evidence that tubular reabsorption of water may be an important factor in the early oliguria and later in diuresis. The volume of urine alone cannot be used as a guide to the extent of renal function, for when concentrating capacity is lost, even early in nephritis, there may be a large volume of dilute urine. In most instances, however, the urinary volume may be used as a guide of renal function. If the volume is not sharply reduced (with an adequate intake) and the specific gravity of the urine is within normal limits, there is no serious functional loss. Persistent oliguria which is not due to severe dehydration is an ominous sign and a measure of renal failure. Retention of nonprotein nitrogenous substances, phosphates, sulfates and potassium is related to the fall in glomerular filtration rate.

Renal plasma flow as measured by para-aminohippurate tends to be normal, or even high. Thus the filtration fraction (F.F.) is almost always reduced, further demonstrating that the glomerulus is the focal point of the disease. Tubular excretory capacity as measured by maximal excretion of para-aminohippurate is reduced in about 50 per cent of patients during the acute phase. The loss of concentrating capacity is additional evidence of tubular impairment.

Recovery of renal function is gradual and occurs with clinical recovery, but may be delayed and return to normal only after several months. Loss of edema and disappearance of hypertension usually antedate recovery of renal clearance functions.

**Diagnosis.** In the usual case of acute glomerulonephritis there are no diagnostic difficulties; the coexistence of hematuria, albuminuria and slight edema, in the absence of cardiac failure, establishes the diagnosis. In cases in which cardiac failure occurs early, the symptoms referable to the failing heart may dominate the picture so that the nephritis may initially not be suspected.

Embolic nephritis is characteristically seen during a bacteremia such as that of subacute bacterial endocarditis; it is transient and disappears when the blood stream is free of bacteria.

Transient hematuria during *acute pyelo-*

*nephritis* may be a diagnostic problem. Large numbers of pus cells in comparison with red blood cells and the bacteriuria aid in the differentiation from glomerulonephritis.

It may be impossible initially to differentiate the hematuria, decreased urinary output and occasional azotemia resulting from sulfonamide crystals. The disappearance of the hematuria and other urinary symptoms within a day or two after withdrawal of the drug is strong evidence against glomerulonephritis. A clinical picture indistinguishable from glomerulonephritis is also occasionally seen in sulfonamide intoxication. Other causes of hematuria such as cystitis (p. 1055), scurvy, blood dyscrasias, calculi, trauma, tumors and tuberculosis of the urinary tract may also require differentiation. The urinary findings at times associated with the Schönlein-Henoch syndrome also require differentiation (p. 921).

Extrarenal azotemia and other waste retention resulting from severe states of dehydration should be recognized. The concentrated urine often contains albumin and hyaline casts, which tend to disappear quickly when the child is hydrated.

Febrile and other benign *albuminurias* at times create diagnostic problems. Febrile albuminuria is usually recognized by its transitoriness and association with febrile states. Since the erect posture may occasionally increase albuminuria in subacute or chronic glomerulonephritis and since the urine in orthostatic albuminuria may rarely contain a slightly increased number of red blood cells and casts, differential diagnosis may be difficult.

**Prognosis.** Although the prognosis of acute glomerulonephritis is generally good, it is unpredictable in the individual case. Thus the mild case may progress to the subacute stage, whereas a patient with fulminating symptoms of hypertensive encephalopathy, cardiac failure and/or renal shutdown may recover completely. There is a positive correlation between the severity of the onset and the fatality rate during the acute stage, but none between the severity of the acute stage and the development of chronic nephritis. Mortality rates during the acute phase have varied from 1 to 5 per cent. Since the availability of antibacterial therapy the rates in most clinics have approached the lower figure. The incidence of chronic nephritis is of about the same order, though rates as high as 5 and 10 per cent have been reported.

Second attacks of glomerulonephritis are

extremely rare. Recrudescence of the disease before healing is complete, however, is common in association with fresh respiratory infections or after removal of infected tonsils or teeth.

In mild cases the entire course may extend for only ten to fourteen days. Protracted cases may show urinary changes for a year, and rarely for a longer period, yet the patients still recover completely. The abnormalities of the urine as demonstrated by routine examination usually disappear within six or eight weeks, and the erythrocyte sedimentation rate becomes normal in about three months, the Addis count in about four months. The persistence of urinary changes for more than one year with evidences of progressing renal failure is indicative of a grave prognosis, death usually occurring within five to ten years.

**Treatment. General.** The treatment of nephritis is largely symptomatic, but should be based on recognized physiologic principles. The child should be confined to bed during the acute phase and until urinary findings approach normal. There is increasing evidence that activity out of bed after the first two or three weeks of the disease does not adversely affect the course. Subsequently the child's urine should be closely watched, and he should be guarded against respiratory infection, chilling and overexertion.

During the first few days of the disease the diet should be a liquid one of sweetened fruit juices and milk. As the acute phase subsides the child may be given a soft diet and soon a regular diet. Salt-free diets are not generally prescribed unless edema is excessive, but during the acute phase salt should not be added to the food during cooking or subsequently. The usual practice is to limit the amount of salt to that used in ordinary cooking. There is little evidence that the protein in the diet needs restriction, except perhaps during the height of the acute stage; certainly restriction of the protein intake below the body requirements beyond this time will lead to the consumption of tissue proteins.

Since positive nasopharyngeal cultures for streptococci are often found at the onset of clinical nephritis, full therapeutic doses of penicillin should be given for a week or so.

Surgical procedures should be restricted to those absolutely essential. Abscesses of the middle ear or in other locations should be drained, but tonsillectomy should not be performed during the first two or three months of the disease. If the operation is performed

at a later date, antibiotic therapy should precede and follow it by two or three days in an attempt to prevent bacterial spread. Nephritis of itself is not an indication for tonsillectomy.

**Treatment of special symptoms.** Children with acute glomerulonephritis may be divided into four general groups on the basis of their clinical patterns.

**GROUP I. Patients with (1) normal blood pressure, (2) good urinary output, and (3) normal or only slightly elevated blood urea nitrogen.** With normal blood pressure, hypertensive encephalopathy will not occur, and there is little likelihood of cardiac failure; with good urinary output and a normal blood urea nitrogen level, acidosis and uremia will not occur. Thus in group I none of the severe complications should arise, and these patients require only general treatment. They should be closely watched, however, for a possible change in their status.

**GROUP II. Patients with (1) elevated blood pressure, (2) good urinary output, and (3) normal blood urea nitrogen.** The elevated blood pressure, indicative of vasospasm, may result in hypertensive encephalopathy and in cardiac failure. For these reasons attempts should be made to lower the blood pressure when the diastolic pressure is over 95 mm. or the systolic pressure is over 140 mm.

Magnesium sulfate has been the most effective and widely used hypotensive agent for the control of hypertension in nephritis. It is toxic and can produce severe respiratory depression and in large doses has a direct action on cardiac muscle. Toxic manifestations can be avoided by appropriate dosage and can be counteracted by the intravenous administration of 5 to 10 cc. of a 10 per cent solution of calcium gluconate or a 5 per cent solution of calcium chloride. In the presence of oliguria, magnesium sulfate should be given with extreme caution (see group IV). A 50 per cent solution of magnesium sulfate in a dose of 0.2 cc. per kilogram of body weight injected intramuscularly will usually lower the blood pressure within one to two hours by relaxation of the vasospasm. In some instances this dose will have to be repeated several times at intervals of four hours to keep the pressure at a satisfactory level. In about half of the cases there is no striking effect of the magnesium sulfate; there seems to be some correlation between the amount of urine and the reduction in blood pressure, the drug being less effective



in the presence of a large urinary output, so that effective blood concentrations are not obtained. In these latter instances larger doses of the drug are needed to produce the desired effect. When there are severe manifestations of encephalopathy such as diplopia, coma and convulsions, the drug can be given intravenously as a 3 per cent solution of the hydrated salt. The total dose of 150 to 200 mg. per kilogram of body weight should be given in the course of one hour, half of it in the first fifteen to twenty minutes. The blood pressure and the respirations should be observed constantly during this time.

Recently the combination of reserpine and hydralazine hydrochloride (Apresoline) has been found to be effective. Reserpine is mildly hypotensive and also allays anxiety; Apresoline is a more potent hypotensive agent. Reserpine is given in a dose of 0.07 mg. per kilogram simultaneously with hydralazine, 0.1 mg. per kilogram intramuscularly. The effect of this combined therapy is elicited within one-half hour and may persist for twelve or more hours; a single administration is adequate in the majority of instances, but may need to be repeated after twelve hours. The dose of reserpine alone often relieves mild hypertension, or the drug may be given orally subsequent to the initial intramuscular injection in conjunction with hydralazine in amounts of 0.02 to 0.03 mg. per kilogram per day in divided doses.

If hypertensive encephalopathy has developed, the reduction of the blood pressure will usually relieve the symptoms. Sedation may be necessary, however, for the control of convulsions, or, in the presence of associated cerebral edema, lumbar puncture may stop them. Oxygen therapy is also indicated.

When cardiac failure has developed, treatment aimed at improving the myocardial status is indicated. Sedation with opiates is perhaps the most helpful measure. Digitalization is effective, and relatively large doses are tolerated. Total doses of 30 to 40 mg. per kilogram of body weight of the powdered leaf are effective. One sixth of the total dose is given orally as a test dose. Then, if there are no untoward symptoms, a similar dose is administered every four hours until the total dose has been given. It is rarely necessary to give a maintenance dose. A more rapid form of digitalization is effective with a single oral dose of digitoxin or some similar product, 0.035 mg. per kilogram of body weight. Oxygen administration in a tent is

beneficial. Phlebotomy is of doubtful value, and dehydrating agents are not without danger. Cardiac failure has been observed after intravenous injection of 50 per cent sucrose; the sudden increase of blood volume induced by this hydropic agent probably accounts for the effect on the heart. When the blood pressure is reduced, the cardiac symptoms rapidly disappear, and bed rest is the only therapy needed for the heart. The cardiac status, however, should be followed by serial electrocardiograms and roentgenograms.

In the presence of hypertension, restriction of fluid intake is advisable in order that enlarging blood volume does not further hamper cardiac action. In these circumstances the fluid intake is limited to an amount equal to insensible water loss and urinary output; for an average seven-year-old child about 800 to 900 ml. a day. If the urinary volume is large, drastic restriction of fluids is not necessary. When the blood pressure is within normal limits, the management is that described under group I.

**GROUP III.** *Patients with (1) normal blood pressure, (2) small urinary output, and (3) elevated blood urea nitrogen.* When the urinary excretion is decreased, there is a tendency toward acidosis, uremia and edema. In this group of patients it would be desirable to increase the urinary output so that the waste products of metabolism could be excreted. There are no therapeutic measures, including the various diuretics, which will increase glomerular filtration.

The daily water intake can be determined on the basis of the volume of urine excreted on the previous day and the estimated insensible water loss (approximately 700 cc. per square meter). One should make certain that enough water is taken to prevent dehydration and to provide the kidneys with sufficient fluid for their maximal excretory capacity of the moment. When there is uremic vomiting, fluids should be given intravenously or subcutaneously to restore body water and electrolytes and so prevent dehydration and acidosis which further depress renal function. *Potassium-containing solutions should be avoided when there is oliguria or anuria.* Sodium lactate is used to correct acidosis if it is severe, and glucose in a 10 per cent solution is given intravenously to prevent ketosis and further tissue breakdown. Owing to the danger of fluid retention, electrolyte-containing solutions are not given

except when the serum levels of sodium and chloride are greatly reduced. When there is severe nitrogenous retention, dietary protein is eliminated. Cation exchange resins may be used when there is potassium retention, as reflected by an elevated serum level and by electrocardiographic changes; for example, 100 ml. of a 10 per cent solution of ammonium carboxylic exchange resin may be instilled rectally at intervals of four hours as a retention enema. If the serum phosphorus rises to high levels, calcium gluconate is administered orally to lessen the possibility of tetany. Thorazine may be helpful in the control of vomiting.

The so-called artificial kidney and peritoneal lavage have been used during periods of prolonged anuria; the technical aspects of such therapy have been improved in recent years, but it is justified only in adequately selected patients and then by experienced clinicians. Exchange transfusions have also been used. Decapsulation of the kidney or denervation of it and roentgen ray treatment over the renal area are not recommended. Anuria lasting several days is compatible with life if the biochemical and water status of the body is properly maintained; therefore these more drastic measures should not be used unless the anuria persists for five to seven days. When diuresis is established, the management is similar to that described under group I.

**GROUP IV.** *Patients with (1) elevated blood pressure, (2) small urinary output, and (3) elevated blood urea nitrogen.* This group is the most difficult to manage because of the potential danger of all three major complications: cardiac failure, hypertensive encephalopathy and uremia. Since little can be done to improve kidney excretion and since diuresis occurs as quickly with water restriction as with the forcing of fluids, water should be restricted.

A hypotensive agent should be administered to reduce the blood pressure and so lessen the possibility of cerebral and cardiac complications. In view of the small urinary output in these patients, magnesium sulfate should be given with extreme caution, the initial dose being only one half the doses listed above. In the presence of severe oliguria it is safer to use the combination of reserpine and hydralazine or reserpine alone (see group II). When the blood pressure has been reduced to a satisfactory level, the management is similar to that described under group III. The blood pressure should be measured at

least three times a day, since it may again become suddenly elevated.

### **NEPHRITIS IN SCHÖNLEIN-HENOCH SYNDROME**

(ANAPHYLACTIC PURPURA) (See also p. 920)

The renal manifestations of this disease, generally believed to result from a state of hypersensitivity, are common and may be serious. In the early stages the lesions resemble those of lupus erythematosus more closely than acute glomerulonephritis, but later they more clearly resemble glomerulonephritis. The renal manifestations may be minimal and be manifest as microscopic hematuria, or they may be severe and resemble classic glomerulonephritis. A striking feature of the nephritis is recurrence of gross hematuria with clearing of the urine in the intervals. The recurrence of hematuria may or may not be associated with recurrent purpura. As in glomerulonephritis, acute renal failure and severe hypertension with encephalopathy may occur. This form of nephritis is more likely to be persistent than is the usual acute glomerulonephritis.

### **IRRADIATION NEPHRITIS**

Acute and progressive glomerulonephritis may follow roentgen therapy of the abdominal area. Usually there is an interval of several months between irradiation and the manifestations of nephritis. The prognosis is generally bad.

### **FAMILIAL HEREDITARY NEPHROPATHY AND DEAFNESS**

This syndrome is characterized by hematuria, cylindruria and albuminuria. The hematuria may be demonstrable only microscopically, or the urine may be grossly bloody. Remissions are common, and exacerbations may be associated with infections. The condition is hereditary. It is more severe and progressive in the male. In the female the disease is often compatible with a normal life span. Nerve deafness has been reported only in patients with renal involvement and apparently is present in almost all affected males. It is not present at birth, but is usually progressive when it becomes manifest. Congenital abnormalities of the eyes also occur in these families.

Nerve deafness is usually the first complaint. Renal function is usually maintained for some time, but occasionally hypertension



and renal dysfunction occur early. There is no specific treatment.

### CHRONIC GLOMERULONEPHRITIS

Whereas acute glomerulonephritis is much more common in children than in adults, the reverse is true for chronic nephritis. On the other hand, acute glomerulonephritis is more frequently followed by chronic nephritis in adults than it is in children (perhaps not more than 1 or 2 per cent). Most often chronic glomerulonephritis in children has an insidious onset without a known origin. The higher incidence of chronic glomerulonephritis in adults than in children is not dependent on progression of the disease from an acute episode in early childhood.

**Pathology.** The kidney is small and contracted. The capsule is adherent, and the surface of the kidney is finely granular as a result of disappearance of many nephrons and hypertrophy of others. Histologically, many of the glomeruli are hyalinized or have completely disappeared. The remaining functional glomeruli reveal varying degrees of endothelial and epithelial proliferation and hyalinization. Many tubules are atrophic or have disappeared; the remaining ones are often enlarged and cystic. Extensive scar tissue replaces the areas in which nephrons have disappeared, where there is often a focal and diffuse infiltrate of lymphocytes. The arteries and the arterioles associated with damaged or destroyed nephrons reveal extensive degenerative changes, with hyalinization of the arteriolar walls and intimal thickening of the arteries.

**Clinical Manifestations.** The chronic form of glomerulonephritis is characterized by repeated acute exacerbations for a number of years. These are often preceded by acute infections in the upper respiratory tract with the beta hemolytic *Streptococcus*. With each acute flare-up there is a further reduction of renal function, which usually does not return to its previous level, and eventually there is terminal uremia and death. It is remarkable how well the child may look and act when renal function has been reduced almost to the vanishing point. Rapid growth which takes place about the time of puberty often is the final strain which disrupts the renal effort and is responsible for death.

Edema is not a striking feature of the so-called dry type of chronic nephritis, although edema may be present more or less constantly about the eyes and ankles. In the nephrotic

phase of chronic glomerulonephritis, edema may be as striking as in the nephrotic syndrome, and there may also be a reversal of the albumin-globulin ratio in the serum and a mild elevation of the cholesterol. Thus differentiation may be difficult. Not infrequently during this phase of chronic glomerulonephritis there is a decrease in retention of nonprotein nitrogen and in the hypertension; hematuria may be inconstant. When renal function is notably impaired, polyuria and low, fixed specific gravity of the urine become evident, and edema often disappears. The patient may even become dehydrated and salt-depleted; when there is cardiac failure associated with hypertension, the edema may return.

The urinary changes are extremely variable. Albuminuria is constant, but varies in amount. In the final stages, owing to the dilution of the urine, there may be only traces of albumin; in the nephrotic phase large amounts are present. Hematuria also varies in degree, blood being present usually in only microscopic amounts and at times being entirely absent. There may be gross hematuria during an acute exacerbation. Casts are found irregularly in the ordinary examination, but by the Addis technique they are consistently increased in number. The urea and other clearance tests show gradual but progressive loss of function, which is also evidenced by the low, fixed specific gravity of the urine.

There are periods when improvement seems to occur, but the trend is definitely downward. Nitrogen retention is constant; anemia is progressive and may be severe. Associated with sudden rises in blood pressure, there may be episodes of hypertensive encephalopathy and cardiac failure; death may occur at such times. For most of the course the child may feel well enough to be, up and moderately active, pallor and undernutrition being the only presenting symptoms. As the terminal stage is reached he becomes bed-ridden, loses his appetite, complains of headaches and muscular cramps and may have convulsions. Diarrhea and vomiting occur. Arteriolar changes appear in the retinal vessels at this stage, resulting in hemorrhages and exudation, and edema of the optic disks. These patients are highly susceptible to infections; eventually they become uremic with coma preceding death. Elevation of the blood potassium level may produce severe changes in the heart which are demonstrable by electrocardiography.

So-called renal rickets with osseous changes is not likely to occur in this form of chronic renal disease, yet stunting of growth, retention of phosphate, low blood calcium levels and acidosis may be observed in association with tetany.

**Differential Diagnosis.** The differential diagnosis from *congenital polycystic* and *hypoplastic kidneys* may be difficult without urographic studies. *Periarteritis nodosa*, *lupus erythematosus* and so-called vascular nephritis (p. 1049) may simulate chronic glomerulonephritis, as may the terminal phase of pyelonephritis.

**Prognosis.** The decrease in renal function may be slow, but the downward course is inevitable; in an occasional case progression downward is rapid, and death occurs from uremia within a few months. More often death takes place within five to ten years.

**Treatment.** Though the downward course of the disease cannot be significantly altered by therapy, many children can have their lives prolonged and made happier by appropriate management. The child should be permitted to lead as normal a life as is compatible with his abilities. Care should be given to the establishment of a healthy mental attitude toward his limitations; it is also important that the parents maintain as bright an attitude as possible in the face of the impending catastrophe.

The child should be guarded against acute respiratory infections, and nutritional needs in all categories should be fully met. The minimal protein requirements of a normal child of the same age and weight should be permitted. Any severe deficiency in the serum protein should be corrected with injections of plasma. Salt restriction is indicated only during a nephrotic phase or in the presence of edema due to congestive cardiac failure. Hypochloremia and hyponatremia during nephritis may be factors further depressing renal function. During episodes of acute hypertension with impending cardiac failure and hypertensive encephalopathy, magnesium sulfate or reserpine with or without hydralazine hydrochloride, in doses as described under the acute form of the disease, is indicated. Severe anemia requires transfusions for its correction. Removal to a warm, dry climate, especially during the "respiratory season," may reduce the acute exacerbations and thus tend to retard the downward progression. When acute infections develop, antibiotic therapy is indicated. (See Treatment of Uremia, page 1051.)

## NEPHROTIC SYNDROME

### (NEPHROSIS)

The nephrotic syndrome is characterized by excessive edema, proteinuria, hypoalbuminemia, hypercholesterolemia and a course lasting many months or years. The frequency of nephrosis is not known; an incidence of about seven cases per 100,000 population under the age of five years has been estimated. In so-called lipid nephrosis, hematuria, hypertension and azotemia may be minimal and transient. Many children who are initially thought to have lipid nephrosis are subsequently found to have chronic glomerulonephritis.

**Etiology.** The etiology of nephrosis is not known. Except for relatively rare instances of a nephrotic clinical pattern, associated with specific diseases such as syphilis, amyloid disease, thrombosis of the renal vein, disseminated lupus erythematosus, poison oak dermatitis, bee sting and toxic reactions to certain metals and drugs (e.g., mercury and Tridione), the clinical condition known as the nephrotic syndrome consists of disturbances which are classified in two categories as lipid nephrosis and the nephrotic phase of subacute or chronic glomerulonephritis. It is not definite whether these two subdivisions are variants of the same pathologic process or are separate entities. If the former, then it would have to be concluded that those children who have unquestioned evidences of progressive glomerulonephritis have irreversible changes which would lead to uremia and a fatal termination; whereas those whose disease at a given moment could be classified as nephrosis have the potential for either complete recovery or development of irreversible changes.

In most instances it is not possible to relate the onset of nephrosis to some other disturbance. Exacerbations, however, in the nephrotic syndrome often follow acute infections. A clinical pattern in rats which simulates the transition from lipid nephrosis to chronic glomerulonephritis was produced by Heymann and Lund by injection of an anti-kidney serum. Initially there is a degenerative phase, characterized clinically by the nephrotic syndrome. This phase is followed by fibrous proliferation in the glomeruli, manifest clinically by hypertension and uremia. These observations in conjunction with those in children of a decrease in blood complement during active phases of the disease and of an increase during remission suggest the



possibility of an antigen-antibody reaction as an etiologic factor.

Nephrosis is primarily a disease of childhood, the average age at onset being about two and a half years; it is uncommon under one year of age. It is more common in boys than in girls. On occasion nephrosis may follow a familial pattern, when the onset may be earlier, even in the newborn period, and the course more severe.

**Pathology.** The kidneys are enlarged and yellowish, with smooth external surfaces and thickening of the cortices; streaks of bright yellow lipid material may be present in the cortex. The tubules are dilated, and the cells show varying degrees of hyaline granular degeneration; many of them contain doubly refractile lipid droplets.

Much of the controversy about this disease as a distinct entity is related to whether glomerular changes occur early in the disease. In so-called lipid nephrosis Ehrlich and others, using a special stain, described consistent changes in the intercapillary basement membrane of the glomeruli with thickening and so-called fibrinoid degeneration. These observations support those of Bell, who described the essential lesion as a thickening of the capillary basement membranes of the glomeruli which renders them permeable to protein. This thickening may progress to such a degree as to bring about closure of the capillaries and renal insufficiency.

The clinical features of the nephrotic syndrome may be produced not only by thickening of the capillary basement membranes, but also by other glomerular lesions which permit excessive loss of plasma protein in the urine, e.g., proliferative glomerulonephritis or amyloid disease of the kidneys. Vernier, using electron microscopy, has consistently demonstrated distorted epithelial foot processes along the surface of the basement membrane in children with the nephrotic syndrome. This alteration has not been present except in association with the nephrotic syndrome. Cellular proliferation similar to that of glomerulonephritis has also been found early in the disease in needle biopsy material by Galán and Masó.

No extrarenal lesions have been discovered.

The pathogenesis of edema in nephrosis is not entirely clear. The low intravascular osmotic pressure secondary to hypoproteinemia is an important factor. The loss of edema fluid when the serum albumin is still at a low level, however, suggests that some additional factor must operate in control of the

edema. Luetscher demonstrated an increase in aldosterone, a potent sodium-retaining adrenal hormone, in the urine of nephrotic patients during the edema phase and a return of it to normal levels after diuresis. During diuresis the excretion of sodium and chloride in the urine increases and may continue for some time after weight loss has ceased. The lowered glomerular filtration rate presumably is also a factor in water retention. However, since higher filtration rates occur early in the disease in many patients, the lowered filtration rate would not seem to play a prominent role.

It is generally believed that the reduction in serum albumin is due primarily to urinary loss. Recent studies of Gitlin, however, suggest that there may be an associated increased catabolism of serum albumin, which at times may be a significant cause of the low serum level.

**Clinical Manifestations.** Edema is the usual presenting symptom. At the onset the child rarely appears ill, except when an acute infection precipitates the attack. The development of severe generalized edema may be abrupt, but more often the edema during the initial stage of the disease is slight and inconstant, appearing only about the eyes and ankles. Finally, edema fluid accumulates in great quantity; in some instances the patient almost doubles his true weight. This phase may last several weeks to months. Characteristically, the course of nephrosis consists in recurrent accumulations of edema fluid after partial or complete remissions resulting from spontaneously induced diuresis. The urinary output varies inversely with the edema. As the disease becomes well established, pallor develops, but may not be related to any significant degree of anemia. The appetite fails, lassitude and irritability generally develop, and malnutrition may become severe. During edema the loss in body tissue is masked, only to become glaringly apparent when the edema is lost. The edema may become so extensive that it seems as if the skin would rupture; at such times ascites is usually marked, and there may be a bilateral hydrothorax. Intense edema of the scrotum is characteristic. The edema in the peripheral tissues is dependent and shifts with change in posture. In well established cases the peripheral edema may be minimal, with large accumulations of ascitic fluid. Diarrhea and vomiting are not uncommon during the periods of generalized edema; edema of the intestinal wall may be the factor in the intestinal disturbance. Under such circum-



FIG. 313. Nephrosis in a boy 4 years of age. Edema of insidious origin started several months before admission without any preceding infection and varied from time to time. The urine contained large amounts of albumin and some hyaline casts, but never blood. There was no increase in blood pressure, and no azotemia. Total blood protein, 3.86 per 100 ml.; albumin, 1.79; globulin, 2.07; cholesterol, 300 mg.

stances there may also be a flat glucose tolerance curve which returns to normal in the edema-free interval. Interference with digestion of other food substances may also occur.

Most of the physical characteristics of the disease (respiratory distress, abdominal distention, umbilical and inguinal hernias, rectal prolapse and decreased ambulation) are related to the extent of the edema. The liver is often moderately enlarged. The blood pressure is usually normal; transient elevation may occur early. Persistent hypertension accompanies advanced renal insufficiency. In the absence of infection there is no fever; in fact, there may be no fever even with a severe infection.

Children with nephrosis are unusually susceptible to infection. Repeated acute upper respiratory tract infections are often engrafted on what appears to be a chronic one. The *Pneumococcus* is a common offending organism, but infection with the hemolytic *Streptococcus* and other pathogens is not uncommon. The clouding of the paranasal sinuses as seen on the roentgenogram is probably more dependent on the edema of the mucous membrane than on the existence of bacterial infection. On rare occasions there has been complete recovery from nephrosis after an acute bacterial infection. Remissions following measles are common.

Erysipeloid lesions which consist of red, blotchy, tender patches occasionally occur on various parts of the body, accompanied by fever and other signs of acute illness. The urinary volume may sharply decrease at this time, and the edema becomes more extensive. Such an episode has been called a crisis. Although many explanations have been given to account for this sudden change in the clinical picture, infection would seem to be

a probable cause. A fall in the blood amino acid level accompanies the attack.

Signs of glomerulonephritis with hematuria, azotemia and hypertension eventually develop in many children who appeared to have had a lipoid nephrosis at the onset. Rarely a nephrotic episode is precipitated by clinical evidences of acute glomerulonephritis. With progression of the disease there is a tendency to persistence of edema with minor fluctuations, and the urine volume tends to be small. In the end stages the patient may become relatively free of edema. Cardiac failure may occur and in the presence of extensive edema can be misinterpreted.

Xanthomatous lesions may be associated with high blood cholesterol levels (p. 1002). The basal metabolic rate is usually within the normal range if correction is made for the overweight due to the edema fluid.

The most important laboratory finding is proteinuria with an albumin-globulin ratio between 5:1 and 1:1. Heymann noted that the ratio was less than 1:1 in a group of patients whose disease was progressive. The total daily urinary output of protein is commonly as high as 10 to 15 gm., and may be higher. During the accumulation of edema fluid the urinary volume is reduced, and the specific gravity of the urine is high. Diuresis of large amounts of urine accompanies disappearance of the edema. Hyaline, granular and cellular casts are found in large numbers, and many contain doubly refractile lipoid bodies. These lipoid bodies are also found free in the urine. There may be some increase in leukocytes. Neither the presence nor the absence of a small number of red blood cells early in the course of the disease seems to have prognostic significance. The development of persistent hematuria, however, is a serious prognostic omen. As with hematuria,



there may be transient and moderate nitrogen retention which does not necessarily indicate progressive renal failure. There is little tendency toward acidosis in the early stage of the disease. In the "non-nephritic" phase renal function tests reveal normal and even elevated capacities. In the "nephritic" phase there is progressively decreasing function as measured by the various tests.

The characteristic changes in the blood are a lowering of the serum albumin sufficient to produce a reversal of the albumin-globulin ratio and an increase in the blood lipids, particularly in the cholesterol fraction, with levels of 300 to 1800 mg. per 100 ml. The ratio of free to esterified cholesterol is unaffected. There is an increase in the ratio of total cholesterol to phospholipids, the greatest increase occurring in the fraction of cholesterol bound to beta-lipoprotein. The major reduction in serum protein is in the albumin fraction; edema develops at levels of about 2.5 gm. per 100 ml. In some cases the albumin is reduced below 1 gm. per 100 ml. These low levels may persist even after edema has entirely disappeared, and then slowly rise as the disease process subsides. The total globulin fraction may be normal or slightly elevated; the gamma globulin fraction is reduced, and the alpha and beta fractions may be increased. The fibrinogen is often increased. The plasma volume is reduced in most cases, but rises during diuresis.

Slight or even severe secondary anemia may be present, the latter usually when clinical glomerulonephritis coexists. The erythrocyte sedimentation rate is rapid. The serum calcium is frequently reduced with chronic glomerular disease; tetany is an occasional complication. Glycosuria occasionally occurs without a coexisting hyperglycemia. Woolf and Giles found two patterns of amino-aciduria: one suggestive of a defect in renal tubular reabsorption and the other of a disturbance primarily in amino acid metabolism. The prognosis was worse with the first pattern.

The ascitic fluid is nearly always opalescent, appearing like slightly soapy water. The protein content averages about 0.2 per cent.

**Prognosis.** The course of nephrosis is variable, but in general is characterized by recurrent episodes of edema of varying length. Though the untreated child is seldom completely free of edema during the active phase of the disease, he may appear to be so after rapid loss of large quantities of edema fluid. Even in cases which go on to recovery, albu-

minuria may persist for weeks or months, and the return of the other chemical changes to normal may be slow. The cholesterol is usually the last blood constituent to return to normal; it may remain elevated for months. The erythrocyte sedimentation rate usually remains rapid as long as the disease exists.

Since mild hematuria and azotemia may be present early in the course of lipoid nephrosis and then disappear, it is not possible to prognosticate the outcome of the individual case early; the patient may eventually recover, or progress to ultimate renal failure. The speed of progression cannot be foretold, owing to the great variations in the clinical course of the disease. Serial renal biopsies may prove to be of some aid in gauging prognosis.

Reports of the incidence of complete recovery from nephrosis differ widely. Antibacterial therapy has greatly reduced the death rate from infection, but seems to have had little effect on the incidence of progressive glomerulonephritis. There is an impression that a higher percentage of children with nephrosis without evidences of loss of renal function are recovering completely than was so before the availability of effective antibacterial agents. The possibility is suggested that control of intercurrent bacterial infections is permitting a large number of children to survive until the nephrosis spontaneously disappears.

The results of therapy with corticotropin or one of the corticosteroids at present appear to be favorable and to justify use of such therapy for a relatively long time. It must be recognized, however, that adequate evaluation of the relative benefits and potential dangers of continued therapy is not possible at this time. There is consensus that short-range therapy directed simply at control of edema has not affected the course of the disease. By contrast, longer-range therapy appears to have reduced the mortality to some extent; whether this merely represents a prolongation of life, and, if so, of what extent, it is not possible to say. Certainly such therapy has enabled many nephrotic children to lead active lives, approaching that of the average child, whereas otherwise their activity would have been greatly restricted. It must be recognized that such therapy is not without risk (see p. 1181).

Unfortunately, adequate data of case fatality rates are not available for comparative purposes; data are currently being collected on a cooperative basis in a number of clinics. Subsequent to the availability of effective

antibacterial agents and prior to the availability of hormonal therapy, recovery rates have been estimated at 30 to 50 per cent. Hormonal therapy apparently has not affected the course of the disease after the appearance of definite evidences of progressive renal failure.

**Treatment.** Treatment aims at prevention and control of acute infections, establishment of good nutrition, readjustment of the disturbed metabolic processes, control of edema, and establishment of good mental hygiene. In view of the chronic and recurrent feature of the disease, which causes great discouragement to both child and parents, time must be spent in acquainting the parents with the nature of the illness and the rationale of the therapy. The child should be kept in bed only during periods of severe edema or when other constitutional symptoms are present. Otherwise the child should be out of bed and active, but should have adequate rest and be reasonably guarded against exposure to infection. Prophylactic administration of sulfadiazine or penicillin in a fashion similar to that in rheumatic fever (see p. 910) is recommended. Acute infections should be treated promptly with appropriate antibacterial therapy. Careful nursing attention is needed to protect the edematous skin from injury and subsequent secondary infection. The flagging appetite should be tempted with attractively prepared food which is easily handled by the disturbed gastrointestinal tract. The diet should be well balanced and contain an adequate amount of protein to compensate for that lost in the urine. When possible, these patients should be treated at home and brought to the hospital only for special therapeutic measures.

Many methods have been used in an attempt to induce diuresis. The administration of corticotropin or one of the corticosteroids has provided the only practical effective means. Attempts to raise serum protein levels by administration of blood plasma have not been very successful. However, plasma, concentrated salt-poor albumin or other plasma substitutes, such as 12 per cent dextran solution, may induce diuresis temporarily. Care should be taken to prevent rapid expansion of plasma volume. Diuretics are most often ineffective in inducing diuresis, and are rarely used now that steroid therapy is available. Death has occurred immediately after intravenous injection of mercury.

Depletion of body sodium by the use of cation exchange resins has not been widely

used in children. Salt-poor diets have been tried in attempts to lower the body's store of sodium, but they are not well accepted by the child, and his nutrition suffers. In the presence of excessive edema it is advisable to reduce the salt intake for short periods. Prolonged dietary salt restriction may lead to hyponatremia, particularly during periods of diarrhea or diuresis.

Hormonal therapy with corticotropin or one of the corticosteroids is now widely used, and there is reasonable consensus that all nephrotic children, except those in renal failure, are entitled to a trial with such therapy. Short-term therapy designed to stimulate diuresis and hence reduction of edema has now been largely supplanted by more prolonged therapy. Corticotropin is infrequently used, since it must be given parenterally; prednisone is perhaps the most widely used of the corticosteroids.

Therapy with a corticosteroid is less effective when started after months of persistent clinical disease and is preferably begun when the disease is first recognized. Steroid therapy should be delayed until any existing infection is brought under control and any serious electrolyte imbalance is corrected. Severe hypertension is a contraindication to corticosteroid therapy and should be controlled before steroids are given. Hematuria, minimal azotemia and minimal hypertension are not contraindications. However, complete clinical and biochemical remissions are less likely in patients with evidences of advanced glomerular damage, and complications of steroid therapy are more frequent.

The dose of cortisone is not sharply defined: amounts ranging from 8 to 11 mg. per kilogram per day (350 to 500 mg. per square meter per day) are used for oral administration in divided doses; prednisone, which has certain advantages, is prescribed in daily doses equal to one fourth to one fifth of those of cortisone. The calculated dose of the steroid is given daily for about four weeks, by which time there are usually clinical remission and disappearance of proteinuria. Diuresis usually occurs within seven to fourteen days, but may be considerably delayed. Albuminuria usually disappears within one to two weeks of continuous treatment, but it may also persist longer. If there is no clinical response after a four-week course of steroid therapy, it may be discontinued for one to two weeks, and then repeated. However, prolonging the initial course of therapy beyond four weeks may result in remission.



If no serious complication arises, steroid therapy may be continued for two months or more. When there is failure to respond to the recommended doses of steroids, increasing the dose is usually not helpful.

After the initial remission various programs of steroid therapy have been used in an attempt to maintain the patient free of symptoms. Some have recommended that steroids be withdrawn until significant proteinuria recurs and then started again. This plan has been largely supplanted by programs of more or less continued therapy. In our clinic "maintenance" therapy is begun immediately after the initial four weeks of continuous therapy, provided remission has occurred. The same daily dose of the steroid is given on the first three days of each week, with none on the remaining four days. This program is continued for six to twelve months. If a recurrence develops during this period of intermittent therapy or after its completion, a full course of continuous therapy for twenty-eight days is again instituted to produce a remission, after which the intermittent therapy is again given.

Significant elevation of the blood pressure is an indication for withdrawal of hormonal therapy if the hypertension cannot be controlled, since severe hypertensive encephalopathy may result. Owing to the increased susceptibility to and the masking of signs of infection during hormonal therapy, prophylactic antibiotic therapy should be given throughout the course of therapy. Occasionally excessive water and salt retention results in severe anasarca necessitating temporary withdrawal of hormonal therapy. The alterations in chemical composition of the body fluids which accompany hormonal therapy necessitate frequent analysis of the plasma electrolytes for guidance of the therapy. The daily administration of 2 to 4 gm. of potassium citrate or chloride daily is indicated as long as there is adequate urinary output. Sodium chloride is not added to the diet in cooking or subsequently. Signs of Cushing's disease usually do not appear during short courses of therapy. Any tendency to "moon facies" disappears after reduction or withdrawal of therapy. Transient glycosuria may occur.

Nitrogen mustard has also been used with some success in inducing remissions similar to those produced by hormonal therapy. Induced or naturally contracted measles may also result in remissions. A similar remission

is occasionally seen in association with other infectious diseases.

In patients with large ascitic collections peritoneal drainage may be necessary to relieve respiratory and cardiac distress or disturbances from pressure on the gastrointestinal tract. Such drainage is rarely required for patients receiving corticosteroid therapy.

When renal failure is advanced, the fluid intake should vary with the urine volume and the capacity for renal concentration. In the face of oliguria excessive fluid intake may lead to pulmonary edema and cardiac failure, and during polyuria restricted fluid intake may lead to dehydration with further impaired renal function. With development of acidosis secondary to tubular deficiency oral alkali therapy may be necessary. Since hypocalcemia may exist, care should be exercised in correcting the acidosis in order not to precipitate active tetany. To decrease the tendency toward potassium intoxication during advanced renal failure, the diet should be low in protein and high in carbohydrate, but care should be taken not to deplete the body stores of protein or potassium. Electrocardiographic tracings are valuable in detecting early evidence of potassium intoxication. Phosphorus retention may be reduced by feeding aluminum hydroxide to decrease intestinal absorption; calcium should be given orally when there is hypocalcemia.

Good pediatric care for the child in his family group is of the greatest importance.

## VASCULAR NEPHRITIS

### (ARTERIOLAR NEPHROSCLEROSIS)

This condition, common in adults, is rare in children, but may occur even in infants. There is arteriolosclerosis of the entire vascular system. The media of small arterioles are at first thickened and then become hyalinized, decreasing the diameter of the lumen. The renal vascular changes are similar to those in chronic pyelonephritis associated with long-standing hypertension. In the latter instance there may also be changes in the arterioles of other organs, but they are minimal. The differential diagnosis between so-called essential arteriolosclerosis and severe hypertension secondary to pyelonephritis may be difficult and, at times, impossible except at autopsy.

Renal impairment and hypertension are regularly present. Death usually results from cardiac failure, cerebral hemorrhage or

uremia. Large volumes of urine with a fixed, low specific gravity are excreted, owing to faulty tubular reabsorption. There is slight to moderate albuminuria. Rarely, massive hematuria occurs, but hemorrhages from other organs, as from the gastrointestinal tract, may occur.

Cerebral symptoms often dominate the picture with headaches, drowsiness and episodes of hypertensive encephalopathy, or signs of cerebral hemorrhage. Retinal changes are common and consist in constriction of the arterioles, hemorrhages, exudation, and choking of the disks. Vomiting and abdominal pain may be prominent features. The course of the disease is usually rapidly downward.

### RENAL FAILURE

#### (UREMIA, LOWER NEPHRON NEPHROSIS AND TUBULAR NECROSIS)

Renal failure as a complication of glomerulonephritis, pyelonephritis, polycystic disease and nephrosis has been discussed under the respective headings of these diseases. It may complicate a variety of other conditions such as generalized infections, ingestion of toxins and poisons, circulatory diseases of the kidney, such as bilateral cortical necrosis, renal vein thrombosis and infarction of the kidney, acute liver disease and a variety of congenital renal anomalies involving both structural and functional systems. Functional disruption may involve the entire nephron or predominate in or be limited to glomerular or tubular dysfunction. The terms "lower nephron nephrosis" and "tubular necrosis" have been ascribed to conditions characterized by evidences of severe tubular dysfunction. The pathologic lesion is not limited to any single portion of the nephron and may involve both glomerulus and tubule and may be found in such conditions as traumatic and postoperative shock, the crush syndrome, sulfonamide intoxication, mismatched blood transfusions, various hemolytic anemias (e.g., blackwater fever of falciparum malaria), heat stroke, thermal burns and many other conditions. Lucké believed that vasoconstriction with decreased renal blood flow (anoxia) is the basis for the renal lesion.

**Clinical Manifestations.** The clinical manifestations vary with the primary disease and with the renal functional derangement. Depression of glomerular function is reflected in nitrogenous and other waste retention, often with an elevation of the plasma phosphorus and potassium levels

and acidosis. The urine usually contains protein and casts; with renal vascular thromboses or infarctions there may be hematuria. Urine flow may be decreased, and edema may result if fluids are excessively administered. With depression of tubular function there may be a loss of renal concentrating capacity with passage of a large amount of urine with a low specific gravity. Loss of acid-base-regulating mechanisms of the tubules may result in passage of an alkaline urine (pH above 6.5) in the presence of acidosis. Renal glycosuria may result from some specific defect in tubular function, and a variety of other defects are described, such as deficiency in bicarbonate reabsorption, excretion of amino acids and other organic acids and deficiency of phosphate reabsorption. In the acute phase of glomerular tubular imbalance a high percentage of the glomerular filtrate may be reabsorbed, leading to severe oliguria. In some instances of acute renal failure with acidosis the symptoms may resemble those of pneumonia. In less advanced cases the presenting and only symptom may be retardation of growth, reflected in both weight and height. Anemia is a common feature, due largely to depression of bone marrow activity, but a hemolytic component has also been demonstrated, and the anemia may require transfusion. Gastrointestinal symptoms may predominate, with vomiting and, less commonly, diarrhea. Dehydration may be severe. In advanced and prolonged cases the serum calcium level may be low and produce tetany. With prolonged derangement of calcium-phosphorus balance, serious bone damage may occur, often referred to as "renal rickets" in the young child and "osteitis fibrosa cystica" in the older child.

The uremic patient is drowsy, complains of headache, and finally becomes comatose. Pericarditis, in contrast to its frequency in the adult patient, is rare in childhood. There is a tendency to hemorrhage, especially in the gastrointestinal tract.

Muscular twitchings are common and may be painful, and there may be convulsions. There is little evidence that retention of creatinine, uric acid, urea and amino acids is responsible for the syndrome of uremia. Other end products of protein metabolism such as guanidine, however, have been thought to play a part in its production. Hyperkalemia may result in severe cardiac dysfunction.

In the "crush syndrome" (lower nephron nephrosis) with severe shock, when there is



extensive leakage of plasma, there is reduction in plasma volume and severe oliguria. Vomiting accentuates the dehydration. The urine contains albumin and casts and a brown sediment of acid hematin granules. Nitrogen retention may be considerable. As the renal symptoms progress, the blood pressure rises. The serum potassium level may be high, associated with electrocardiographic changes. Renal function may be impaired for months; in other instances the salient feature may be rapidly progressing renal failure which may lead to death in uremia. Complete recovery can be expected in the reversible lesions.

Renal insufficiency secondary to tubular blockage by precipitation of sulfonamide crystals is an occasional complication of chemotherapy. In addition to this evident mechanical injury, there have been a number of instances of renal tubular damage resulting in renal insufficiency without evidence of crystalline precipitation. In many ways the renal lesion is similar to that seen in the "crush syndrome." A tendency to sodium and chloride retention has been noted in association with this disturbance. So-called salt-losing states may develop during the recovery phase of lower nephron nephrosis and may dominate the clinical picture.

The so-called transfusion kidney and the renal lesion associated with other forms of hemoglobinuria may produce a similar clinical picture.

**Treatment.** During acute uremia from any cause frequent blood chemical determinations are necessary for guidance in therapy. Water and sufficient sodium chloride must be administered to restore the depleted levels in the body fluids, care being taken not to over-expand the extracellular fluid compartment. Severe acidosis should be treated with sixth-molar sodium lactate. When there is a low blood calcium level, alkali therapy may induce a severe form of tetany by decreasing the ionization of the available calcium. Alkali should therefore be given with caution, and calcium gluconate should also be administered. Bywaters advocates the use of alkali in the treatment and prevention of the renal lesion of the "crush syndrome" in order to forestall precipitation of acid hematin granules.

In the presence of oliguria during renal insufficiency the giving of excessive amounts of fluid is dangerous. The total fluid intake should be limited to an amount equal to the daily urinary output plus the estimated insensible loss (approximately 300 cc. in a

child weighing 10 kg. to 800 cc. in an adult). If vomiting develops, more fluid may be needed. Daily accurate weighing of the child can provide an estimate of fluid needs. A loss of 100 to 200 gm. a day is well tolerated. The administration of glucose decreases tissue breakdown and ketosis. Transfusions of blood and plasma should be used to overcome shock, hemoconcentration and/or severe anemia. Fewer reactions occur in chronic nephritis when fresh blood or fresh packed cells are used. Recovery from anuria of several days' duration is not unusual and is possible even when it persists as long as two weeks. It is important, therefore, that therapy should be conservative. The so-called artificial kidney has been improved technically and in the hands of an experienced person may be a useful adjunct when the patient's clinical and chemical situation deteriorates to a dangerous degree.

When diuresis sets in, during recovery in so-called lower nephron nephrosis, large volumes of dilute urine are passed and electrolytes "washed out"; these must be replaced. In patients with chronic renal insufficiency the sodium, potassium and chloride losses may be great and must be restored by oral feeding. Hyponatremia and hypochloremia are commonly attended by a fall in glomerular filtration rate and oliguria despite a normal fluid intake. Patients who have been greatly depleted may present the manifestations of adrenal insufficiency.

In chronic renal acidosis oral alkali therapy is of value and should be continued as long as the acidosis exists. Aluminum hydroxide is administered orally to reduce phosphate absorption from the intestinal tract in order to retard the development of hypocalcemia, and calcium therapy may be indicated.

#### DISEASES OF THE RENAL TUBULES

The various functions of the renal tubules in regulating the biochemical status of the body (see renal physiology, p. 1005) may be individually altered by acquired or congenital disease and produce a number of distinctive syndromes. The list of such syndromes is steadily increasing with improved knowledge of renal physiology and cellular biochemical mechanisms.

For example, the following diseases, most of which are described elsewhere, are due in part or totally to renal tubular defects: baselosing nephritis (hyperchloremic acidosis, Lightwood syndrome, Albright syndrome),

vitamin D-refractory rickets; Fanconi-de Toni-Debré syndrome; rickets associated with congenital glaucoma (Lowe), cystinosis, cystinuria, glycogen storage disease, Wilson's disease, renal glycosuria, renal diabetes insipidus, lead and other toxic poisoning, including vitamin D intoxication, aldosteronism and chronic potassium deficiency (kaliopenic nephropathy).

In chronic undernutrition in infancy, usually secondary to diarrheal disease, there may be a reduction in glomerular filtration rate, in renal plasma flow and in tubular concentrating capacity. In severe dehydration and acidosis of acute diarrheal disease in infancy, renal tubular concentrating capacity (passage of a dilute urine) may be temporarily lost.

### SUPPURATIVE NEPHRITIS

#### (ABSCESS OF THE KIDNEY)

Although suppurative nephritis occurs most often in adults, it may occur in the newborn period and at any age thereafter.

**Etiology.** The infection may be hematogenous in origin, or it may reach the kidney by contiguity from another suppurating lesion; or it may result from the presence of a calculus, from trauma or from urinary obstruction secondary to a congenital anomaly. Many microorganisms may be causative, but the more common ones are the *Streptococcus*, *Staphylococcus* and colon bacillus. Pathologically, the lesions vary somewhat with the origin. In those of hematogenous origin both kidneys are usually involved, with numerous abscesses of varying size. At times there may be a localized abscess (*renal carbuncle*), the remainder of the renal structure being normal.

**Clinical Manifestations.** The symptoms of suppurative nephritis, when it is a manifestation of another severe infection, are overshadowed by those of the primary infection. Only when these are in the renal region and blood and pus in the urine is the diagnosis possible. In cases of abscess secondary to pyelonephritis the urinary findings are inconclusive. If the abscess is walled off, the urine may be normal.

**Prognosis.** The prognosis is unfavorable in the metastatic cases, and the course is usually short. In other forms the outlook is grave, being best when there is free communication with the urinary tubules to afford drainage. A perinephritic abscess may develop, or the pus may burrow beyond the perinephritic region.

**Treatment.** The treatment for abscess of

the kidney, which is part of a general septicemia, is primarily that of the general infection. Operative removal of an abscessed kidney may be indicated when it is reasonably certain that the other kidney is healthy. Appropriate antibiotic therapy is indicated in all instances.

### TUBERCULOSIS OF THE KIDNEY

Tuberculosis of the kidney is uncommon in early life except as a manifestation of generalized miliary tuberculosis. Pathologically, it is manifest by the presence of small tubercles developing on the surface and in the parenchyma of the kidney. There are rarely any symptoms related to the kidney.

*Localized tuberculous lesions of the kidney* are rare in infants and children. They are usually unilateral. The renal lesion may develop by contiguity from a tuberculous pleuritis or peritonitis or another lesion in the urinary tract, but it usually is hematogenous in origin.

There may be no symptoms, but most often there are general symptoms of fever, emaciation and the like and localized ones as pain, tenderness and enlargement in the renal region. There is frequent and painful urination, the urine being acid and usually containing blood, pus and tubercle bacilli. A persistently sterile pyuria is suggestive of tuberculous infection. The duration of caseous renal tuberculosis depends upon the local lesion and upon the course of tuberculous lesions elsewhere in the body.

Renal tuberculosis may be differentiated from pyelonephritis by the discovery of tubercle bacilli in the urine. Occasionally, urographic studies aid in the diagnosis by showing deformity of the renal pelvis with cystic malformations. Tuberculosis of the bladder can be detected by cystoscopic examination; its presence is presumptive evidence of renal involvement. The function of the individual kidney may be tested by ureteral catheterization. However, the renal function may be good even though the kidney is diseased.

In examining the urine for tubercle bacilli care must be taken to differentiate them from smegma bacilli; culture of the urine on appropriate media and testing for virulence in guinea pigs are required.

**Treatment.** All possible means must be used to sustain the general health. Operative removal is indicated in extensive unilateral lesions, if the other kidney is shown to be functioning normally and is not infected.



Streptomycin and isoniazid should be used with or without para-aminosalicylic acid (p. 464).

## HEMORRHAGIC INFARCTION OF THE KIDNEY

### (THROMBOSIS OF THE RENAL VEIN)

This condition usually occurs in the early weeks of life. It is usually associated with thrombosis of the renal veins, although it may occur in the absence of demonstrable thrombosis. Conversely, thrombosis of the renal vein may occur without hemorrhagic infarction of the kidney.

Thrombosis of the renal veins is rarely primary and is usually secondary to an infectious process in some other part of the body, often an enteritis. The symptoms may be masked by the primary infection, but the sudden appearance of albumin and blood in the urine of an infant with severe dehydration secondary to diarrhea is sufficient reason to consider renal thrombosis in the differential diagnosis of the renal lesion. Oliguria is common, and there may be such additional manifestations as sharp pains in the loin and the sudden development of a large, tender mass in the renal area. In about half the cases the thrombosis is unilateral. Operation is advised when the disease is apparently unilateral as demonstrated by physical examination and direct urologic studies.

Thrombosis of the renal veins may result in the nephrotic syndrome.

MITCHELL I. RUBIN

### REFERENCES

- Addis, T.: *Glomerular Nephritis—Diagnosis and Treatment*. New York, Macmillan Company, 1948.
- Alving, A. S., and Mirsky, A. E.: The Nature of Plasma and Urinary Proteins in Nephrosis. *J. Clin. Investigation*, 15:215, 1936.
- Ash, R., Rubin, M. I., and Rapoport, M.: Electrocardiographic Variations in Acute Glomerulonephritis. *Am. J. Dis. Child.*, 67:106, 1944.
- Bates, R. C., Jennings, R. B., and Earle, D. P.: Acute Nephritis Unrelated to Group A Hemolytic Streptococcus Infection. *Am. J. Med.*, 23:510, 1957.
- Bell, E. T.: Relation of Lipoid Nephrosis to Nephritis. *Ann. Int. Med.*, 6:167, 1932.
- : *Renal Diseases*. Philadelphia, Lea & Febiger, 1946.
- Blumberg, R. W., and Cassady, H. A.: Effect of Measles on the Nephrotic Syndrome. *Am. J. Dis. Child.*, 73:151, 1947.
- Campbell, M. F., and Matthews, W. F.: Renal Thrombosis in Infancy. *J. Pediat.*, 20:604, 1942.
- Conn, J. W., and Johnson, R. D.: Kaliopenic Nephropathy. *Am. J. Clin. Nutrition*, 4:523, 1956.
- Ehrich, W. E., Forman, C., and Seifter, J.: Diffuse Glomerular Nephritis and Lipid Nephrosis; Correlation of Clinical, Morphological and Experimental Observations. *Arch. Path.*, 54:463, 1952.
- Etteldorf, J. N., Smith, J. D., and Johnson, C.: The Effect of Reserpine and Its Combination with Hydralazine on Blood Pressure and Renal Hemodynamics during the Hypertensive Phase of Acute Nephritis in Children. *J. Pediat.*, 48:129, 1956.
- Galán, E., and Maso, C.: Needle Biopsy in Children with Nephrosis. *Pediatrics*, 20:610, 1957.
- Gitlin, D., and Janeway, C. A.: An Immunochemical Study of the Albumin of Serum, Urine, Ascitic Fluid and Edema Fluid in the Nephrotic Syndrome. *J. Clin. Investigation*, 31:223, 1952.
- Goldbloom, R. B., Fraser, F. C., Waugh, D., Aronovitch, M., and Wiglesworth, F. W.: Hereditary Renal Disease Associated with Nerve Deafness and Ocular Lesions. *Pediatrics*, 20:241, 1957.
- Guild, H. G., Kindell, F. B., and Gibson, T. A.: Arteriosclerosis in Childhood, with a Report of Two Cases. *Bull. Johns Hopkins Hosp.*, 62:159, 1938.
- Harrison, H. E., and Harrison, H. C.: Aminoaciduria in Relation to Deficiency Diseases and Kidney Function. *J.A.M.A.*, 164:1571, 1957.
- Illingworth, R. S., Philpott, M. G., and Rendle-Short, J.: A Controlled Investigation of the Effect of Diet on Acute Nephritis. *Arch. Dis. Childhood*, 29:551, 1954.
- McCrory, W. W., and Macauley, D.: Recent Advances in the Management of Renal Disease in Childhood. *Pediatrics*, 19:481, 1957.
- Merrill, J. P.: *The Treatment of Renal Failure*. New York, Grune & Stratton, 1955.
- Metcoff, J., ed.: *The Nephrotic Syndrome*. Proceedings of the 5th Annual Conference, Philadelphia; the 6th Annual Conference, Cleveland; and the 7th Annual Conference, Boston.
- Piel, C. F.: Review—Diseases of Renal Tubules. *Pediatrics*, 20:337, 1957.
- Piel, C. F., Dong, L., Goodman, J. A. and Moore, R.: Electron Microscopy of Experimental Renal Disease. *Am. J. Dis. Child.*, 94:514, 1957.
- Rammelkamp, C. H., Jr., and Weaver, R. S.: Acute Glomerulonephritis. The Significance of the Variations in the Incidence of the Disease? *J. Clin. Investigation*, 32:345, 1953.
- Rubin, M. I., and Rapoport, M.: The Mode of Action of Magnesium Sulphate in Reducing the Hypertension of Acute Glomerulonephritis. *Am. J. M. Sc.*, 201:734, 1941.
- Ryersback, G. C., and Butler, A. M.: Congenital Hereditary Hematuria. *New England J. Med.*, 251:377, 1954.
- Smadel, J. E., and Farr, L. E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum. *J. Exper. Med.*, 65:541, 1937.
- Stetson, C. A., Rammelkamp, C. H., Jr., Krause, R. M., Kohen, R. J., and Perry, W. D.: Epidemic Acute Nephritis: Studies on Etiology, Natural History and Prevention. *Medicine*, 34:431, 1955.
- Trueta, J., and others: *Studies of the Renal Circulation*. Springfield, Ill., Charles C Thomas, 1947.

- Vernier, R. L., Farquhar, M. G., Brunson, J. G., and Good, R. A.: Renal Biopsy in the Study of Chronic Renal Disease in Children by Light and Electron Microscopy. Univ. Minn. M. Bull., 28:1956.
- : Electron Microscopic Pathology of the Various Forms of the Nephrotic Syndrome. Am. J. Dis. Child., 94:514, 1957.
- Zuelzer, W. M., Seymour, C., Kurnetz, R., Newton, W. A., Jr., and Fallon, R.: Circulatory Diseases of the Kidneys in Infancy and Childhood. Am. J. Dis. Child., 81:1, 1951.

## RENAL CALCULUS

**Etiology.** Uric acid infarction of the kidney in the newborn infant was mentioned on page 1010. Renal calculi may occur in infants and children of all ages. Calculi are found more frequently in some geographic regions than in others, and an inherited tendency has been observed. Suppuration of bone, prolonged recumbent posture, and infection of the urinary tract may be contributing factors. Precipitation of the acetyl forms of sulfonamides in the kidney may produce obstruction. Urinary calculi are common in parathyroid disease, in cystinuria and in renal tubular insufficiency with associated acidosis and an alkaline urine. A condition described as *oxalosis* is associated with widespread deposits in the tissues of calcium oxalate crystals.

**Pathology.** The calculi consist most often of uric acid or its salts, although they are occasionally made up of oxalates, phosphates, carbonates, cystine or xanthine. Of over 500 calculi removed from children, 58 per cent were composed of uric acid or urates and 33 per cent of phosphate of lime. The stones vary in number and in size from that of gravel to calculi which fill the entire pelvis of the kidney. In about 20 per cent of cases both kidneys are involved. There may be inflammation of the tissue surrounding stones in the renal parenchyma and in the urinary tract.

**Clinical Manifestations.** Characteristic symptoms are tenderness in the renal region, pyuria, hematuria, attacks of renal colic with pain radiating to the lower part of the abdomen, the testicle, penis and thigh, and a frequent desire to urinate. Vomiting may occur with the renal colic, and there may be convulsions and collapse. The attack lasts for a few hours or sometimes, with remissions, for several days. The calculus may return to

the pelvis of the kidney, or advance and be passed into the bladder and later voided as a single stone or as gravel. The description given applies to typical cases; in infancy, symptoms may be absent or indefinite, and the pain of renal colic may be misinterpreted as intestinal in origin. In other instances there is hematuria without colic, particularly when the calculi are in the substance of the kidney. Infection of the urinary tract is often present and may dominate the clinical picture. Roentgenograms and pyelograms are of value, except in the case of uric acid stones, which do not cast a shadow. The appearance of uric acid crystals in the urine does not necessarily mean that they have been passed from the kidney, since they may have been precipitated after the urine was voided.

**Prognosis.** The prognosis is usually good in children when there is no systemic disease (see p. 1223). There is a tendency for new calculi to form. If the stone is impacted, pyonephritis or hydronephrosis may develop. In long-standing cases renal function may be permanently impaired.

**Treatment.** During attacks of colic, morphine and atropine can be administered. Ureteral catheterization may be necessary to dislodge an impacted stone. Persistent renal stones should be removed surgically. After an attack any infection of the urinary tract should be treated, and an attempt made to discover whether other stones are present. To aid in preventing recurrence, water should be taken freely. If the stone passed is composed of uric acid, it may be advisable to keep the reaction of the urine alkaline and to avoid excessive ingestion of meat. In the case of phosphatic calculi the urine should not be alkalized. When calculi result from tubular dysfunction with loss of base producing an acidosis, alkali therapy may be helpful (see p. 1223). Such foods as rhubarb, eggplant, spinach and asparagus increase the urinary excretion of oxalates.

MITCHELL I. RUBIN

## REFERENCES

- Albright, F., Sulkovitch, H. W., and Chute, R.: Non-surgical Aspects of the Kidney Stone Problem. J.A.M.A., 113:2049, 1939.
- Anderson, W. A. D.: Renal Calcification in Infancy and Childhood. J. Pediat., 14:375, 1939.
- Campbell, M. F.: Clinical Pediatric Urology. Philadelphia, W. B. Saunders Company, 1951.



# DISTURBANCES OF THE URINARY BLADDER

For Exstrophy of the Bladder, see page 1024.

## VESICAL CALCULUS

About two thirds of urinary calculi are found in the bladder. Vesical calculi during childhood are most common from the age of two to seven years, and occur oftener in boys, inasmuch as the short, wide female urethra permits stones to be passed while they are still small. The calculus is usually formed in the kidney, but increases in size in the bladder. Occasionally a foreign body introduced into the bladder forms the nucleus for a stone.

The *symptoms* are vesical irritability, enuresis and often attacks of pain, especially at the close of micturition, which is felt in the neck of the bladder or at the end of the penis, or in the vagina, rectum or perineum. Tenesmus is frequent both on urination and defecation, and may produce prolapse of the rectum. There may be a sudden arrest of micturition, accompanied by severe pain and straining. Pain may be relieved by having the child void while lying down if the stone is not lodged in the urethra. Priapism is common, and incontinence may occur. If cystitis develops, the symptoms are accentuated, and the urine contains mucus, pus and red blood cells. The only positive *diagnosis* is by cystoscopic or roentgenographic examination. The *prognosis* depends upon the size of the stone and upon treatment. *Medical treatment* is similar to that for renal calculi. Large stones must be removed surgically, smaller stones by crushing.

## FOREIGN BODIES IN THE BLADDER

Occasionally boys and girls, especially at the age of puberty, introduce foreign bodies into the urethra, and these may pass into the bladder. The nature of the bodies is varied, among them being hairpins, pencils, shot, beads, and the like. They may give rise to inflammation or form the basis of a calculus. Irritation of the bladder may also result from a foreign body which has been inserted and withdrawn. *Treatment* usually consists in removal through the operating cystoscope, or surgical removal if necessary.

## CYSTITIS

Cystitis as an isolated infection is uncommon; it is usually secondary to a pyelonephritis or

an obstruction at the neck of the bladder or in the urethra (p. 1026). Other causes include vesical calculi, foreign bodies, tumors, rupture of an abscess into the bladder or extension of a gonococcal infection. Actually the bladder is relatively resistant to infection; if an associated infection is controlled or an obstructing or irritating lesion removed, the cystitis tends to disappear spontaneously except when there are extensive changes in the vesical wall in long-standing infections. A rare form is *cystitis emphysematosa*, in which there are gas-containing vesicles in the wall of the bladder.

The constitutional *symptoms* include fever, restlessness and anorexia. The local disturbance varies in intensity, being greater in older children, in whom there is pain and tenderness in the region of the bladder and painful and frequent urination. The straining may produce prolapse of the rectum, and there may be constant dribbling of urine. In infants the painful urination may be evidenced only by crying. The urine is cloudy and contains white and red blood cells, mucus, vesical epithelium, bacteria and albumin. The *diagnosis* is established by cystoscopic examination. An acute, apparently infectious, *hemorrhagic cystitis* is occasionally seen in infants and children as well as in adults. Low grade fever, urinary frequency and dysuria are common manifestations. Bacteria are not usually isolated from the urine, and the possibility of a viral etiology has been considered. Gross bleeding may last for several days, and acute glomerulonephritis must be differentiated. The lesion tends to be self-limited.

*Treatment.* The only effective treatment for the secondary infections is removal of the cause. In acute cases bed rest is required, and the child should be encouraged to drink large amounts of water. Bacterial infections should be treated with a sulfonamide or an appropriate antibiotic in full therapeutic doses. Pain and straining may be relieved by hot or cold applications over the bladder or by administration of opiates or other analgesics. In severe and obstinate cases, lavage may be indicated.

## TUBERCULOSIS OF THE BLADDER

This infection, infrequent during childhood, may exist with tuberculosis of other parts of

the genitourinary system, especially the kidney, or it may be the only tuberculous lesion in the urinary tract. The lesion may consist of scattered, grayish, caseous nodules, or of ulcers in the mucous membrane. The *clinical manifestations* are those of chronic cystitis with hematuria. The *diagnosis* can be made by the discovery of tubercle bacilli in the urine and by cystoscopic examination.

### SPASM OF THE BLADDER

This symptom is more frequent in early childhood than later. Among causes are sudden chilling of the body, vesical calculus and secretion of highly concentrated urine. It may also be a reflex symptom of renal calculus or disorders of the rectum, vulva, urethra, hip

joint, appendix or other neighboring structures. There may be a spasm of the sphincter, and the child is unable to void; more commonly there is irritation of the detrusor apparatus, resulting in frequent emptying of the bladder. In the former instance there is pain and straining without passage of urine. In the latter the urine is passed frequently, sometimes only in drops, and there may or may not be pain.

*Treatment* consists in elimination of the cause if possible. When the urine is highly acid, alkalis may be given, water should be ingested freely, and atropine with or without a sedative may be administered. During spasm of the sphincter hot compresses may be applied over the bladder, or the child may be placed in a warm bath. Catheterization is rarely required.

## MALFORMATIONS AND DISEASES OF THE MALE AND FEMALE GENITAL ORGANS

### ADHERENT PREPUCE

In the majority of newborn male infants there is some adherence between the inner lining of the prepuce and the glans. When this persists after the first months of life, it may be considered pathologic. The adhesions may be complete or involve only the posterior part of the glans. The smegma collects behind the corona and may cause irritation, leading to a balanitis. At three to four months of age the adherent prepuce of the noncircumcised infant should be gently retracted, breaking the adhesions, if necessary, with a blunt probe. The glans is then cleansed, a bland ointment applied, and the foreskin returned over the glans. After this the prepuce may be retracted during the bath so that the sulcus behind the corona can be cleansed.

### PHIMOSIS

Phimosis is a narrowing of the preputial opening such that retraction of the prepuce is impossible. Rarely there is no opening whatsoever. The prepuce may be of normal length or much elongated and hypertrophied (*redundant prepuce*); the latter is not necessarily accompanied by phimosis. When the opening of the prepuce is small, urination can be accomplished only by straining; the urine is voided in drops or a small stream.

If adhesions are not present, the foreskin during micturition is ballooned by the urine beneath it. Hernia or prolapse of the rectum may be produced by the straining, and there may be infection of the urinary tract. Concretions may form under the prepuce.

*Treatment* by forcible retraction or stretching with dressing forceps is often sufficient, or the preputial orifice may be widened by incision; in severe forms circumcision is indicated. A redundant prepuce without phimosis does not necessitate circumcision.

### PARAPHIMOSIS AND STRANGULATION OF THE PENIS

In this condition the prepuce which has been retracted beyond the corona cannot readily be replaced. The circulation in the glans is interrupted by the constriction; edema, bluish discoloration and even gangrene may develop. Pain and dysuria are usually severe. The accident usually follows retraction of the prepuce by the patient himself or by the mother or nurse when cleansing the penis. Cold compresses should be applied to reduce the swelling, and an effort made to draw the foreskin forward into the normal position. To aid in this the glans should be well oiled and steadily compressed, and the forward pull should be as evenly placed around the constricting prepuce as possible. If this pro-



cedure does not succeed, incision of the constricting ring of skin at the rear of the swelling may be required. If the foreskin is unduly narrow, circumcision should be performed after the inflammation has subsided.

A condition similar to that of paraphimosis may be produced if the patient ties a string around the penis or slips a ring or other object over it. Treatment consists in division of the constricting body and application of cold compresses.

### ABNORMAL SIZE OF THE PENIS

The size of the penis varies greatly. At times in the prepuberty period the penis appears to be unusually small, owing to a large deposit of fat in the mons and scrotum, which partially buries it from view. In rare instances it may remain a rudimentary structure, and on occasion surgical intervention may be necessary, owing to obstruction of urinary flow. The penis may become greatly hypertrophied in certain cases of physical precocity (p. 1157). Congenital absence of the penis is rare, and rarely it is displaced from its normal position. The penis may be duplicated, usually in association with duplication of the bladder. Torsion of the penis may be associated with hypospadias.

### BALANOPOSTHITIS

Inflammation of the prepuce (*posthitis*) and glans (*balanitis*) is most often produced by phimosis, resulting in retention of smegma. It may follow injury by masturbation or other means, or it may occur as a complication of urethritis. Diphtheritic balanoposthitis is rare. The prepuce becomes red and edematous, and itches; the orifice is narrowed, and there is a purulent secretion from the inflamed mucous membrane. There is dysuria and cystitis; hydronephrosis may be a complication in severe cases. In ordinary cases the inflammation lasts but a few days. *Treatment* consists in administration of an appropriate antibiotic. Cold compresses should be applied to reduce the swelling. In extreme instances splitting the foreskin or circumcision is necessary in spite of the infection present.

### MALFORMATIONS OF THE URETHRA

#### HYOSPADIAS

In this congenital malformation the urethra does not extend the entire length of the

penis, but opens on its lower surface just behind the glans, in the body of the organ or, in extreme cases, in the perineum, or at times as a fissure, the scrotum being split in half. There is usually some degree of congenital chordee. Since the penis is usually rudimentary in the severe cases, and the testes undescended, the appearance of the external genitals simulates that of the female (*pseudohermaphrodisim*). Only the severe forms interfere with procreation. *Treatment* is surgical, and in many cases a plastic operation is successful. In the mild cases no treatment is necessary. One should be certain that the opening is sufficiently large to permit free urinary flow.

Rarely an analogous condition is seen in girls, the opening of the urethra being within the vagina beneath the hymen.

#### EPISPADIAS

In this uncommon congenital anomaly the opening of the urethra is upon the dorsal surface of the penis. It may be small and situated just behind the glans; in the more extreme varieties it may take the form of a fissure extending the entire length of the penis in combination with exstrophy of the bladder. Treatment is surgical.

#### OTHER ANOMALIES

Congenital atresia of the urethra may vary from mere closure of the meatus by adhesions to complete obliteration. A patulous urachus or exstrophy of the bladder may accompany the latter. There may be a congenitally narrow urethra, perhaps only at the meatus, or a cylindrical narrowing of some part of the canal. Congenital stricture of the meatus in the female is an occasional anomaly. Acquired stricture may be the result of gonorrheal urethritis or rarely of cicatricial contraction from other causes. Urethral diverticulum or a valvelike obstruction of the posterior urethra is not uncommon. The end results of urethral obstruction of any sort, if continued, are dilatation of the bladder and ureters and hydronephrosis. Fusion of the urethra and intestine may occur. Urethral fistula is rare, and may be congenital or due to injury by a calculus or foreign body in the urethra, or to trauma. The external opening of the fistula may be in the penis, in the perineum or elsewhere. Double urethra and persistent cloaca have been described.

## INFLAMMATION OF THE EXTERNAL

### URETHRAL ORIFICE

This lesion, often a manifestation of amoniacal dermatitis, is apparently confined to circumcised infants. It causes dysuria and a tendency to retention of urine. Superficial ulceration of the orifice may be produced. A thick layer of bland ointment should be applied locally, and the diaper should not be tight-fitting (see p. 1298).

### URETHRITIS

Urethritis is not common in early life. It may be due to extension of inflammation from balanoposthitis, to irritation by highly acid urine, to introduction of foreign bodies into the urethra or to other onanistic acts. Urethritis due to the *Gonococcus* is seen oftener in females, in whom it is secondary to gonorrheal vaginitis, but by no means a common complication. The *symptoms* are dysuria, swelling and redness of the urethral orifice, and discharge of pus from it. In the non-gonorrheal lesion the course is usually short; in the untreated gonorrheal infection it is longer, and balanitis, proctitis, epididymitis, arthritis, conjunctivitis and prostatic abscess are possible complications. Stricture may be a sequel. An etiologic *diagnosis* should be established by bacteriologic culture. *Treatment* consists in keeping the parts clean and in administration of an appropriate antibiotic. A protective dressing should be worn to prevent extension of the infection and the carrying of it to the eyes.

### FOREIGN BODIES IN THE URETHRA, INCLUDING URETHRAL CALCULUS

A stone, after its passage from the kidney and bladder, may become impacted in the urethra, most often in the membranous part of the penis. Foreign bodies may be introduced into the urethra during later childhood and become impacted there. The *symptoms* depend somewhat upon the size and kind of stone or foreign body. There is dysuria and obstruction to the flow of urine. Urethritis may develop, at times with periurethritis and infiltration of urine into surrounding tissues; the flow of urine may then be completely obstructed. The detrusor force of the bladder may finally succeed in expelling smooth calculi and foreign bodies, but frequently surgical intervention is necessary.

## INFLAMMATION OF THE SCROTUM

The most common cause of scrotal inflammation in infants is uncleanness, but the scrotum may also be the site of eczema, erysipelas and secondarily infected scabies, or it may be involved by contiguity from inflammatory lesions of neighboring structures. The skin is intensely red, and the tissues, owing to their laxness, are often considerably swollen. *Treatment* consists chiefly in cleanliness and in keeping the scrotum dry with mildly antiseptic powders and in leaving the parts exposed to the air. In severe inflammation antibiotic therapy may be indicated. Eczema, erysipelas and scabies require special treatment, which is described under the respective headings of these diseases. Surgical intervention is necessary if there is abscess formation.

### GENITAL EDEMA OF THE NEWBORN INFANT

The cause of this unusual condition is not understood. The condition may possibly be due to the action of an estrogenic substance transmitted in utero by the mother. It occurs especially in premature infants, and consists in noninflammatory edema of the entire genital region, at times extending over the abdomen and thighs, and appearing at any time in the first month or two of life. It usually disappears within a few days, but may last a month or more. The disorder is differentiated from sclerema by its localization and the good general condition; from erysipelas by the lack of local and general evidences of infection. No particular treatment is indicated.

### UNDESCENDED TESTES

#### (CRYPTORCHISM)

The testes should descend into the scrotum in the eighth month of fetal life, but arrest in the descent of one or both testes takes place in about 0.1 to 0.7 per cent of male infants, and one or both organs may remain in the abdomen or, more frequently, in the inguinal canal. Careful examination is necessary before a diagnosis of cryptorchism is made since the testes are frequently out of the scrotal sac in children under normal circumstances. Infrequently they may be situated in some abnormal position, most often in the perineum. A testis retained in the inguinal canal may



descend into the scrotum in the course of weeks or months or at any time up to puberty. When in the inguinal canal, the testis is a small, movable body and may be mistaken for a hernia, by which it is accompanied in half or more of the cases. There may also be an associated hydrocele or torsion of the spermatic cord. A testis remaining persistently out of place finally becomes atrophic and does not produce sperm, but the interstitial cells are usually not affected. In persistent bilateral cryptorchism the adult will probably be sterile, but the development of masculine characteristics is usually normal. Psychologic disturbances may occur in late childhood.

*Treatment* is not required in infancy, since the testes may descend spontaneously. There is lack of unanimity about a plan of therapy. Some recommend early treatment despite the fact that in about two thirds of instances testes undescended at birth will descend spontaneously by the completion of puberty. Early treatment is designed to prevent "unjustifiable" hazards and the possibility of aspermatogenesis of the involved testis. Wilkins does not believe that available evidence justifies this assumption. When there is a demonstrable hernia, the testis can be anchored in the scrotum when the hernia is repaired. In bilateral cryptorchism Campbell recommends trial with hormonal therapy for two or three weeks by about three or four years of age; if treatment is not successful in bringing the testes into the scrotum and/or if they do not remain there, surgical correction is then carried out. In unilateral cryptorchism he feels there is less urgency for treatment even though there is the possibility of atrophy in the undescended testis. Others recommend that therapy be deferred until the prepuberty age, ten to twelve years. If hormonal therapy is to be tried, an accepted dose of gonadotropin (Antuitrin-S) is 500 to 1000 units three times a week for four or five weeks. Larger doses administered over a longer period are not likely to be more beneficial and may be harmful. It is likely that favorable results are obtained only when descent would have occurred spontaneously at puberty. Testosterone has been used, but is no more effective than gonadotropin and has greater potentiality for harm. Failure of response to hormonal therapy is indicative of mechanical interference or testicular absence. In all cases of mechanical interference orchidopexy should be performed.

## POLYORCHISM AND ANORCHISM

Polyorchism, more than the normal number of testes, and anorchism, absence of the testes, are extremely rare anomalies.

## ORCHITIS AND EPIDIDYMITIS

Acute orchitis occasionally occurs in boys as the result of trauma, rheumatism or infectious fevers, especially mumps. Mumps orchitis (p. 505), however, is rare in comparison with its incidence in adults. Gonorrhea is more liable to produce epididymitis than orchitis. Epididymitis may also be caused by the Staphylococcus, Streptococcus, colon bacillus and other organisms. The *prognosis* of both orchitis and epididymitis is generally favorable unless suppuration occurs, when atrophy and subsequent sterility of the involved side may result. The testes should be elevated, cold wet dressings applied, and an antibiotic administered. Syphilitic orchitis runs a more chronic course, is painless, and does not suppurate.

## TORSION OF THE SPERMATIC CORD

Torsion of the spermatic cord is more common in incompletely descended testes than in those residing in the scrotal sac. Sloughing, infection and subsequent atrophy may occur. Torsion must be differentiated from epididymo-orchitis, strangulated hernia and inguinal adenitis.

## HYDROCELE (See page 691)

## TUBERCULOSIS OF THE MALE GENITAL ORGANS

Primary tuberculosis of the penis has been acquired from the older form of ritualistic circumcision. This is extremely rare in modern practice. Tuberculosis of the testis is rare in infants and children. It is usually unilateral; trauma may be a predisposing factor. The testis and the epididymis become enlarged and hard, and the scrotum is discolored. The process may undergo absorption, but, especially in infants, is more likely to become caseous and liquefy. The course is protracted, the *prognosis* being dependent on both the local lesion and whether the tuberculous process has extended to other parts of the body. A locally infected testis may be removed, provided the other testis is pre-

sumed to be uninvolved and the general condition warrants the surgical procedure. Treatment with streptomycin and isoniazid should be instituted before and for several months after the surgical removal (p. 464). When surgery is not feasible, drug therapy may be tried.

## MALFORMATIONS OF THE VULVA, VAGINA AND CLITORIS

Atresia of the vulva is rare, but epithelial adhesions of the greater or lesser labia are common. Even though the adhesions are not completely obstructive, they may cause retention of mucous secretions, and later of the menstrual discharge; and, if complete, they also interfere with urination. Retention of menstrual discharge is also produced by an imperforate hymen. There may be partial or complete absence of the vagina. It may be divided into two compartments by a membranous partition, or there may be two complete vaginas. Malformations of the vulva and vagina are often associated with those of the rectum, anus and bladder, and communication may exist between the vagina and the rectum or bladder.

There is frequently adherence between the labia and the clitoris, sometimes causing irritation from retained smegma, which may be responsible for the instigation of masturbation. Congenital fissure of the clitoris is rare and may occur in combination with a fissure of the urethra.

Adhesions between the labia or between the labia and the clitoris may be broken with a probe; an imperforate hymen should be ruptured.

## VULVOVAGINITIS

Vulvovaginitis is a relatively common infection which may be divided into two categories: nongonorrheal and gonorrheal.

### NONGONORRHEAL VULVOVAGINITIS

**Etiology.** Infections of the vagina may occur at any age and be caused by practically any pathogenic organism. Herpetic lesions may occur, and rarely diphtheria is localized in the vagina. *Trichomonas* vaginitis occurs infrequently before puberty; vaginal thrush is seen on occasion in weak and sickly infants. The vesicles of varicella may appear upon the mucous membrane of the vagina, and in measles a catarrhal inflammation may de-

velop. During various acute infections, including upper respiratory ones, there is evidence of vulvovaginal inflammation which tends to subside with recovery from the systemic infection. In undernourished or debilitated girls or when hygiene is poor, the genital infection may be persistent.

Predisposing factors include tight undergarments, uncleanness, traumatism, masturbation, eczema, threadworms and various foreign bodies in the vaginal canal.

**Clinical Manifestations.** The symptoms of vaginitis are redness and swelling of the genitals. There is a vaginal discharge which is scanty or abundant, thin or purulent and often offensive in odor.

**Differential Diagnosis.** Differentiation from gonorrheal vaginitis depends upon bacteriologic studies. In vaginitis dependent on the *Trichomonas* there is a foamy leukorrhea, and the active flagellate parasites can be found in vaginal smears. *In all instances of persistent vaginal discharge the possibility of a foreign body must be investigated by direct inspection through a speculum and/or roentgenographically.*

**Prognosis.** If the cause can be removed, the prognosis is good, but in debilitated children the discharge may continue for a long time in spite of treatment.

**Treatment.** Treatment is directed primarily at removal or correction of the predisposing or underlying factor and at improvement in the general health. Cleanliness of the genital region is of the greatest importance. In thrush vaginitis a 1 per cent aqueous solution of gentian violet may be used locally, or Mycostatin can be used locally and systemically. In *Trichomonas* infection lactic acid (0.5 per cent) douches are used, or acetarsone in powder form may be insufflated into the vagina. In bacterial infections appropriate antibiotic therapy is indicated.

### CONORRHEAL VULVOVAGINITIS

This condition, once comparatively common in the first five years of life, is now relatively uncommon.

**Etiology.** In infants the disease may be acquired during the process of birth, or later from a mother with a gonorrheal discharge; or it may be spread in other ways, as by the hands or garments of the attendant or by infected bath tubs, diapers, bedclothing, washcloths or thermometers. Contraction of the disease by any sort of sexual act is uncommon in children.

**Clinical Manifestations.** In mild cases



there may be only a small amount of thin discharge, but in more severe ones there is an abundant, yellow, purulent discharge. The mucous membranes of the vulva and vagina are inflamed, and there may be involvement of the urethra and of the rectum. Ordinarily there is little or no discomfort, but in severe cases there may be fever, dysuria, and excoriation of the skin of the vulva and thighs.

**Diagnosis.** All leukorrheal discharges, particularly in infancy and early childhood, should be considered gonorrheal until proved otherwise. Material for examination should be secured from the vagina itself or the cervix of the uterus, using a speculum or a small vaginoscope. Another procedure is to irrigate the vagina with a small amount of physiologic saline solution and then examine the sediment obtained by centrifugation. The bacteriologic examination should include a *culture* as well as a direct smear.

**Complications.** Serious complications are much less frequent than in adult life and occur chiefly in later childhood. The more common complications are inguinal adenitis, urethritis and proctitis; much less common are cystitis, pyelonephritis, endometritis, salpingitis, peritonitis, arthritis, septicemia and ophthalmia. A careful inspection of the vagina should be made in every case of suspected peritonitis in girls.

**Prognosis.** Although seldom serious, without effective treatment the infection is often prolonged and is a source of great anxiety. It tends to clear up spontaneously, but usually not before puberty. It apparently does not cause sterility and rarely leaves other residuals. Therapy with penicillin is highly effective, and cure can be expected in most instances within a few days.

**Prophylactic Measures.** It is good practice to inspect the vagina during all physical examinations; if there is evidence of inflammation, a bacteriologic examination should be made. It should be remembered that urethritis in the male or proctitis in either sex may be gonorrheal in origin.

Hospitals should provide individual thermometers, bedpans and other toilet articles for all children. A single-service diaper made of cotton, absorbent gauze, or paper, which can be destroyed afterwards, may be used instead of the ordinary textile one; or the latter, if used, may be disinfected before being sent to the general laundry. A U-shaped toilet seat should be provided for older infants and children, and individual paper pro-

tectors used. Spray baths are preferable to tub baths.

A patient with vaginitis or other gonorrheal discharge must be completely isolated from other children, since even the greatest precautions will not always prevent spread of the disease within a hospital ward or other unit of a hospital.

When a case develops in an institution other than a hospital, the same principles should be followed. School authorities should be familiar with the disease and its implications. All children with known gonorrheal vaginitis should be excluded from school until cure is effected.

**Treatment.** Scrupulous local cleanliness should be observed, but douching is not indicated. Sulfonamides are effective in most instances, but penicillin would appear to be the drug of choice. Daily doses of 300,000 units should be continued for four or five days. A bacteriologic examination should be obtained two weeks after completion of therapy. There is little or no place for estrogenic therapy.

## ABSCESS OF THE VULVA

Abscesses are usually secondary to trauma, erysipelas, or extension of inflammation from a vaginitis. The external labium on one or both sides becomes red, tender and swollen, and suppuration usually occurs. The general constitutional symptoms of infection are present. *Treatment* consists in application of hot compresses, and in incision when necessary. Sulfonamide and antibiotic therapy is of distinct value.

## GANGRENOUS VULVITIS

Gangrenous vulvitis is analogous to noma of the mouth. It occurs in malnourished children, especially after such infectious diseases as measles or erysipelas, or it may follow herpetic vulvitis. Spirochetes and fusiform bacilli may sometimes be found. A swollen, tense, dark red area which proceeds to gangrene appears on one of the external labia. In severe cases the process spreads with great rapidity. There is pain, fever and great prostration, often followed by death. In mild cases the process is limited to a small area which heals with cicatricial deformity. *Treatment* in the past consisted in supportive measures and prompt excision followed by cauterization. It seems probable, however, that antibiotic therapy may decrease the need for such radical measures.

## GENITAL HEMORRHAGE; PRECOCIOUS MENSTRUATION

Discharge of blood from the vagina other than during menstruation may result from inflammation, injury, foreign bodies, neoplasms, or asphyxia at birth, or may be a manifestation of a hemorrhagic disease. It may occur in the newborn as a result of the influence of maternal hormones. The blood may arise from the vulva, vagina or uterus. Precocious menstruation, in which the flow takes place at more or less regular intervals, is often accompanied by other evidences of sexual and somatic precocity (p. 1157). *Treatment* of genital hemorrhage itself is seldom needed, although the underlying cause may demand appropriate therapy.

## DISEASES OF THE UTERUS AND FALLOPIAN TUBES

The uterus may be absent, rudimentary, doubled or divided in varying degrees. One or both fallopian tubes may be absent or rudimentary. Rarely there is extension to the uterus and tubes from a gonorrheal vaginitis. In cases of imperforate hymen the vagina and uterus may become dilated by mucous or watery secretion, and after puberty a hematocolpos or hematometra may develop. Uterine prolapse is often combined with spina bifida.

Complete prolapse has been reported in the newborn. Both malignant and benign tumors are rare, but have been recorded.

## DISEASES OF THE OVARIES

One or both ovaries may be absent, or there may be accessory ovaries. *Ovarian hernia* is not rare. It may be congenital or acquired, and the ovary on one or both sides may be found in the inguinal canal, less often beneath the femoral ring, and occasionally elsewhere. In inguinal prolapse the pedicle of the ovary may become twisted and the organ strangulated. Appendicitis may be simulated.

*Tuberculosis* of the female reproductive system is uncommon, and is generally secondary to tuberculous peritonitis or enteritis, or is part of a generalized miliary infection. The internal genital organs are more frequently involved than the external ones.

*Neoplasms* are described on pages 1201 and 1358.

MITCHELL I. RUBIN

## REFERENCES

- Campbell, M. F.: *Clinical Pediatric Urology*. Philadelphia, W. B. Saunders Company, 1951.
- Gross, R. E.: *The Surgery of Infancy and Childhood*. Philadelphia, W. B. Saunders Company, 1953.
- Young, H. H.: *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*. Baltimore, Williams & Wilkins Company, 1937.



# The Nervous System

## DIAGNOSTIC STUDY OF NEUROLOGIC DISEASE\*

### HISTORY AND PHYSICAL EXAMINATION

The physical examination in neurologic disease localizes the disease process; the history suggests its nature. No other procedures can replace these two; carelessness, indifference or inadequacy in performing them ends in neglect of serious illness or in performance of unnecessary, painful or dangerous special procedures.

**History** (see also p. 161). As the history is taken one has opportunity to establish the beginning of a friendly relationship with the child and to observe his spontaneous behavior and activity, which suggest many of his physical signs.

Many neurologic ailments of childhood are present at birth or acquired soon after, so that, when such origins are possibilities, the family history and the details of pregnancy and labor must, if possible, be more detailed than with illnesses more clearly of recent onset. Repeated review of the history often brings out valuable information. The following outline may be expanded or reduced as circumstances indicate.

**Family history.** For parents, grandparents, aunts, uncles and cousins: present health or cause of death; symptoms similar to patient's; common neurologic symptoms, such as convulsions, visual or motor failure, disturbance of gait.

For the immediate sibship: date, parentage and outcome of each pregnancy; causes of any deaths; present state of survivors; presence of symptoms similar to patient's.

**Pregnancy.** Difficulties in conception; duration as exactly as possible; onset and quality of fetal movements; date, duration, severity, treatment and effect if noted on fetal movement and heart rate, of maternal toxemias, illness or infections, injuries, radiation,

exposure to drugs or toxins, vaginal bleeding and severe emotional stress.

**Labor.** Hour of onset and delivery (total duration); presentation; anesthesia and analgesia; operative procedures, indication for, if known; evidence of fetal distress.

**Neonatal period.** Birth weight; initial breathing and crying; cyanosis, asphyxia pallida or livida; resuscitative procedures, use of oxygen or incubator; signs of trauma; jaundice; duration and treatment of convulsions; infection; notable listlessness, vomiting, "jitteriness," stiffness or limpness.

**Growth and development.** Serial weights and heights, if available; age at puberty; age at such developmental acquisitions as social smile, sitting alone, standing, walking and the like; school progress, if any. Compare with siblings.

**Past health.** Date and severity of each significant illness, injury or operation, with special note of high fevers, delirium, head trauma, convulsions, disturbances of gait, vision or hearing, and changes of personality.

**Present illness.** List the symptoms with record of time of onset and further progression; try to document the way each came to attention. Summarize onset and principal features of each salient event of the illness chronologically.

**Technique of Physical Examination.** No rigid scheme of examination is necessary if the examiner remembers a few principles. No neurologic examination is complete without a general physical examination. A regular method of recording findings is essential for completeness and clarity. The physiologic and emotional condition of the child may affect his signs; fright, cold or embarrassment heightens reflexes and impairs fine motor performance; warmth, a full stomach, and sedatives diminish reflexes and alertness. At some time all clothing must be removed from the child; "much more is missed from not look-

\* See also page 295.

ing than from not knowing." History and physical examination generally provide a reasonable differential neurologic diagnosis. Conclusions made before these two are completed are usually erroneous. The neurologic examination includes (1) vital signs, (2) mental status, (3) gait, station and handedness, (4) cranial nerves and special senses, (5) motor system and reflexes, (6) sensory system, (7) coordinative system, (8) autonomic system, (9) special findings.

The *vital signs* require no special comment. An estimate of the *mental status* in infants is based on alertness, response to examiners and quality of cry; in older children, from the playing of simple games, inquiries about siblings, pets, illness and the like, and by formal evaluation of the intelligence. *Gait, station and handedness* are determined by simple observations.

The *special senses* should be examined early, before fatigue impairs cooperation.

**Vision.** In the infant, or child with very low vision, the ability to follow a light or to avoid threatening movements is noted. If there is real doubt as to the presence of vision, demonstration of optokinetic nystagmus is useful. A cylinder marked with alternating wide black and white stripes is rotated slowly before the child; if cortical vision is present, the eyes follow the stripes slowly, then jerk quickly back to midposition; this response appears normally within the first few weeks of life. Older children are tested with charts, or by having them pick up coins or bits of paper scattered on floor or table top; the latter procedure tests both fields and acuity.

To test *visual fields*, the child and examiner stand about 3 feet apart and cover opposite eyes, and each fixes on the other's uncovered eye. The examiner brings his finger, or other test object, inward along radii of a circle, the center of which is on the axis of fixation, midway between examiner and child. The child states when he sees the object, the examiner's visual field serving as a check. The test object should be carried inward to the center, to detect central defects. With infants or young children attention is held with a light or toy, and the hand moved in until the child notices it. Accurate visual fields can be obtained by confrontation methods alone. Color fields and perimetry may be necessary for exact work.

Ophthalmoscopy should be reserved till last with small children, who often struggle. Common errors are (1) overlooking early

papilledema, the first signs of which are not blurring of the disk margins, but dilatation of retinal veins and obliteration of the optic cup; indistinct disk margins without the other signs usually represent refractive error or congenital peculiarity. (2) Mistaking optic neuritis or pseudoneuritis for papilledema; the appearances may be identical, but loss of acuity and color vision is marked with neuritis, slight or late with papilledema. (3) Mistaking the normal grayish disk of infancy for optic atrophy.

**Hearing.** Startling or blinking at loud sounds tests only lowermost levels of the auditory system, and may persist despite cortical deafness. Turning toward a sound or smiling at a parent's voice is a better sign of hearing. Children who can speak are asked to repeat aloud numbers whispered at their ears.

**Labyrinthine function.** Hold the child aloft, his face at a level with the examiner's, who turns round rapidly several times; after three or four turns the normal child shows definite nystagmus. To test one labyrinth instill 5 to 10 cc. of iced water into the external ear with a soft catheter or syringe. Normally, nystagmus with the slow component to the stimulated side appears in about forty seconds, and persists about two minutes. Lesions of the vestibular apparatus, the eighth nerve or brain stem diminish or obliterate the response; in decortication the slow phase alone is present, and the eyes deviate to the stimulated side.

**Smell and taste.** Tests of *olfaction*, with some familiar odor, and *taste*, with salt or sugar solutions applied to the tongue, are seldom informative, and done only when first, seventh, or ninth nerve lesions are suspected.

**Cranial nerves.** To test the oculomotor group, the third, fourth and sixth nerves, observations are made for pupillary size, direct and consensual response to light and response to convergence, range of movement of eyes, ptosis and nystagmus. Tests of the facial group, the fifth and seventh nerves, include determinations of facial symmetry at rest and in movement, equality of palpebral fissures, strength of lid closure, corneal reflexes, facial sensation to pin prick and light touch, and jaw movements. For the ninth, tenth, eleventh and twelfth nerves one should note the quality of voice, gag reflex, swallowing actions and the function of the trapezii and sternomastoids. Palatal asymmetries are not significant unless marked and associated



with diminished gag reflex. The tongue should be examined carefully for size, symmetry, movement and fibrillation.

**The motor system.** The child should be observed stripped at rest, and partially clothed in spontaneous and induced activity. He is asked to lie down, stand up, hop on one foot, walk, walk tandem, run and climb stairs; he is offered some attractive toy, plays a game of catch, or writes or colors simple drawings. Note bodily proportions, spontaneity and symmetry of movements, handedness, evidence of generalized or localized weakness, steadiness of gait and presence and kind of any involuntary movement. Look carefully for the following:

#### 1. PHYSICAL STATUS OF MUSCLES.

*Atrophy* may be part of generalized wasting or may be due to disuse. If it is due to progressive motor neuron disease, it is accompanied by *fasciculations*, brief repetitive twitches, occurring at rest, increased by movement or percussion of the muscle. Completely denervated muscle *fibrillates*, producing a slow undulating movement, visible clinically only in the tongue. *Aplasia* or *hypoplasia* most frequently involves facial and extraocular muscles (Moebius' syndrome), but any muscle may be affected. Arrest of development with smallness of limbs, slight muscles, narrow nails and slender bones is seen in limbs paralyzed at an early age. *Hypertrophy* may be compensatory, as in the arms and shoulder of a patient with paralyzed legs, or result from constant overaction in choreo-athetosis. In *pseudohypertrophy* size is increased by fatty infiltration, and the muscle itself is weak.

**2. DISORDERS OF TONE.** *Tonus* is the contraction in a muscle voluntarily relaxed. It is tested by inspection and palpation of the muscle and passive movement of joints. *Flaccidity*, the absence of tone, is seen in organically or physiologically denervated muscles. *Hypotonia* is a reduction of normal tone. *Spasticity* is an exaggeration of stretch reflexes, depending on impairment of central inhibition with maintenance of central facilitation of these reflexes. It expresses itself as diminished voluntary movement and the appearance of postures in the limbs indicating movements particularly impaired. It is characterized by (1) increased resistance to passive movement, giving way suddenly when overcome—"clasp knife" rigidity; (2) increased myotatic reflexes; (3) clonus. It is not produced by isolated lesions of the motor

cortex, but rather by widespread damage to the motor system.

*Rigidity* implies increased tone and resistance, not accentuated in any particular movement. The hypertonus may appear to abolish reflexes, but they are present and increased. When overcome, hypertonus may give way in a series of brief relaxations, producing the cog-wheel phenomenon, or maintain a constant, plastic resistance.

**3. INVOLUNTARY MOVEMENTS.** *Myoclonic jerks* are brief contractions of whole muscles occurring irregularly and without pattern; massive myoclonus is a sudden jerk involving neck, shoulders and upper trunk. *Myotonus* is sustained contraction following voluntary contraction or direct percussion of the muscle. *Tremors* are usually regular movements, principally flexion-extension, of segments of limbs, entire limbs or head and trunk; the rate varies from three to ten per second. Tremor at rest, with limbs relaxed, suggests disease of the extrapyramidal system; intention tremor, or tremor on movement, indicates involvement of cerebello-rubro-thalamo-cortical circuits. *Athetosis* is an irregular wandering movement, most marked in fingers or toes. *Chorea*, often associated with athetosis, is a coarse, jerking, irregular movement involving large joints or segments of a limb. *Dystonia* is a slow, twisting movement of limbs or trunk, about the long axes of the segment involved. *Tics*, by contrast, are repetitive movements without organic dysfunction, which could be purposive, and can be stopped for a time by the patient.

**4. MUSCULAR STRENGTH.** The strength of muscles, and of particular movements, should be carefully tested. Certain patterns of weakness characterize special types of neurologic impairment. Pyramidal lesions weaken extension more than flexion in the upper extremity, while the converse is true of the leg. In polyneuritis proximal muscle groups are usually weaker than distal ones in legs, the distal ones weaker than proximal ones in the arms. Most dystrophies weaken limb girdle, axial and proximal muscles much earlier than distal ones.

**5. REFLEXES.** The stimulus for the *myotatic* or *stretch* reflexes is deformation of nerve endings in the muscle or tendon; the reflexes are segmental, with afferent and efferent neural limbs, and a segmental center within the brain or cord. They are diminished or abolished by any process which (1) impairs nerve conduction, such as peripheral

neuritis; (2) lowers the central excitatory state, such as spinal shock; (3) reduces reactivity of muscle, such as atrophy or metabolic disturbance. They are increased by processes which lower the central inhibitory state or reduce synaptic resistance, such as pyramidal tract lesions or tetanus.

The limb should be relaxed, and the muscle to be stimulated should be able to act at maximal mechanical advantage; usually this is a position of about half-flexion of the joint involved. The stimulus is a brisk tap on tendon or bony prominence, putting a muscle on stretch. The muscle itself should not be tapped. The contraction which follows is not a myotatic reflex. Reflexes should not be considered absent until reinforcement has been tried by causing muscular activity in another part of the body—having the older child squeeze the examiner's hand, or provoking the infant to tears.

The following myotatic reflexes, with their segmental arcs, are usually adequate:

<i>Reflex</i>	<i>Central Arc</i>
Jaw jerk .....	Pons
Biceps jerk .....	C 5-6
Triceps jerk .....	C 8
Supinator jerk .....	C 5-6
Finger jerks (Hoffmann sign) .....	C 8-T 1
Knee jerk .....	L 3-L 4
Ankle jerk .....	S 1-S 2

The important superficial reflexes are the plantar, abdominal, anal, and grasp reflexes.

**ABDOMINAL REFLEXES.** Stroking away from the umbilicus, horizontally, upward or downward, with a blunt point causes contraction of the homolateral abdominal muscles, with some localizing significance depending on the level stimulated. A cerebral as well as spinal arc is present, and reduction of abdominal reflexes characterizes most pyramidal lesions, though they usually persist in hemiparesis of early onset.

**ANAL REFLEX.** Stroke the perianal skin with a pin; a prompt constriction of the anus follows, mediated through the lowermost sacral segments.

**PLANTAR REFLEX.** Stroke along the lateral margin of the sole, from the heel forward, in a J curve ending medially at the base of the great toe. A reasonably firm stroke with key, fingernail or blunt pencil is best; the more lateral the stroke, the less the likelihood of avoidance reflexes. The foot should be warm and the initial strokes gentle. Three responses may occur. (1) The toes may plantar flex; this is the response in all normal waking persons over one to two years. (2) The great

toe may dorsiflex, with or without fanning of the other toes; the movement, unlike avoidance, is slow and maintained. This response, the only one properly called Babinski's sign, is evidence of structural or functional pyramidal tract deficit. A similar response occurs up to one to two years of age, and in sleep. (3) There may be no movement at all, as in spinal shock, deep anesthesia or coma or peripheral neuritis.

**GRASP REFLEX.** Stroking the palmar surface of the metacarpophalangeal joints toward the fingers brings out a sudden grasp reflex, followed by maintained contraction if the stimulus is continued. The reflex is normally present in infants under four months of age; at later ages it suggests frontal lobe lesions, though its localizing value is not absolute. When it is present, gentle stimulation of palmar and volar surfaces of fingers will bring out groping movements of the hands as well.

**The sensory system.** Awareness of pin prick, the light touch of a tuft of cotton, position of fingers and toes and vibration are all that need ordinarily be tested. Sensory findings are less reliable than motor or reflex change, and minor aberrations, unless repeatable, should be disregarded. Sensation is best tested from a suspected toward a normal area, or from the distal to the proximal portion of a limb.

**Coordinating system.** Most disorders of co-ordination are apparent in spontaneous movement. Watch the child reach for a toy, build a block house, tear paper, "do his buttons," or open and close a safety pin. Have him touch his nose and the examiner's finger alternately; move the target about, to prevent decomposition of movement and bring out ataxia. Romberg's sign, standing on either foot singly, and hopping on one foot, together with the heel-shin test, suffices for the legs.

**Autonomic system.** Color and temperature of the skin, mottling, edema and trophic sores should be looked for. Sweating, usually abolished below a transverse spinal cord lesion, may be demonstrated with the starch-iodine test (see below). A distended bladder should always be sought for; defects of sphincter function usually appear in the history.

**Special findings.** Percussion over the sphenion gives a flat note if the sutures are separated; this, *Macewen's sign*, is inapplicable to infants and unreliable in early sutural separation. In about 10 per cent of young children *auscultation* over the vertex, temples or eyeballs discloses a bruit, systolic in time



or accentuated in systole. Most bruits are innocent, transmitted from the heart or due to angulation of basal vessels; some accompany anemia, hydrocephalus or increased intracranial pressure. Rarely they indicate vascular malformations. A significant bruit is usually loud and often lateralized. Hydranencephaly, extreme hydrocephalus and sometimes subdural hematoma can be demonstrated by *transillumination of the skull* of the infant; a strong flashlight with a sponge rubber cuff about the end and a completely dark room are necessary. Sweating tests, using starch powdered over iodine dried on the skin, or an old-fashioned indelible pencil drawn from suspected to normal regions, aids in demonstrating spinal cord or autonomic lesions.

## EXAMINATION OF NEWBORN AND YOUNG INFANTS

The most constant sign of neurologic abnormality in newborn and young infants is failure of development of reflex patterns appropriate to age, and persistence, reappearance or exaggeration of less mature ones. Generalized reflex responses are more important than in examination of older children. The intrinsic reflex arcs and conducting systems through mesencephalic levels are intact and functioning at birth, and most testable reflexes are those of brain stem or spinal cord, uninhibited or only partially modified by suprasegmental control. The cerebral hemispheres exert some influence, since signs of suprasegmental lesions may be detectable in the newborn, presumably while the lesion is acute, only to disappear in early months of infancy and reappear when normal functioning of the damaged areas should be evident.

**Postural Reflexes.** Afferent impulses for the *tonic neck reflex* originate in neck muscles. With the infant supine, turn the head sharply to one side. The arm and leg on the side to which the jaw is turned extend, or extensor tone increases; their fellows of the opposite side flex, or extensor tone decreases. In normal newborn infants these reflexes are incomplete, often more definite in leg than in arm; they tend to disappear during the first year, but partial responses may persist until the second or third year. Persistent asymmetry or complete and easy elicitation of the full response suggests a cerebral lesion.

Similar postural reflexes originate in the labyrinth (otolith righting reflex). Tilting the body of the erect infant while his eyes are covered induces a reflex righting movement

of the head, returning it to the erect position. When the head is turned, with the infant supine, the pelvis initially tilts opposite to head movement, then turns strongly in the other direction, the trunk thus following the head. Absence of this body righting reflex is an early sign of spasticity. In the *Landau reflex* the child is held prone, horizontally; head and neck extend, shoulders draw back and hips extend, the entire body forming a convex arc upward. Gentle pressure on the head or gravity flexes the neck, and legs and arms drop with it, reversing the arc. The same response may be seen when the normal child is learning to sit; he balances his head briefly, usually overextending slightly, then slumps forward with flexed neck and trunk, and arms dropping forward on the chest. When the spastic child attempts to sit, weakness of extension of trunk and neck forces him to slump forward, but pressure on the occiput produces overextension of neck and trunk, opisthotonos, exaggerated backward movement of shoulders and arms and extension of legs. The *Moro reflex* is a generalized extension and abduction of limbs and trunk followed by flexion and adduction; a sudden loud clap or slap on the table top elicits it. It is most valuable as an indication of general reflex irritability and normally disappears around four or five months of age.

**Placing and Stepping Reflexes.** Spontaneous limb movements of the newborn are either symmetrical or a part of quadrupedal progression. The prone newborn makes clear crawling movements; when held erect, with feet touching the table top and trunk inclined forward, he takes regularly alternating steps. If the dorsum of the foot is drawn against the under edge of the table top, the foot is lifted and placed atop the table. The infant, supported about the trunk, feet touching the table top, should be lifted suddenly up and down; this normally produces a supporting extensor thrust of the legs. Persistent extension or scissoring of the legs (*DeLange's sign*) is abnormal, as is asymmetry in any of these responses.

**Local Reflexes.** Myotatic reflexes are normally present, though extremely variable. Areflexia or persistent hyperactivity is abnormal; otherwise, only persistent asymmetry between the two sides is significant. The plantar response is usually extensor, and the grasp reflex present. Abdominal reflexes are generally present, though sluggish and perhaps with prolonged latency. Pupillary constriction and reflex closure of lids on exposure

to bright light and a corneal reflex are all demonstrable. Stroking the lips produces sucking (*sucking reflex*), and stimulating the side of the cheek close to the mouth causes the infant to turn his mouth and face toward the stimulus, the "*rooting*" reflex. Nystagmus on rotation and the Moro response to a loud sound indicate function of the lower levels of the vestibular and auditory system. The skin is sensitive to pinprick.

## EXAMINATION OF THE HYSTERICAL PATIENT

Malingering is rare in childhood, but hysterical symptoms are fairly common; only very young children are exempt. Organic symptoms may coexist with, or be perpetuated as, hysterical ones. The diagnosis of hysteria depends anamnesticly on demonstration of an appropriate emotional constitution and, almost always, a precipitating emotional crisis, sometimes clearly indicated by the kind of disability evoked. This portion of diagnosis, together with therapy, belongs in the domain of psychiatry. The role of the neurologist is to demonstrate the hysterical quality of the signs; he can best achieve this by physical examination without mechanical aids, hypnosis or narcosynthesis.

Hysterical symptoms, usually sudden in onset, tend to involve anatomic units or physiologic functions as a whole, and the victim shows a calm indifference inappropriate to his handicap. Common manifestations in childhood are (1) visual impairment or blindness, (2) paralysis of a limb or impairment of walking, (3) sensory loss or anesthesia, (4) loss of speech, (5) tremors or involuntary movements, (6) fits or disturbances of sensorium, (7) urinary retention.

*Visual defect* includes constriction of fields, amblyopia and amaurosis; hemianopsia and central scotomas are seldom if ever hysterical. Size of fields may change during perimetry, producing expanding, contracting or helical forms. If fixed in size, the field is very small and central and remains the same at whatever distance charted, a finding impossible for an organic constriction, owing to the divergence of the light rays subtended by the field. Impossible aberrations of color fields, e.g., red larger than blue, may be present. *Hysterical amblyopia* can generally be improved during examination by persuasion alone. In *hysterical amaurosis*, pupils and pupillary reflexes are normal and optokinetic nystagmus is present, establishing the

diagnosis. Photophobia, blepharospasm and convergence paralysis are common.

*Hysterical paralysis* may be paraplegic, monoplegic or hemiplegic. Normal reflexes and tone are preserved, and pathologic reflexes and the patterns of organic weakness are absent. The hemiparetic child may be tricked into movement by asking him to abduct or adduct both arms or both legs simultaneously; only conscious simulation will keep a normal limb from moving, palpable voluntary contraction then keeping it still. In *Hoover's test* the child elevates the normal leg strongly while the examiner keeps his hand beneath the heel of the paralyzed one; strong effort to raise the normal limb brings out downward pressure from a hysterically, but not an organically, paralyzed one. If partial movement is possible, the paretic limb regularly misses a mark set for it by about the same distance, whether a large or a small movement is required. Walking and standing are generally impaired together; both may be lost, though voluntary movement and coordination need not suffer (*astasia-abasia*).

*Ataxia* is usually greater in the trunk than in the limbs, and the stance is seldom wide-based; ataxia improves considerably if the child walks with two examiners ringing, but not touching, him with their arms.

*Tremors* are generally coarse, sometimes fairly rhythmic, but always reproducible by the examiner; they rarely cause difficulty in eating or dressing, except during observation.

*Hysterical sensory loss*, usually associated with paralysis, may be of glove or stocking type or involve a whole limb or one side of the body. It disregards neurologic boundaries and is usually absolute and to all modalities rather than incomplete or dissociated as in most organic illness. The level of sensory loss can be changed by shifting the point at which stimulation is begun; if one starts higher, the level is proportionately higher. Ask the child to close his eyes and say "Yes" when he feels a touch, "No" when he does not; hysterical children readily acquiesce and respond with "No" when the anesthetic area is touched. If one hand is involved, the Japanese illusion is useful; the child crosses his arms, palms opposed, clasps his fingers and brings the locked hands inward and upward. It is then very difficult for him to distinguish right from left; sensory stimulation or demand for movement produces gross inconsistencies.

*Hysterical aphonia* is seldom absolute; the child may not speak, but can whisper, sing or whistle; he may be mute with parents or



physician, but speak to his fellows. Normal movements of tongue, palate and vocal cords are preserved. *Hysterical fits* are distinguished from epileptic ones by absence of tongue biting, incontinence, cyanosis or pallor, change in pupillary reflexes, Babinski sign and incidental injuries. In the *stupors* or *catatonias* which may follow them the eyes are actively closed; Bell's phenomenon is present when the lids are forcibly opened, and pupils are normally reactive. *Urinary retention* is seen almost exclusively in girls; it does not alter the cystometrogram unless secondary infection has occurred.

## EXAMINATION OF THE UNCONSCIOUS PATIENT

This should include the following:

1. **Vital Signs.** Character of pulse and respirations, color and responsiveness to stimuli. Record these at beginning and end of the examination to secure a time-lapsed record and an estimate of changes due to stimulus of examination.

2. **Visuo-oculomotor System.** Position of eyes at rest, spontaneous movement and movement of eyes against passive movement of the head—a rough test for integrity of the vestibulo-ocular pathways. Note pupillary size, shape and reactivity to light and painful stimuli. Examine fundi carefully, but *do not dilate pupils*.

3. **Facial and Bulbar Functions.** Symmetry of movement of face on breathing and on painful supraorbital pressure, corneal reflexes, presence of spontaneous swallowing movements and gag reflex.

4. **Extremities.** Position at rest, the patient supine. Midbrain decerebration adducts, extends and internally rotates the arms, and extends and adducts the legs; tonic neck reflexes may appear spontaneously or be induced by turning the head. Note spontaneous and induced movements of limbs; hemiparetic limbs move less under both circumstances than normal ones; the leg in hemiplegia rotates externally at the hip, the oval outline of the thigh is transverse rather than vertical, and the foot points downward and outward. Raise the arms together and allow them to fall—a hemiplegic one falls more quickly and with less minor movements of adjustment than a normal one. Draw the legs up, knees flexed and soles flat, then release them suddenly—a hemiplegic leg falls outward, and the foot slips down on the sheet faster than a normal one. Check myotatic

reflexes, which may be absent in recent hemiplegia, spinal shock or deep coma; asymmetries are more significant than generalized changes.

5. **Sensation.** Stimulate fairly vigorously with a pin, especially on soles of feet and on hands. Cross the midline of the trunk and ascend either side with a series of pinpricks. Sensory impairment may be detected by a sudden twitch or an incomplete protective movement when one crosses from hyperesthetic to normally innervated skin.

6. **Trophic and Circulatory Changes.** Note color, mottling and temperature of the skin. Fresh hemiplegias or transverse cord lesions cause warmth of the affected limbs from vasodilations. Palpate carefully for distended bladder.

7. **Miscellaneous Signs.** Meningisms, bruises, rashes, fractures, and odor of breath.

## SPECIAL DIAGNOSTIC PROCEDURES

Special studies may be desirable for the information they provide and for the reason that abnormality demonstrated by a mechanical procedure often seems more comprehensible to the parent than that resting on clinical opinion. Some are harmless; others entail real hazard, which must be weighed carefully against the potential value of the information they may provide.

Such special studies include (1) lumbar puncture, (2) subdural and ventricular punctures, (3) radiologic studies (plain films, pneumoencephalography, ventriculography, angiography, isotope scanning and myelography), (4) electroencephalography, (5) psychologic and psychometric studies, and (6) biopsy.

**Lumbar Puncture.** Carelessness and failure to pay attention to essential details often negate the potential value of the lumbar puncture. Contraindications are increased intracranial pressure due to space-taking lesions, local sepsis in the lumbar region and a bleeding tendency. The equipment consists of no. 19 and 20 lumbar puncture needles, 1½, 2 and 2½ inches in length, well sharpened, short-bevelled and with smoothly fitting stylets, an Ayer type of glass manometer, procaine, hypodermic needles and syringes, a three-way stopcock, collection tubes and the usual equipment for a minor, sterile procedure. Older children usually cooperate, younger ones need to be held; sedation is desirable, but volatile anesthetics should be avoided, since many raise intracranial pres-

sure. The child lies with his back, widely "prepped," absolutely vertical to the table, and knees, hips and neck flexed as little as necessary. A procaine infiltration is worth while, even in infants. The needle is introduced absolutely in the mid-sagittal plane of the child's body, at the third, fourth or fifth lumbar interspace, its point slightly cephalad; it is advanced slowly, the stylet repeatedly withdrawn, until cerebrospinal fluid drips out. This slow approach avoids passing entirely through the theca. When fluid is dripping, the stopcock and manometer are attached, and the child is encouraged to relax by every reassurance and entertainment possible; a proper approach can accomplish much, even with infants. A resting pressure is recorded as soon as the fluid column stabilizes, oscillating freely. Jugular and abdominal compression is done, if indicated, and appropriate quantities of cerebrospinal fluid removed stepwise, in 1-cc. aliquots; the closing pressure is recorded, the needle removed, its track broken by firm massage with the finger, and a small dry sterile dressing placed over the site. Bed rest after the procedure is unnecessary, since postpuncture headache is rare in children; occasionally, stiff back and headache, with persistent low cerebrospinal fluid pressure, occur; these complications appear unrelated to technical errors of the procedure.

Proper examination of the cerebrospinal fluid is of great importance in differential diagnosis of central nervous system disease, though the values determined are few. One wishes to know (1) pressure, and freedom of oscillation; (2) color; (3) cellular constituents; (4) protein; (5) glucose and rarely chloride; (6) evidence for infection.

**Pressure** normally varies from about 60 to 180 mm. of fluid if the child is really relaxed; the mean is about 120 mm., pressures in infancy being somewhat lower. Pressure must be read from a manometer; estimation by speed of flow is completely inaccurate. Compression of the abdomen raises cerebrospinal fluid pressure by about 10 to 20 per cent by raising the pressure in epidural veins and compressing the theca; pressure on the jugular vein raises cerebrospinal fluid pressure by 30 to 50 per cent by increasing the intracranial vascular compartment; if a block exists in the spinal theca, abdominal compression is effective, but jugular compression ineffective, in causing these rises, since intracranial changes cannot be communicated to the lumbar theca. Jugular compression in the face of increased intracranial pressure can be

dangerous by causing or worsening a cerebral hernia.

**Color.** Normal cerebrospinal fluid is as clear and colorless as distilled water; it should be compared to a tube of distilled water, held against a white background. High increase in protein gives a faint opalescence to a definite yellow tint; old hemorrhage produces definite xanthochromia, leukocytes above a hundred or so casual turbidity, and fresh blood, opalescence to pinkness or outright bloodiness. The bloody tap tends to clear on removal of successive quantities of fluid, xanthochromia after centrifugation is absent, and the proportions of erythrocytes to leukocytes is that of the child's peripheral blood; a differential count of red and white cells in the fluid, and an immediate red and white cell count on peripheral blood, must be done if blood from a traumatic tap is to be distinguished from endogenous blood.

**Cells.** The cerebrospinal fluid normally contains less than 5 leukocytes per cubic millimeter. More than 5 white blood cells, and polymorphonuclear or red cells in any number, are abnormal. Cells must be counted within thirty minutes, since sedimentation or breakdown soon occurs.

**Protein.** This varies with the location of the source of the fluid and with different laboratory methods. Ventricular fluid contains 15 mg. total protein per 100 ml. or less, cisternal fluid about the same or a trifle more, and lumbar fluid 15 to 40 mg. For a quick estimate, one drop of cerebrospinal fluid is dropped into 1 cc. of 5 per cent aqueous phenol (Pandy's fluid) and observed without shaking. A clouding or precipitate at the interface usually represents increased protein content, the test being much more sensitive for globulin than for albumin. The fluids must be at the same temperature, since chilled Pandy's reagent will produce a faint clouding. A quantitative total protein determination should always be obtained.

**Glucose.** This normally is about one half to two thirds of the blood sugar. The glucose level of the blood should be determined at the time of lumbar puncture.

**Evidence of infection.** Serologic tests for syphilis, colloidal gold or colloidal mastic and sometimes Treponema immobilization tests should be obtained when indicated. A cellular fluid should always be cultured for bacteria at the time of puncture and on warmed media; if meningitis is a possibility, even an acellular fluid should be cultured. Cultures for fungi and acid-fast bacilli should be obtained when



indicated. All cellular fluids should be centrifuged, and a stained smear should be examined for a differential count of cells and for organisms.

The cerebrospinal fluid of infants in the first few days or weeks of life is often xanthochromic, with protein as high as 80 to 100 mg. per 100 ml., and often has an excess of red and white blood cells. These findings, though not normal, are usually an expression of intracranial complications of birth, such as venous congestion or minor trauma, often without other symptoms or recognized residuals.

**Cisternal Puncture.** The only indication for cisternal puncture is unavailability of the lumbar route. Possible cerebellar herniation or the Arnold-Chiari defect is a contraindication. The child is placed so that his head rests evenly on one side or in the sitting position with his chin flexed on his chest. The spine of the axis is located, and a line joining the external auditory canal and glabella is determined. The needle is introduced immediately above the axial spine in the midline, inclining slightly upward from the auditory-glabellar plane until it touches the occipital bone; the approximate depth is noted, the needle is then withdrawn to the skin, but not through it, and reintroduced in planes successively closer to the auditory-glabellar one with the stylet withdrawn repeatedly until fluid drips out or the needle strikes the occiput again. The depth of the cistern from the surface varies from about 1.5 cm. in infants to 3 to 4 cm. in adults. The danger of fatal injury to the medulla or of hemorrhage is real, and the procedure should not be attempted for the first time on a live child.

**Subdural and Ventricular Punctures.** These important diagnostic procedures are carried out only on infants whose sutures are open. The equipment is that for lumbar puncture. The child is entertained with a sugar or brandy nipple, his head shaved at least to the bregma or, better, entirely. A wide sterile preparation is made over the vault, and the head draped with a "posterior drape" towel. The lateral angle of the anterior fontanel is palpated, and a procaine skin wheal raised. A short lumbar puncture needle is then introduced, perpendicular to the scalp surface, not less than 1 to 1½ inches lateral to the midline, firmly supported and not allowed to wobble. Scalp and skull once penetrated, the stylet is withdrawn. If subdural fluid is present, it usually drips out at once. More than

1 ml. of fluid, or fluid discolored by anything other than proved fresh blood, is abnormal. If fluid is not encountered, the needle is passed inward about 1.5 cm., then withdrawn slowly, since occasionally membrane or outer clot of a hematoma may occlude it. Cell count, color estimation, protein and culture are secured on any fluid obtained; both sides should be tapped, since four fifths of infantile subdural hematomas are bilateral. No more than 10 to 15 ml. of fluid should be removed at any time from either side, nor more than a total of 20 to 25 ml.; removal of 30 ml. or more may cause sudden intracranial decompression and shock. A sterile dressing is applied, and the track of this puncture avoided in succeeding ones.

Puncture of ventricles is accomplished in the same manner, except that the needle point is inclined forward toward the root of the patient's nose. If freely entered, the ventricles are almost always enlarged. Phenolsulphonphthalein, 1 cc., or Evans blue, 1 cc., may be injected, and patency of the foramina of Monro demonstrated by its recovery from the other ventricle; this is not always reliable, since fenestrae are sometimes present in the septum pellucidum. Rapid recovery of dye from the lumbar theca indicates a patent ventricular system; failure to appear in more than twenty minutes almost always means midline obstruction of the ventricular system or spinal block.

**Radiologic Studies.** 1. *Plain films.* These should always precede any special radiologic study. Views of the skull, anteroposterior, postero-anterior, lateral and basal views are adequate for most neurologic studies. Films of the vertebral column in spinal cord disease, of the optic foramina, of bones and joints in metabolic disease and of the chest and abdomen may be indicated.

2. *Pneumoencephalography.* In this procedure air or other gas such as helium or oxygen is introduced into the subarachnoid space, usually in the lumbar region, sometimes by cisternal puncture. By proper positioning ventricles and/or subarachnoid spaces may be filled. The procedure usually requires general anesthesia; in so-called total replacement large volumes of cerebrospinal fluid (80 to 120 cc.) are replaced by air; in fractional replacement only 25 to 40 cc. of air are used. The former gives more complete filling, especially in the hands of the less skilled operator; the latter is more time-consuming and requires more skill and care in introducing the air and positioning the

head and more of the radiologist's time. It is a much less severe procedure for the patient and better adapted to deliberate filling of specific parts of ventricular or subarachnoid systems. When time and personnel permit, it is to be preferred.

Pneumoencephalography can be dangerous; the mortality rate attributable to the procedure is 0.2 to 0.3 per cent, usually in patients with a mass lesion; it is higher in young children and when too much air is used. Most patients have headache, irritability, fever and vomiting for a day or more afterward. Air accidentally entering the subdural space may cause subdural hematoma. The procedure causes pleocytosis and increased protein in the cerebrospinal fluid, sometimes with meningeal signs; cerebrospinal fluid studies should always precede it.

The pneumoencephalogram demonstrates shape, size, symmetry and position of the ventricular system and subarachnoid spaces. Its greatest value is in visualizing localized static defects, atrophies and congenital malformations. A film taken twelve or twenty-four hours after the procedure may show porencephalic cysts and similar defects more clearly than the original films.

3. *Ventriculography.* When there is reasonable possibility of an expanding lesion or of increased intracranial pressure, ventriculography should be used. Here the gas is put directly into the ventricular system, through the patent fontanel of the infant or burr holes in the older child. The mortality rate of the procedure is almost impossible to calculate, since the subjects often are seriously ill; it can be the direct cause of death in patients with high intracranial pressure by causing hemorrhage from subependymal veins. Visualization of the fourth ventricle and of the subarachnoid spaces is less satisfactory than with the pneumoencephalogram.

4. *Angiography.* A radiopaque substance, usually Diodrast or Hypaque, is injected into a carotid or vertebral artery or into a dural sinus. General anesthesia and, especially in smaller children, surgical exposure of the vessel to be injected may be necessary. Angiography is the procedure of election for vascular anomalies and vascular lesions; it is also of value in localization of tumors, especially in the cerebral hemispheres. It is not without danger. Hemiplegias, usually transient, occur in as many as 4 per cent of cases. Convulsions, petechiae, transient loss of vision, occlusion of retinal arteries, throm-

bosis of the artery at the site of puncture, hematoma of the neck requiring tracheotomy and even sudden death have all been reported. For the delineation of vascular lesions the procedure is indispensable; for space-taking lesions its great advantage over gas-contrast studies is that it does not demand immediate operation if a mass is demonstrated.

5. *Isotope scanning procedures.* The use of scintillometer scanning of the head after injection of a short half-life isotope which concentrates in tumor tissue, such as RIHSA (radioactive iodized human serum albumin), is becoming common. Supratentorial masses seem to be demonstrated better than infratentorial ones. Its possibilities and limitations are not yet clear, but it is certainly much less traumatic and potentially less dangerous than any of the other radiologic methods used to locate tumors.

6. *Myelography.* Contrast radiography is also used in the localization of intraspinal masses; the common contrast medium is Pantopaque. Three to 6 ml. or more are introduced within the theca, either in the lumbar region or cisternally, and the flow of dye and irregularity or obstruction to the column observed fluoroscopically and on spot films taken on the tilting table. The dye should be removed, the reason being principally medicolegal.

The procedure is not especially dangerous, though in a few instances transverse myelitis, severe lesions of the cauda equina or obliterative arachnoiditis have seemed to follow it; if dye enters the cranium, a fatal progressive obstructive hydrocephalus may ensue. Such accidents are thought to be due to contamination of equipment or dye with detergents or disinfectant solutions. The procedure regularly causes a pleocytosis and an increase in cerebrospinal protein, and often a mild fever for a day or so.

*Electroencephalography* (see also p. 1120). This procedure, having the advantage of being harmless and repeatable, can be given too great weight in neurologic diagnosis. It is of value in establishing the presence of a central nervous system abnormality, and of assistance in the diagnosis of epilepsy, though the electroencephalogram alone is seldom the determining diagnostic factor. It sometimes localizes expanding lesions, but its accuracy is only about 60 per cent; it has prognostic value in following the course of encephalitis, encephalopathy or head injury. A great limiting factor is the variability of interpretation



put on the same tracing by different observers. One should not commit himself irrevocably to a diagnosis whose sole support is an electroencephalogram.

**Psychologic Studies.** These are of great value. A carefully performed intelligence quotient test often resolves the difficult differentiation of mental retardation from emotional disturbance. Too frequent repetition should be avoided, and the clinician should remember that such evaluations are not absolute measurements.

**Biopsy.** Muscle biopsy is quite innocuous

and often indispensable in differentiating myopathic wasting from neural atrophy; a muscle showing clear, but not the most extreme, degree of involvement should be selected and a wedge of skin always included. Biopsy of brain is indicated when a definitive diagnosis of a degenerative disease becomes imperative for reasons of genetic counseling or overpowering family emotional stress. The right temporal tip or a wedge of cerebellum is removed through a small craniotomy; punch or needle biopsies are dangerous and usually histologically worthless.

## SYMPTOMATOLOGY OF NEUROLOGIC DISEASE IN CHILDHOOD

*Visual loss* in infancy usually impairs optic fixation and the conjugate movements of the eyes. Failure to focus or wandering movements of the eyes are the complaint; in later childhood these changes suggest early visual loss. In older children the holding of objects close to the eyes and the mistaking of colors are the common symptoms. Poor vision in one eye, unless the eye deviates and strabismus develops, often goes unsuspected until a chance test of acuity reveals it. Vision may blur and fail from diplopia before strabismus is apparent. The child then tilts his head into positions in which diplopia is less, usually turning the face in the direction of the weak muscle, so that binocular vision is attained for objects directly ahead without use of the weak muscle. Head-tilting in association with a posterior fossa tumor may not be ocular in origin, but due to tonsillar herniation, meningeal irritation or stiff neck; the head then usually turns toward the side of the lesion.

Right vertical halves of visual fields represent left vertical halves of retinas, left optic tract and visual centers, and vice versa. Vertical defects are termed *hemianopsias*. *Homonymous defects* involve either the right or the left halves of the visual fields, and are caused by retrochiasmatic lesions. *Heteronymous hemianopsia* is almost always bitemporal and is due to pressure on optic fibers decussating in the chiasm. Since fibers of the papillomacular bundle are more sensitive to pressure and toxins than the remainder of the nerve, early chiasmatic compression and toxic states may cause central scotomas.

*Hemianopsias* lead to persistent ignoring or bumping into objects on one side and can be confused with lateralized cerebellar lesions, in which the child may constantly deviate to the side of his lesion. The child with tubular vision or a bitemporal hemianopsia attends only to objects directly ahead. Cortical blindness is almost always accompanied by mental change or other signs of cortical deficit.

*Impaired hearing* (p. 766) has two major symptoms. The first is inattention to sounds unless they are very loud or productive of vibrations transmissible through the body; the child will not react to a call when his back is turned, but will turn if one stamps on the floor. The second, appearing with hearing loss in early childhood, is failure of development of normal speech; in such cases hearing loss must be differentiated from mental retardation.

*Vertiginous children*, especially young ones, are unwilling to move; they wedge themselves, face down and eyes closed, in a corner of the crib or playpen.

*Organic headache* is due to distention and deformation of pain-sensitive blood vessels and meninges. Meninges of the supratentorial region are supplied by the trigeminal nerve, those of the posterior fossa by upper cervical roots and the vagus. The pain from supratentorial lesions is usually bifrontal, that from infratentorial irritation, suboccipital. Organic headache is dull, throbbing or bursting; functional headache more commonly is manifest by a feeling of pressure. Though

subjective descriptions are of less value in children than in adults, a headache lavishly described is usually not organic.

In young children the presence of headache is inferred from fretfulness and irritability, furrowed brow and sometimes ear-pulling or head-rolling. In older children the pattern of the headache is most important. Headache of increased intracranial pressure accompanies change of position, such as rising in the morning, stooping, straining or exercising; at first it is not constant; when it becomes so, lethargy and drowsiness usually accompany it. Vascular headache, common in cyanotic heart disease, is due to increased cerebral oxygen demand and distention of blood vessels; it is regularly caused by activity and relieved by rest. The distinctive feature of *migraine* is the episodic, periodic, repetitive pattern of attacks. Prodromes and auras usually go unnoticed, though the mother may comment on a period of quiet before the child complains of headache and photophobia, becomes listless and, after an hour or so, is nauseated or vomits; vomiting relieves the headache, and after deep sleep the child awakens feeling as well as ever. Neurotic headache lasts for indefinite periods and fluctuates in relation to surrounding events; the child can often be distracted from his pain. Vomiting as a neurologic symptom is distinctive only when it becomes projectile with severely increased intracranial pressure.

With *cerebellar lesions* unsteady gait is usually the first recognized symptom. Ataxia of the extremities, such as impaired manual dexterity in writing, awkward steps or rarely slurred ataxic speech is noted later. Alert parents may note dysmetria, a tendency to overshoot or undershoot when reaching for objects, or decomposition of movements, each movement being broken into a series of lesser ones to control ataxia. Hypotonia reduces associated movement; thus an affected arm hangs limp and motionless as the child walks.

Nystagmus, the only ocular symptom of cerebellar disease per se, is noted by parents only if extreme and by children as blurring or dancing of objects. Expanding cerebellar lesions rarely cause spontaneous nystagmus, and then only in conjunction with a conjugate deviation. The nystagmus is slow and coarse when looking to the side of a lesion, fine and rapid when looking away from it. Skew deviations, the homolateral eye deviating downward and inward and the opposite one upward and outward, signify acute le-

sions. Vertigo or giddiness makes the young child unwilling to move, but it may be mentioned spontaneously by the older one.

*Lesions in the brain stem* produce cranial nerve palsies early. Involvement of long motor pathways is more apparent than that of sensory ones and causes unsteady gait; sphincters are spared until late. Medullary lesions cause vomiting without increased intracranial pressure; mesencephalic ones combine hemiplegia or tremor with oculomotor palsy. Interference with the reticular systems disturbs consciousness. This may vary from deep coma with bradycardia, bradypnea and hypertension in lower-placed lesions to states of akinetic mutism, in which the patient appears awake, but does not speak or respond, or to simple hypersomnolence in upper brain stem or thalamic lesions.

*Disorders of the cerebral hemispheres* produce a variety of motor symptoms. Hemiparesis, if cortical, is usually flaccid; if the deeper white matter or basal ganglia are involved, spasticity, rigidity or choreo-athetosis appears. The first symptom of motor impairment is disuse of affected limbs. In congenital lesions disuse of the paretic hand causes apparent precocious handedness with the opposite member; when the child walks, he drags or circumducts the paretic leg. The older child uses the affected hand clumsily, shifts his handedness or limps. Growth arrest characterizes congenital or slowly progressive hemiparesis, especially if the lesion is parietal. Apraxia impresses parents only as clumsiness.

Sensory loss with cerebral lesions is almost always dissociated. For example, discrimination of shape and texture and of two-point tactile stimulation suffers more than general cutaneous sensibility. The latter is reduced rather than lost, and the deficit is seldom mentioned. Simultaneous bilateral stimulation may reveal an otherwise unnoticed sensory loss, the child disregarding stimuli on the involved side. Specific sensory disorders, notably hemianopsias, and sensorimotor dysfunctions, particularly aphasias, may be present and aid in localization. Mental changes in the young child usually cause hyperirritability first, less frequently lethargy. Older children become more emotionally labile and lose their powers of concentration and do poorly at school; lethargy and general restriction of interest come later. Seizures, the commonest symptom of discharging lesions, for practical purposes limit the lesion to the cerebral hemispheres; they may be of any sort.



## STATIC AND DEVELOPMENTAL LESIONS

About two thirds of neurologic disease in childhood is caused by lesions which are themselves static. The clinical manifestations progress only as structural and functional maturation of the nervous system is altered and secondary complications, such as hydrocephalus or repeated seizures, may further damage the brain or cord. These lesions result from various sorts of antenatal, perinatal or postnatal injuries to the developing nervous system.

**Etiology.** In the antenatal period the time and nature of the injury, together with genetic and environmental factors, affect the fetus (see p. 242). Similar injuries may cause different maldevelopments; conversely, widely differing agents may produce identical defects. *Antenatally*, genetic factors, hormonal or dietary disturbances, placental disease, maternal toxemia, age and parity of mother, age of father, intrauterine infection and hypoxia, toxic agents or radiation may all be factors. *Perinatally acquired lesions* are due principally to prematurity, hypoxia, trauma, hemorrhage, toxic states and infections. *Postnatal lesions* are mainly sequels of infections, trauma, metabolic disturbances such as hyperelectrolytemia and hypoglycemia, and vascular disease.

The *incidence* of such static lesions is difficult to estimate, since accuracy of diagnosis and reporting vary tremendously. Further, the problem is one of continuous reproductive wastage; the loss due to abortion and stillbirth is seldom included. About 6 per cent of all children at some time require special management for organic or functional illness referable to the central nervous system; about 1 per cent are handicapped by a static lesion of the brain.

**Clinical Features and Pathology.** Antenatal defects are often called maldevelopments. Many represent either failure of closure or cleftlike arrests of the neural tube.

In *anencephaly* the trunk and limbs are normally formed, but the neck is short. The brain is represented by a vascular mass in which optic nerves end blindly; the condition is incompatible with maintained extrauterine life.

*True porencephaly* is a defect (cavity or cyst) of the cerebral hemisphere, often bilateral and close to the midline; it extends

from the ventricle to the pia, without entering the subarachnoid space. It is distinguished from *false porencephaly*, single or multiple cavities which do not communicate with the ventricles and are caused by vascular damage at birth. Symptoms are hemiplegias, seizures or mental retardation.

*Arrhinencephaly* is an arrest of development of the forebrain, particularly the olfactory portions; the brain consists of a solid mass anteriorly with a single ventricle or cyst posteriorly. The children are spastic and profoundly retarded.

*Agenesis of the corpus callosum* (Fig. 314) combines partial or complete absence of the corpus callosum with microgyria, porencephaly or heterotopias. Hydrocephalus is usually present, and lipomas or meningiomas sometimes develop in the defect. Many patients are mentally defective, not from the callosal defect, but because of associated abnormalities. Mental and motor retardation, hydrocephalus, spasticity and sometimes seizures are the usual manifestations.

In the posterior fossa three major defects occur.

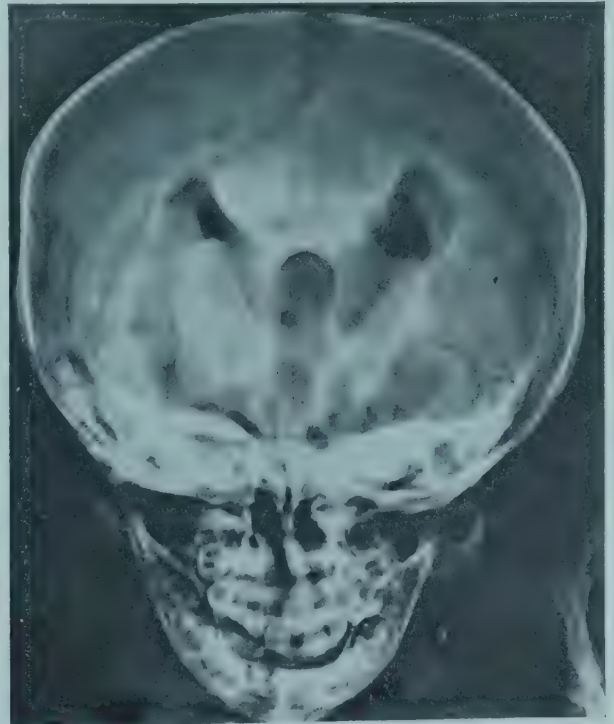


FIG. 314. Agenesis of the corpus callosum. Ventricles are dilated, and the lateral ventricles widely separated.



FIG. 315. Thoracolumbar meningocele, Arnold-Chiari defect and intrauterine hydrocephalus.

*Atresia of the aqueduct of Sylvius* is a congenital narrowing of the upper portion of the channel, which is sometimes forked or obstructed by a transverse septum. Secondary stenosis may follow ependymitis, intraventricular hemorrhage or birth trauma. Other developmental defects coexist. Symptomatically, the stricture causes obstructive hydrocephalus, the posterior fossa remaining shallow.

The *Arnold-Chiari deformity* is a tongue-like projection of the cerebellum and choroid plexus extending with an elongated fourth ventricle into the cervical canal; the upper cervical spinal cord is kinked backward, and the cerebellar tonsils are drawn into and are adherent to the foramen magnum. Lumbosacral spina bifida and myelodysplasia are present in about half the cases, and at times there are aqueductal stenosis and heterotopias. The defect appears between the sixteenth and twentieth fetal weeks and seems to be due to local overgrowth of the neural tube rather than to fixation and traction on the neuraxis by myelodysplasia. It causes obstructive hydrocephalus.

In *atresia of the foramina of Luschka and Magendie* (Dandy-Walker deformity) the fourth ventricle is ballooned out into a large cavity, above which lie the cerebellar vermis, the elevated lateral sinus and the torcular Herophili. Hydrocephalus is the common

manifestation; demonstration of the elevated torcular by roentgenogram or sinography or, in the infant, simply by transillumination, establishes the diagnosis.

In the spinal cord, defects are most frequent in the lumbosacral region, but may be cervical or thoracic. They include asymptomatic *spina bifida occulta* and *spina bifida with an associated lipoma or dermoid* or with a *meningocele* or *meningomyelocele*, a sac containing malformed cord and roots and covered by a thin, vascular membrane; the trunk and limbs below the level of the deformity are paralyzed, often underdeveloped and anesthetic, and bowel and bladder sphincters are nonfunctional (Fig. 315). *Dysrhapism* is a duplication of parts or all of the cord. Complete duplication is *diplomyelia*; incomplete duplication, usually accompanied by vertebral defects and an osseous spur extending upward from the vertebral body separating the duplicated cords, constitutes *diastematomyelia*.

*Congenital dermal sinuses* are persistent, epithelium-lined defects extending from the skin toward or into neural structures. The pilonidal sinus in the sacral area is the most common one, but they may be found anywhere along the vertebral column or in the occipital or frontal regions of the skull. Externally, a tiny pore is surrounded by hair or a port-wine mark, and it may exude a whitish secretion.

Skull growth is in large part dependent on brain growth, and arrest of it can result in *microcephaly*; the head reaches a maximal circumference of 42.0 cm.; the brain is agyric or microgyric and weighs less than 1000 gm. Secondary microcephaly occurs after a variety of injuries and is usually accompanied by neurologic manifestations. A rare variety is familial, in which the involved persons may show surprisingly few evidences other than generalized hypertonus. Severe mental retardation is present in both groups.

True *megalecephalon* is rare, most large heads being due to hydrocephalus or space-taking lesions. In adult life the megalencephalic brain usually weighs 2000 gm. or more. The cortical gray matter is increased in amount; heterotopias and developmental defects are frequent; neurons are poorly differentiated, and glial cells increased in number. A few cases are associated with adrenal abnormalities and with tuberous sclerosis. The patients are mentally retarded, usually epileptic and occasionally spastic. Pneumograms are necessary to distinguish megalen-



cephalon from hydrocephalus, space-occupying lesions or, rarely, diffuse granulomatous or parasitic lesions.

The brains of many congenitally defective persons are not grossly or obviously deformed, but only small, with simple or irregular convolitional patterns, poor lamination of the cortex, immature nerve cells and defective myelination; the term *oligocephalon* has been applied. The patients themselves are moderately defective, their genetic backgrounds often complicated by mental deficiency and emotional instability. Neurologic manifestations are usually absent or slight.

Brain injury of the *perinatal period* is due principally to metabolic and toxic disorders, trauma, hemorrhage and infections; vulnerability is accentuated by premature birth.

The commonest and most important metabolic disorder is *inadequate oxygenation*. Hypoxia is a part of almost all forms of birth injury to the brain (p. 321). Hypoglycemia, especially in infants of diabetic mothers, is another metabolic cause.

The most important toxic state damaging the newborn brain is *hyperbilirubinemia*, which produces the syndrome of *kernicterus* (see pp. 334 and 958). In this condition excess bilirubin of the indirect type accumulates in the blood, owing either to overproduction or perhaps to defects of conjugation with glucuronic acid; incompatibilities of blood type, immaturity of mechanisms of conjugation and excretion, neonatal sepsis and therapy with sulfisoxazole in the premature infant and excess administration of vitamin K are known causes. Permeability of the blood-brain barrier in the first few days of life permits bilirubin to reach nerve cells, which it damages probably by inhibiting intracellular enzyme systems. Certain regions, particularly the corpus subthalamicum, hippocampus, striate bodies, thalamus, inferior olives, cerebellar nuclei and cranial nerve nuclei are stained intensely yellow. This selectivity may depend on attainment of a specific state of maturation of neuronal enzyme systems; at any rate the cells involved are all large and phylogenetically old. Nonpigmented areas may also be damaged. Loss of neurons, reactive gliosis and atrophy of involved fiber systems are late findings.

The clinical features of kernicterus are constant and usually appear from the second to the sixth day of life. Minimal cerebral damage may not be apparent at this time. Usually the infant either appears gravely ill, prostrated, with diminished Moro and tendon

reflexes, failure to suck and respiratory distress, or he becomes opisthotonic, with bulging fontanel, twitching of face or limbs and convulsions. Rarely is there rigidity or involuntary movements. Many such infants die; the remainder, usually seriously damaged, appear to recover and for two or three months manifest few abnormalities. In later months of the first year of life, opisthotonos and muscular rigidity return and irregular movements and convulsions occur. In the second year opisthotonos and seizures abate, but involuntary movements, muscular rigidity and, in some infants, hypotonia increase steadily. By three years of age the complete neurologic syndrome is apparent. About 80 per cent of affected children have bilateral choreo-athetosis with involuntary mobile spasm. Pyramidal signs are rare in proportion to extrapyramidal ones, and hypotonia and ataxia distinguish a few. Seizures, mental deficiency, explosive dysarthric speech, high tone hearing loss, squints and defective upward movement of the eyes are common. It is possible that Rh incompatibility without neonatal jaundice may result in hearing loss, mental limitation and learning disorders, though the relationship is not proved.

*Prematurity* (p. 306) may be an expression or a cause of brain abnormality. At least one fifth of prematurely born infants later show signs of cerebral involvement. Some of this results from birth injury to the soft premature skull, hyperbilirubinemia, intraventricular hemorrhage or hypoxia, but the possibility of antenatal defects always exists.

*Trauma* (see also p. 315) of the perinatal period affects the brain more by deforming the skull and its contents than by impact force. Molding of the head and overriding of sutures tear small veins, sinuses or the tentorium, producing subarachnoid or subdural bleeding; large veins, sinuses or major arteries may be compressed and venous stasis or areas of hypoxia produced. Direct compression of the skull by forceps or ischial spines can cause local ischemia or vascular damage.

*Hemorrhage* is a less common primary source of damage than was formerly thought; microscopic hemorrhage and slight xanthochromia of cerebrospinal fluid occur in perhaps one fifth of all newborn infants, but per se are not evidence of significant brain injury. Gross hemorrhage is now rare, but smaller petechial or perivascular hemorrhage following vascular compression or hypoxic damage to endothelium is common. Intra-

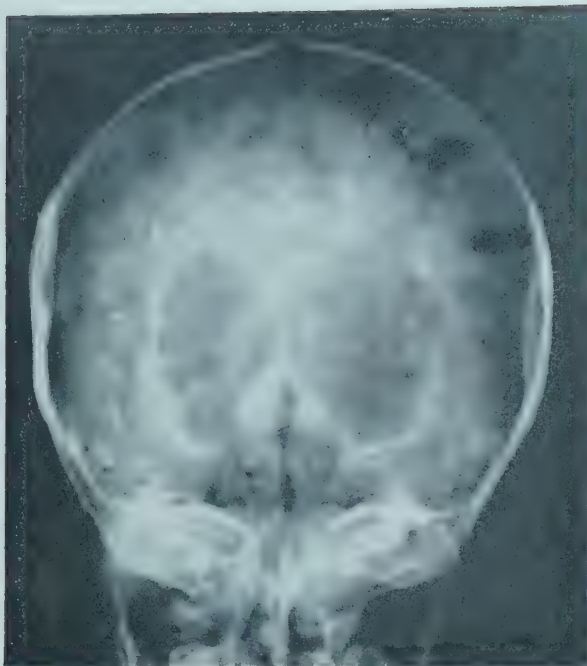


FIG. 316. Calcified ependymitis and hydrocephalus following cytomegalic inclusion body disease in the newborn.

ventricular hemorrhage, immediate or delayed, from the terminal veins is frequent in small premature infants (p. 316).

*Infections* include both intrauterine and neonatal encephalitis and complications of neonatal sepsis. Toxoplasmosis (p. 615) and cytomegalic inclusion body disease (p. 524) produce a severe encephalitis, the lesions of which may be calcified at birth (Fig. 316). Neonatal sepsis may cause hyperbilirubinemia, meningitis, venous or sinus thrombosis or toxemias severe enough to damage the brain.

It is still difficult to relate any particular form of abnormal birth to any constant form of brain injury. Difficult labors with pallid asphyxia of the newborn seem associated with severe damage to the basal ganglia and thalamus (Fig. 317); a peculiar marbled appearance, called *status marmoratus*, is found in the basal ganglia, thalamus and sometimes the cortex. Clinically there usually are combined pyramidal and extrapyramidal syndromes and mental retardation. Venous stasis, compression of the galenic vein and perhaps sudden fluctuations in intracranial pressure, when the head is delivered through a contracted pelvis or rapidly in breech delivery, may result in cystic degeneration of the white matter. Spastic diplegia is the usual result. Other than this, prediction of types of clinical abnormalities or of pathologic le-

sions of abnormalities recognized at birth can seldom be made.

*Postnatal lesions* are sequels of infections, principally meningitis and encephalitis, injuries, subdural hematomas, metabolic disturbances such as hyperelectrolytemia or embolic and inflammatory cerebral vascular disease. Their etiology is usually clearer than that of prenatal or perinatal lesions, the principal exception being the infant or young child, previously said to be well, who begins to have seizures, goes into status epilepticus and is left with definite signs of cerebral injury. It is often impossible to tell whether the seizures, hypoxia and perhaps hypoglycemia injured the brain, or whether they further damaged a brain of whose abnormal-

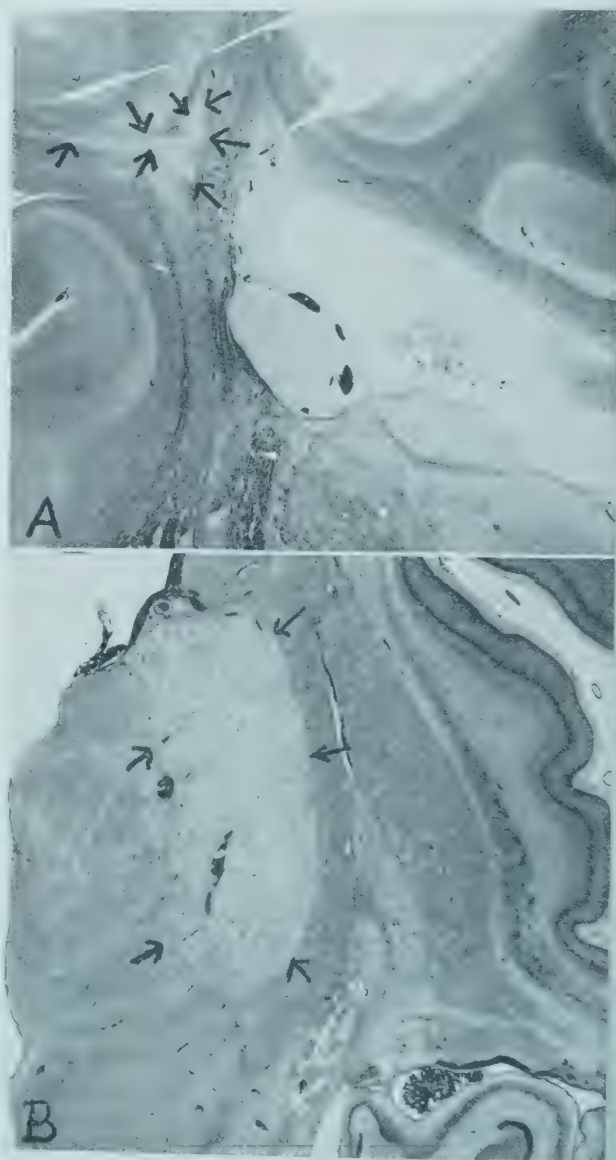


FIG. 317. Cerebral birth injuries. A, Focus of softening in internal capsule in a prematurely born spastic child. B, Necrosis of cells in the lateral thalamic nucleus in a severely molded head.



ity they were the first recognized manifestations.

**Treatment.** Prevention of static lesions is obviously the desired goal. This demands far greater knowledge of etiology and pathogenesis than is presently available (see p. 293).

Some static lesions can be treated surgically. Aqueductal atresia, the Dandy-Walker or Arnold-Chiari defects all produce obstructive hydrocephalus and are so managed (p. 1092). Simple cranium bifidum requires no treatment, but cranial meningocele or meningoencephalocele should be repaired by amputation of the sac and repair within the skull. Congenital dermal sinuses should be excised in toto as soon as discovered, since they offer a portal of entry for infection and entail constant risk of meningitis or brain abscess. Diastematomyelia and spinal meningocele, with or without lipoma or dermoid, are better left alone, unless they are producing increasing disorders of gait or sphincter control.

*Myelodysplasia (spina bifida with meningocele)* offers one of the most serious problems. Operation can remove the sac, close the skin defect and lessen the nursing problem, but it does not improve the neurologic deficit. A life of paraplegia and incontinence, ending in the second or third decade with pyelonephritis and uremia, is the usual pattern. Since the Arnold-Chiari defect, aqueductal atresia, or both, are present in more than half the cases of myelodysplasia, obstructive hydrocephalus frequently develops, and early operation is blamed for its appearance. Good results cannot be expected from sur-

gery in infants with (1) severe paralysis of the legs, (2) fecal and urinary incontinence, (3) hydrocephalus, (4) severe mental retardation, or (5) multiple congenital defects. With such infants the sac and skin should be kept clean with dry dressings, and excoriation of the perineum and buttocks should be avoided by careful hygiene and exposure to air and sunlight. If hydrocephalus does not appear and mental development seems normal, repair may be done some months later. When the paralysis is incomplete, and there is no evidence of incontinence or hydrocephalus, the lesion is usually repaired at once. Results, even with orthopedic assistance, physiotherapy, efforts at bowel and bladder training, fluid restriction and low residue diets, are seldom very good.

Perinatal and postnatal static lesions are seldom treated surgically. If hydrocephalus appears, it is usually early, and the prognosis for surgical improvement is poor. Resection of scarred or atrophic areas or even hemispherectomy occasionally relieves otherwise intractable seizures, but should be considered only after intensive medical therapy has failed. Destructive operations on the brain or cord to relieve tremor, involuntary movements or spasticity to date have given few good results.

Most children with static lesions of the brain or cord present a variety of problems: mental limitation, neuromuscular handicaps, seizures, learning difficulties and problems of emotional and social adjustment. These are discussed in the treatment of the cerebral palsied child (p. 1141).

## ECTODERMAL DYSPLASIAS

These hereditary conditions, also known as phakomatoses, combine congenital lesions of the skin and nervous system with a wide variety of visceral and somatic abnormalities. Often inapparent at birth, they may appear as mixed and incomplete syndromes.

*Tuberous sclerosis* is inherited as a dominant trait. The widespread lesions include those (1) of the *skin*, fibroadenomas of sebaceous glands over the nose and cheeks (butterfly area), "shagreen" or leathery patches, *café-au-lait* and depigmented spots and subungual fibromas; (2) in the *viscera*, hemangiomas or mixed tumors of kidney, liver and spleen, multiple tiny mixed tumors

of the lung associated with spontaneous pneumothorax, and rhabdomyoma of the heart, sometimes causing failure; (3) in the *eye*, nodular or cystic lesions; (4) in *bone*, osteoporosis, thickenings, osseous islands and cysts; (5) in the *brain*, cortical and subependymal nodules containing abnormal or neoplastic glia and neurons, which frequently calcify and are visible roentgenographically. The symptoms are seizures and usually mental deficiency. Treatment is limited to symptomatic relief of the seizures.

*Neurofibromatosis* or *von Recklinghausen's disease* is inherited as a nonsex-linked dominant. The lesions are sharply outlined *café-*

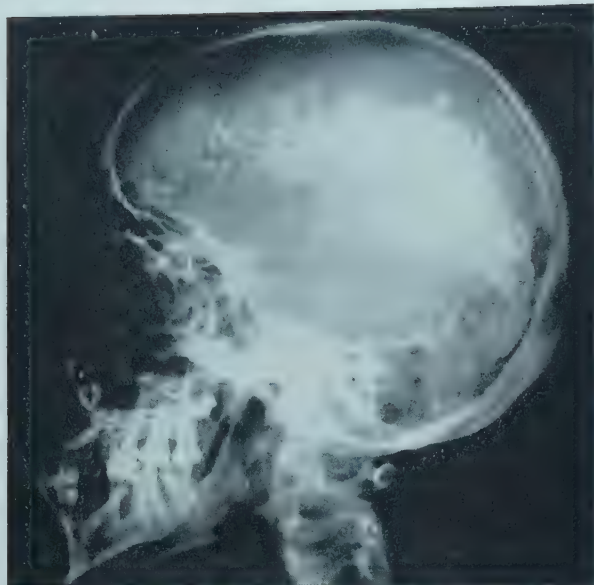


FIG. 318. Unusually extensive calcification in Sturge-Weber's disease.

*au-lait* areas on the skin, cutaneous and subcutaneous neurofibromas which are often pedunculated, neurofibromas along cranio-spinal nerves and roots, osteitis fibrosa cystica disseminata without hyperparathyroidism and multiple central nervous system lesions which are mostly nodules similar to those of tuberous sclerosis, or are located in the aqueduct or central canal. Localized gigantism may occur, and neurofibromas may undergo sarcomatous degeneration. Four related syndromes are (1) glioma of the optic chiasm with extensive *café-au-lait* marks; (2) pheochromocytoma, 10 per cent of which have associated *café-au-lait* patches or neurofibromas; (3) neurofibromatosis, cysts in the arachnoid, deepened middle cranial fossa, elevated sphenoidal wing and pulsating exophthalmos; (4) neurofibromatosis with generalized craniospinal nerve involvement and

muscular wasting resembling interstitial hypertrophic polyneuritis. Treatment is limited to removal of locally troublesome neurofibromas, particularly those on nerve roots, which compress the brain stem or cord.

*Encephalo-trigeminal angiomatosis* or *Sturge-Weber's syndrome* is genetically not completely understood. The distinctive feature is a large telangiectasis or port-wine stain, trigeminal in distribution, involving skin, scalp, skull and meninges. It is most common in the ophthalmic division, but may extend downward over the face. The typical, double-contoured opacities in the roentgenogram of the skull (Fig. 318) represent intracortical calcification and ferrugination secondary to circulatory slowing, and may appear within the first year of life. Congenital glaucoma and buphthalmos on the affected side are due to nevi in the choroid; there is crossed hemiparesis and hemianopsia, the vault on the affected side is small, and the skull is thick. Telangiectasis, especially on the upper extremity, may result in localized gigantism. The patients are often mentally defective and have lateralized seizures; sub-arachnoid hemorrhage occurs rarely. Local resection of the intracranial nevus or hemispherectomy may relieve seizures; glaucoma usually requires surgical treatment. Other treatment is symptomatic.

*Von Hippel-Lindau's disease* comprises hemangioma of the retina, hemangiomatous cysts of the cerebellum and spinal cord and cysts of the kidney, pancreas, liver and testes. It is hereditary, but its mode of inheritance is not clear. The retinal lesions cause retinal detachment and blindness; they require coagulation. Cerebellar cysts symptomatically resemble other cerebellar tumors and, though sometimes multiple, are usually operable.

## CONGENITAL VASCULAR LESIONS

These include saccular aneurysm, congenital arteriovenous fistulas, venous angiomas and telangiectases. Despite their congenital origin, clinical manifestations may appear at any time.

*Saccular aneurysms* in childhood arise from stumps of the arteries, which normally disappear in fetal life, or from thin spots at major arterial bifurcations; their incidence is high in coarctation of the aorta. Rarely

they are acquired, either as mycotic aneurysms or from other local arterial disease. Three fourths of cerebral aneurysms are located anteriorly on the circle of Willis, one fourth posteriorly or on the basilar system. The symptoms are (1) localized palsies due to pressure of the aneurysm (those of the third, the sixth and the ophthalmic division of the fifth cranial nerves being commonest) and (2) generalized manifestations due to rup-



ture, subarachnoid hemorrhage and local damage to the brain. Incomplete rupture is common. There are sudden, severe headache, vomiting, loss of consciousness and convulsions; the clinical findings include nuchal rigidity, fever, flame-shaped or subhyaloid retinal hemorrhages, altered consciousness and bloody cerebrospinal fluid under increased pressure. The initial mortality rate is about 40 per cent. Such leaks tend to recur and subsequent bleeding is more likely to dissect into the brain and produce hemiplegia. With each recurrence the mortality is about the same. Massive rupture is usually rapidly fatal.

*Congenital arteriovenous fistulas* are composed of one or several hypertrophied feeding arteries, a mass of communicating vessels often having aneurysmal dilatations, and a tangle of arterialized draining veins (Fig. 319). They may be anywhere in the brain or cord. Fistulas between the posterior cerebral arteries and the galenic system compress the aqueduct and may produce hydrocephalus; some form long tracts from the optic papilla to the midbrain. They usually become symptomatic in one of three ways: (1) migrainous headaches followed by lateralized seizures and, after several attacks, hemiparesis on the affected side; (2) evidences of subarachnoid hemorrhage or massive intracerebral bleeding which occurs without warning; and (3) increased intracranial pressure, due to enlargement of the malformation. Manifestations include a cranial systolic bruit, best heard over the eyeball and diminished by carotid compression, dilatation of scalp veins and often polycythemia.

*Venous angiomas* on the surface of the cortex or in the subependymal area do not produce a bruit and do not progress as do the arteriovenous fistulas. Their manifestations are usually focal seizures which appear early and are possibly due to thrombosis in the malformation. *Telangiectases* are most commonly found in the pons; thrombosis or rupture may occur.

The spinal cord may be involved by any of these malformations, though saccular aneurysm is rare. The manifestations are pain due to compression of the cord and subarachnoid hemorrhage. At times there is a cutaneous nevus over the cord defect.

**Diagnosis.** Spontaneous subarachnoid hem-



FIG. 319. Intracranial arteriovenous fistula and aneurysm. Note large feeding vessels.

orrhage or intracranial bleeding always suggests such a vascular lesion. Prior to rupture, aneurysm may be suspected from otherwise unexplained unilateral ocular palsies; arteriovenous fistulas, if a bruit is associated with lateralized signs and headache. Polycythemia with arteriovenous fistula may be intense, and, if the bruit is transmitted to the heart, congenital heart disease may be suspected. Brain tumor is the principal differential consideration and must usually be excluded by angiography.

**Treatment.** If a saccular aneurysm is demonstrated, it should be removed if it is in an operable site. Subarachnoid hemorrhage is treated with complete bed rest for four to six weeks, and sedation and lumbar puncture for relief of headache if it can be accomplished without a struggle. Hypothermia may be used at the onset. Some time in this period, usually in the second week, angiography should be done and operable lesions removed. Aneurysms on the left side or posteriorly placed are not usually favorable for operation; anterior, right-sided ones may be. Arteriovenous fistulas and venous angiomas are seldom operable; if they produce increased pressure, ligation of feeding arteries may be helpful for a time, but eventually these lesions fill from all the major arteries of the brain.

# EXPANDING LESIONS AND INCREASED INTRACRANIAL PRESSURE

The lesions to be discussed in this division, though of widely differing nature, all cause intracranial hypertension, and so are grouped together.

## INTRACRANIAL PRESSURE

**Physiologic and Anatomic Considerations.** The skull and vertebrae constitute a rigid case, vented to the outside only through the vascular system; they enclose the central nervous system and its membranes, a huge vascular bed, and cerebrospinal fluid under a pressure varying normally from 60 to 180 mm. of fluid, with an average of about 120 mm. The pressure of the cerebrospinal fluid is equated with the intracranial pressure. Volume change in any of the intracranial components is reflected in changed cerebrospinal fluid pressure, change in relative volumes of intracranial components, or both.

Cerebrospinal fluid is formed in the choroid plexuses of the four ventricles and in perivascular spaces of the brain and subarachnoid system by filtration and secretion. The process involves a two-way exchange at least of water and certain ions between blood and cerebrospinal fluid. The volume of this exchange is large, far exceeding the net formation of cerebrospinal fluid, which varies from 45 to 130 ml. of fluid per day in the ventricles alone. Water, most monovalent electrolytes and protein are added to cerebrospinal fluid in the ventricular and subarachnoid spaces; water is added more rapidly in the subarachnoid space, as protein probably is, but sodium and chloride excretion is mainly in the ventricles. The fluid is moved through the ventricles into the subarachnoid space and finally to the great absorptive bed of the arachnoidal villi of the dural sinuses, the spinal and some cranial nerve foramina.

Pressure and circulation of cerebrospinal fluid are the result of mechanical and vascular factors. Hydrostatic pressure alone accounts for about 50 mm. in the horizontal position; it falls in the head-up position and rises in the head-down position. The principal regulating factor is pressure in the cerebral vascular bed, the cerebrospinal fluid pressure rising or falling sharply with changes in arterial pressure, but accommodating smoothly

to slow changes. Sudden changes in venous pressures cause similar fluctuations. Additions to or removal of cerebrospinal fluid, though reflected in an immediate fall or rise, is rapidly compensated by a decrease or increase in cerebral venous volume.

Maintained increased intracranial pressure without a space-taking lesion represents a primary abnormality of one of the space-taking components within the skull, followed by secondary changes in the others. Formation of cerebrospinal fluid itself may be increased with meningitis, papilloma of the choroid plexus, benign increased intracranial pressure and "toxic hydrocephalus." Obstruction to the flow of cerebrospinal fluid causes a rise in pressure, but formation of fluid persists until pressures in excess of 700 mm. of fluid are attained. Increase in arterial pressure does not result in a persistent intracranial hypertension unless it is extreme or paroxysmal; the total blood flow remains constant. Venous drainage without the skull is so well provided with anastomoses that obstruction, unless close to the heart, causes little change in pressure; within the skull, sinus thrombosis, unless it is extensive or involves the posterior sagittal sinus or torcular or the usually larger right lateral sinus, may have no persisting effect at all.

Space-occupying lesions increase intracranial pressure by their own bulk and by compression on the ventricular system with production of obstructive hydrocephalus. They are compensated for initially by reduction in cerebrospinal fluid volume, but ultimately the vascular component suffers and the total intracranial blood flow is reduced. A significant increase of tissue fluid in edema of the brain causes similar effects.

**Clinical Features.** Headache, the most common complaint, is due more to distortion of pain-sensitive meninges and basal blood vessels than to pressure itself. Blunting of intellect, forgetfulness and, in the young child, fretfulness and irritability are common. Low-pitched, roaring or buzzing tinnitus, giddiness, vomiting, diplopia and sometimes visual loss due to extreme papilledema are additional manifestations.

The patient may be dull and given to rubbing the face or nose. Young children often



have separated sutures, a cracked-pot note on percussion and a nonlateralized bruit over the head. Focal neurologic signs, except for the nonlocalizing abducens palsy, are absent. Papilledema is almost the rule, unless extreme myopia or previous optic atrophy prevents it. The retinal veins become distended and pulsation diminishes; the disk reddens and its polar and nasal margins blur, and the cup disappears. Extreme elevations, hemorrhages, arterial narrowing, exudates, retinal folds and pallor are late severe signs which may develop rapidly on pre-existent swelling. Visual acuity and the visual fields, except for enlarged blind spots and later concentric constrictions, are well preserved; these distinguish papilledema from optic neuritis. Alterations in consciousness, projectile vomiting, bradycardia and bradypnea, systemic hypertension and seizures are late events brought about by brain stem distortion, ischemia and disturbed cortical circulation.

**Hernia Cerebri.** The intracranial cavity is incompletely divided into compartments by dural and osseous septa. The posterior fossa communicates with the anterior and middle fossae through the tentorial incisure; inferiorly, it communicates with the spinal thecal space through the foramen magnum. Shifts of supratentorial contents can occur toward either side across the midline, but, if sufficiently great, always cause herniation of brain into and through the tentorial notch. Shifts of infratentorial contents may herniate the cerebellar tonsils downward through the foramen magnum or the anterior lobe of the cerebellum upward through the notch. These shifts with resultant herniations of brain substance and pressure on neural and vascular structures are the basis for the signs and symptoms of severe increased intracranial pressure.

Increase of the supratentorial volume from whatever cause forces brain substance into the tentorial notch. Anteriorly the uncinate lobe and posteriorly the hippocampal gyrus are pushed downward to form a ring about the mesencephalon. The aqueduct and cerebrospinal fluid cisterns traversing the notch are compressed and obstruct the flow of fluid; the posterior cerebral arteries and the galenic veins are squeezed, causing hypoxia in the posterior thalamus and occipital lobes and venous congestion of the interior of the hemispheres. The sixth and third nerves are stretched and pinched, producing abducens, oculomotor or pupillary palsy (Fig. 320). Finally, the brain stem is itself deformed,

and hemorrhages occur into it. Acute anterior hernia of the uncinate lobe compresses the hypothalamus, damaging it by direct and vascular compression. Such brain stem hemorrhage and hypothalamic damage must in most cases be irreversible; small hernias need not be. It has been suggested that uncinate herniation during birth produces temporal lobe scarring which may later become epileptogenic.

Increase in the bulk of the posterior fossa contents forces cerebellar tonsils into the foramen magnum, causing meningeal irritation, nuchal rigidity and ultimately fatal medullary compression, or the anterior lobe may be forced upward through the tentorial notch, compressing the brain stem from above.

The development of shifts and hernias is affected by the rate of increase of intracranial pressure. Slowly increasing masses may, through reducing cerebrospinal fluid and vascular volume and producing local brain atrophy, cause little or no distortion or increased pressure. Slowly developing hernias may be well tolerated; at any time a sudden change in pressure, such as may follow a small hemorrhage into a pre-existing hematoma, the overhydration of an infant, an ill-advised lumbar puncture or even the increase in blood volume on coughing or straining, may convert a well tolerated hernia into a symptomatic or even a lethal one.

The cranial sutures of the infant and



FIG. 320. Tentorial herniation with acute subdural hematoma. A, Margin of herniated hippocampal gyrus; B, compressed oculomotor nerve; C, hemorrhages into brain stem.

young child are separable and provide some control of otherwise increasing pressure. This separation may occur suddenly, explaining sudden remissions in the history of expanding intracranial lesions of young children.

**Treatment.** Mildly or moderately increased pressure is an indication for immediate study, but not for immediate treatment. The best indicator of borderline cases is papilledema. If it is high grade with hemorrhages, arterial narrowing, pallor of disks, visual loss or recurrent transitory blurring or blacking out of vision, immediate intervention is necessary. Signs of herniation also indicate prompt treatment.

The procedures are all decompressions; most are surgical, and their choice depends on the specific lesion and the preference of the surgeon.

**Chemical decompression.** Hypertonic solutions, 50 per cent glucose or sucrose, 10 per cent sodium chloride solution or salt-poor serum albumin injected intravenously will cause immediate shrinkage of the brain through the osmotic effect on tissue fluid. The improvement is transitory and the procedure valuable *only for controlling herniation and reducing brain bulk at operation*; these should not be used to maintain patients with mass lesions, and they have no effect on edema of toxic or inflammatory origin. A 25 per cent solution of urea has a more maintained effect, and its use over prolonged times, renal function being adequate, may be valuable. Acetazolamide, though it may decrease cerebrospinal fluid formation and pressure, is not constant in its effect; administered parenterally, it may increase the pressure.

**Removal of cerebrospinal fluid.** When intracranial pressure is high, the volume of cerebrospinal fluid adequate and the danger of herniation slight, repeated lumbar punctures reduce discomfort and may prevent progression of papilledema. The procedure is dangerous with mass lesions and often so with severe cerebral edema. Its greatest value is in "benign increased intracranial pressure."

When danger of herniation exists, ventricular puncture or closed constant ventricular drainage may be used as semi-emergency procedures. These procedures require an adequate cerebrospinal fluid volume and hence are inapplicable for the small ventricles of a swollen brain. Tapping of ventricles under high pressure may produce disastrous hemorrhage from the subependymal veins or fatal upward herniation of the cerebellum in the presence of a posterior fossa lesion.

**Surgical decompression.** The ideal treatment is internal decompression by removal of the lesion. With inoperable lesions producing obstructive hydrocephalus, a suitable bypassing procedure, such as a variant of the Torkildsen tube, or ventriculostomy is indicated. Generalized swelling or increased pressure, otherwise uncontrollable, requires extensive decompression by large fronto-temporo-parietal flaps. When severe herniation has occurred at the tentorial notch or foramen magnum, immediate decompression of the medulla or section of the free margins of the tentorium may be lifesaving.

## BRAIN TUMOR

**Epidemiology.** Neoplasms of the central nervous system make up a large portion of tumors in childhood. There is no general predilection for race or sex. There is a definite age incidence; tumors are rare in infancy, but increase rapidly to a peak at the five- to six-year age level, probably owing to the high incidence of medulloblastoma at this age; thereafter a more uniform level is maintained through childhood.

**Pathology.** Two factors, histologic structure and location, require particular consideration. About 75 per cent of intracranial tumors in childhood are gliomas, of which two thirds are astrocytomas and medulloblastomas. Ependymomas, brain stem gliomas and gliomas of the hemispheres constitute another 15 per cent, and the remainder are craniopharyngiomas, meningiomas, sarcomas, pituitary adenomas, hamartomas, hemangiomas and dermoids. The acoustic neurinoma, meningioma and pituitary adenoma of adult life are rare, as are metastases from noncerebral neoplasms.

Sixty to 70 per cent of brain tumors in childhood are beneath the tentorium cerebri, in contrast to a reverse pattern in the adult. Of the supratentorial tumors, more than half are in the midline. Thus the gravity of the problem in children is pointed up by the facts that about three fourths of all brain tumors are incapable of being completely removed, owing to their cellular pattern; that about half of them are also difficult or impossible to remove, as a result of their location, and that others are so situated in relation to the brain stem or to the ventricular system that functional embarrassment of these structures is a possibility.

**Clinical Manifestations.** The general symptomatology of brain tumor in childhood is



that of increased intracranial pressure. *Vomiting* is seldom absent. It usually occurs in the morning around breakfast time, often without nausea, the child returning at once to his meal; rarely it is pernicious. Only late in the course does classic, projectile vomiting appear. *Headache* is less constant and is encountered in only about 70 per cent of cases, perhaps in part because the child's descriptive powers are limited. Like vomiting, it is more frequent when the child rises from sleep. It is usually bifrontal or suboccipital; suboccipital headache may herald tonsillar herniation and be accompanied or followed by stiff neck. Persistently lateralized headache, especially if accompanied by percussion tenderness, is more suggestive of abscess than tumor. *Diplopia* is usually due to abducens palsy, the sixth nerve or nerves being stretched by intracranial deformity; such palsy has no localizing value. It is responsible for most of the complaints of visual failure, since papilledema itself usually produces little disturbance in acuity. *Enlargement of the head* is most frequent in children under four years. *Mental change* is usually a matter of lethargy, indifference or some irritability, giving way to drowsiness, stupor, coma and death. *Convulsions* are rare, generally indicating tumor of a cerebral hemisphere. In late stages of cerebellar tumor, "cerebellar fits" with head retraction, rigidity and extension of limbs and disturbances of pulse and respiration indicate intermittent decerebration, probably by vascular disturbance of the mesencephalon; these signs are of ominous portent.

**Regional characteristics.** The common *infratentorial tumors* are cerebellar medulloblastoma, cerebellar astrocytoma, brain stem glioma and ependymoma.

The *medulloblastoma*, most common of all brain tumors of childhood, has its peak incidence around five years of age and occurs twice as often in boys as in girls. The tumor usually originates in the posterior vermis; of all tumors, it most frequently spreads to the meninges of the brain and cord. The course is rapid, early morning vomiting and unsteadiness of gait being soon followed by enlargement of the head. Most children have papilledema and sutural separation; the gait disturbance is one of disequilibrium. Except for hypotonia, cerebellar signs are slight in the limbs. Fifth or seventh cranial nerve palsies and pyramidal signs are evidence of compression or invasion of the brain stem; nystagmus is common. Obstructive hydrocephalus

is constant. Nuchal rigidity, cerebellar seizures and even cord signs are late events. Total removal is impossible; the best treatment is decompression and roentgen therapy. Survival is usually less than one year.

The *cerebellar astrocytoma* has a peak incidence around eight years of age and a slight predilection for the female. The tumor usually begins close to the midline and is often cystic with a tough, gliosed wall enclosing a mural nodule and containing a yellow, protein-rich fluid. Occasionally the mass invades the cerebellar peduncles or brain stem. The course is slower, and lateralizing cerebellar signs, hypotonia, ataxia, diminished reflexes, rebound phenomenon and nystagmus are usually demonstrable. Headache and vomiting are later and less persistent manifestations than with medulloblastoma; papilledema is too often allowed to proceed to irreversible optic atrophy. Total surgical removal is usually possible, and a complete cure is attainable. Roentgen therapy is not very effective and should be used only for tumors which have infiltrated too extensively to permit removal.

*Brain stem gliomas* account for 8 to 10 per cent of brain tumors in children; there is no sex preference; the peak incidence is about the seventh year of age, but no age except perhaps infancy is exempt. The common syndrome is one of multiple cranial nerve palsies, particularly of the seventh, sixth, ninth and tenth nerves and of the sensory portion of the fifth nerve combined with ataxia of the trunk, mild pyramidal signs usually without spasticity, little sensory loss and vomiting without other evidence of increased pressure. Cerebrospinal fluid pressure is elevated only late, and the fluid, which is usually normal, infrequently contains 5 to 20 lymphocytes and a slight excess of protein. Pneumoencephalography demonstrates backward and upward shift of the floor of the fourth ventricle 3.5 to 3.8 cm. beyond the clivus, encroachment on pontine cisterns and some ventricular dilatation. Hypersomnia and hyperthermia are evidence of extension into the upper brain stem and hypothalamic area. The tumor usually begins in the deep strata of the pons. Such tumors are inoperable, but the course is sometimes slow, and roentgen therapy may permit a surprisingly long survival in fair condition.

*Ependymoma* in childhood has no sex or age predilection. The initial symptom is almost always vomiting followed by headache, unsteady gait, enlarging head and pyramidal and cerebellar signs. The clinical pattern is

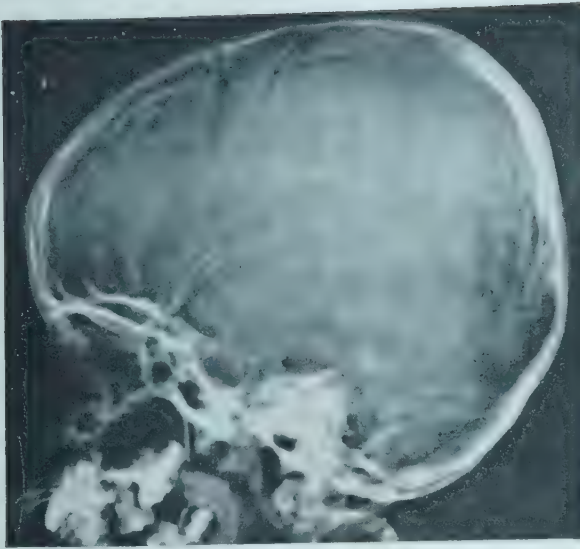


FIG. 321. Craniopharyngioma in a boy of 8 years. Note fluffy suprasellar calcification, enlarged sella turcica, digital marking of skull, and early sutural separation.

variable, since the tumor invades and exerts pressures in widely differing directions. Regression of symptoms is also often a feature. Flecklike calcifications evident on the roentgenogram and internal hydrocephalus are common. The tumor is best treated by incomplete internal compression and roentgen therapy.

The common *supratentorial tumors* are those of the suprasellar and chiasmatic regions, of the thalamus and posterior third ventricle and of the hemispheres.

*Tumors of the suprasellar and chiasmatic regions* include craniopharyngioma and glioma of the optic chiasm. The *craniopharyngioma*, or suprasellar cyst, occurs in late childhood and through adult life. It is a solid tumor, at times with a cyst above it. The symptoms are those of increasing pressure due to distortion of the foramina of Monro and third ventricle, of compression of the optic chiasm, causing bitemporal field defects and later optic atrophy, and of pressure on the pituitary and hypothalamus, leading to arrest of growth and osseous development, fatigability, diabetes insipidus and disturbances of the sleep rhythm. Any one of these manifestations may bring the child to the physician, but since the visual and the hypophysis-hypothalamic changes advance slowly, headache and vomiting are the usual chief complaints. Hypothalamic attacks of semistupor, fever, cardiac irregularities and miosis may occur. The child usually appears less than his stated age, his head somewhat large.

The roentgenogram of the skull reveals separated sutures, very often suprasellar calcification and some sellar deformity (Fig. 321). Hypoglycemia, a flat glucose tolerance curve, diabetes insipidus, a high eosinophil count, lowered excretion of 17-ketosteroids and hypotension are common. The optic disks may be elevated, atrophic or normal. Surgical removal of the tumor in toto is almost impossible. The usual procedure is drainage of the cyst and removal of the cyst wall and as much of the solid tumor as is accessible. Preoperative and postoperative corticosteroids greatly reduce operative mortality; postoperative diabetes insipidus is frequent. Roentgen therapy will often control the solid portion of the tumor for years.

*Glioma of the optic chiasm* initially causes visual disturbances; later there are manifestations of increased pressure and of hypothalamic involvement. It is often accompanied by extensive cutaneous *café-au-lait* spots. Optic atrophy is more frequent than papilledema. Excavation beneath the anterior clinoids is a common roentgen finding. The tumor is inoperable; roentgen therapy is indicated.

*Tumors of the posterior third ventricle* are pinealomas, gliomas and hamartomas. All produce obstruction early in the course with signs of increased pressure. The pineal neoplasms compress the mesencephalon from above and cause pupillary dilatation and failure of upward conjugate gaze, the syndrome of Parinaud. They may produce precocious puberty in the male by pressure in the hypothalamic area. Gliomas in the thalamus or hypothalamus may cause similar hypothalamic disturbance, together with increased pressure and frequently hemiplegia. They are best treated by draining the ventricle with by-passing tubes and by radiation.

*Tumors of the hemispheres* are gliomas, ependymomas of the ventricle and sometimes sarcomas. Clinical manifestations are hemiplegia, seizures and those of increasing pressure. They are frequently enormous in size. Treatment, surgically or by radiation, is unsatisfactory in almost all cases.

**Treatment.** In general, treatment is unsatisfactory. Complete cure, for practical purposes, is restricted to the cystic cerebellar astrocytoma, and thus to only about 15 per cent of children with intracranial neoplasms. Death is hastened by intervention in about an equal percentage of instances. Even when complete cure is impossible, relief of symptoms and return to enjoyable life for months



or years is often possible, and should never be denied a child. An attitude of pessimism and nihilism breeds inadequate study of a case and leads in turn to death or permanent disability from treatable lesions. When there is a reasonable likelihood of an expanding lesion, diagnostic study should not cease until the lesion is located, its nature determined beyond reasonable doubt and the appropriate therapy decided.

Definitive study of such cases is a matter for experienced neurosurgeons and neurologists; the responsibilities are great, and the diagnostic procedures themselves are often major operations. The pediatrician performs two roles: the vital one of suspecting the lesion and initiating study, and support and maintenance of a critically ill child. Careful correction of water and electrolyte disturbances, corticosteroid or corticotropin therapy during operations about the hypothalamus, restoration of nutrition and maintenance of the patient's and parents' morale are responsibilities he must share.

## EXTRACEREBRAL ACCUMULATIONS OF FLUID

Subdural hematoma is an accumulation of blood, its degradation products and fluid within the subdural space. It may be acute, subacute or chronic and usually results from direct trauma to the head.

### CHRONIC SUBDURAL HEMATOMA OF INFANCY

**Etiology.** Direct or transmitted trauma to the head at any age may produce bleeding into the subdural space. In the older child or in the adult a positive history of trauma is elicitable in 80 per cent of cases; in infants relationship to trauma is less clear. Molding and other trauma of the head at birth are considered possible causes, but supportive evidence is inconclusive. The lesion is not common in premature infants, in whom the possibility of molding trauma to the head is very great. Scurvy and purpuric states increase the hazard; in hemophilia subdural hematoma is rare. Deliberate violence is probably more often the cause than is suspected.

**Epidemiology.** More common in male than in female infants, subdural hematoma is rare in the newborn and rarely demonstrated in the stillborn. The incidence rises sharply in the second month of life to a peak by about four months, followed by a rather sharp fall and virtual disappearance by fourteen to six-

teen months of age. Ill-cared for, unwanted infants, being more subject to trauma, are more frequently affected, and the illness is rarer on private than on ward services.

**Pathology.** The subdural space is occupied by a sac which usually extends frontally and laterally over the hemispheres; it is bilateral in about 80 per cent of cases. The dural wall of the sac is thicker, heavily vascularized and fused with the dura mater; the arachnoid wall is thinner, less vascularized and less firmly attached to the meninx. This sac contains a variable mixture of fresh and old blood and xanthochromic fluid; the protein content is high, and there are many white cells. The brain beneath is compressed and its leptomeninx often thickened. In long-standing cases the cortex shows considerable convolutional atrophy.

**Pathogenesis.** At the time of trauma delicate bridging subdural veins, most numerous along the falx (Fig. 322), are torn. Small hemorrhages occur in the subdural space. Originally insignificant in amount, this blood breaks down, and imbibition of fluid occurs across the arachnoid membrane. The break-

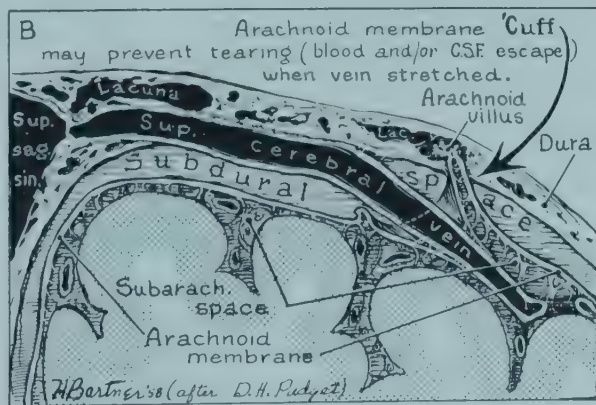
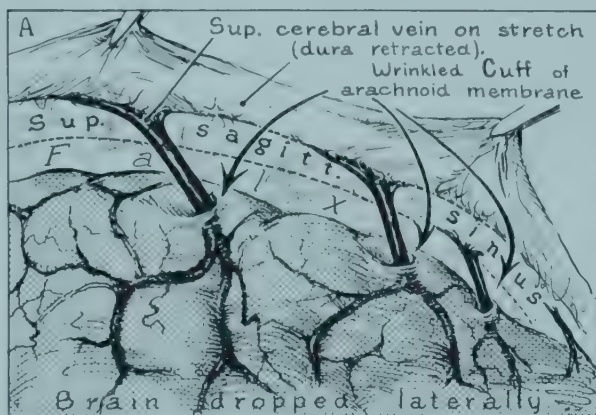


FIG. 322. Relation of subdural veins to dura mater, dural sinuses, arachnoidal granulations and arachnoid membrane. Tearing of these veins may cause subdural hematoma. (Preparations of D. H. Padgett.)

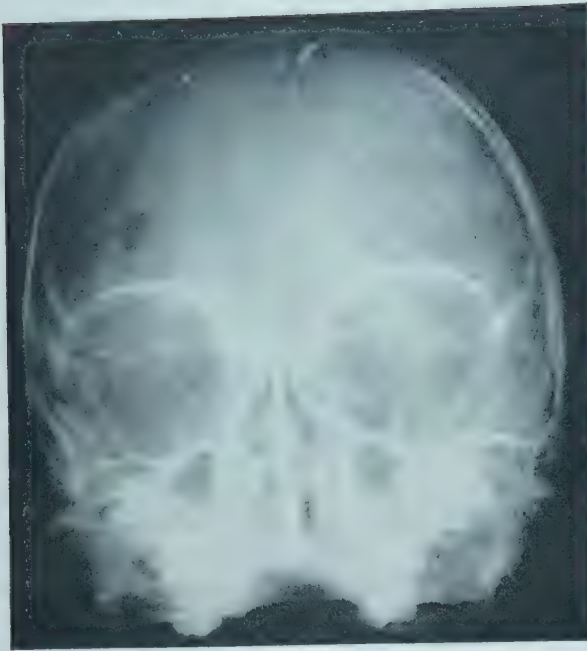


FIG. 323. Calcified subdural membrane in a microcephalic idiot. Right subdural hematoma drained in infancy (note trephine), left side not explored. Calcified membrane discovered years later.

down products of blood stimulate the growth of connective tissue and capillaries, largely from the dura. As fluid increases the width of the subdural space, these capillaries are torn, further hemorrhage occurs, and the lesion enlarges. If unrelieved, the mass expands the skull, ultimately causing cerebral atrophy or death from compression and herniation. At any point the lesion may spontaneously arrest, only to be discovered as a calcified membrane over the brain in older defective patients. Additional trauma may increase symptoms due to an already existing sac. The formation of such sacs occurs more readily over a previously atrophic brain, the *hematoma ex vacuo*.

**Clinical Manifestations.** The most characteristic ones are a restless irritability and failure to thrive. There is a history of convulsions and vomiting in half the cases and of recurrent fever, drowsiness and birth or post-natal trauma in descending order. On admission, more than half the infants have fever; the reflexes are hyperactive, but frank paralysis and hemiplegia are uncommon. About half of the infants have bulging or tense fontanels, and the head is measurably enlarged, with a square, boxlike expansion of the vault in about one third. The scalp is tight and glossy, and the scalp veins are dilated. Almost 90 per cent of the infants ultimately show retinal hemorrhages, frequently subhyaloid; this may be a late change and is often absent at the

time the diagnosis is made. Strabismus, pupillary inequality and ocular palsies are infrequent and of little localizing value.

**Laboratory Data.** One third to one half of the infants have an anemia of blood loss and a low serum protein level, each of which is progressive if untreated. Sutural separation is demonstrable roentgenographically, but fractures are rare. Multiple fractures of long bones suggest trauma as a cause of the subdural bleeding. The electroencephalogram may reveal reduction in voltage over very large hematomas; minor asymmetries, spikes or slowings are evidence only of brain injury. The cerebrospinal fluid is often under increased pressure and often contains red blood cells, a slight excess of white cells and increased protein. The definitive diagnostic procedure is a carefully performed subdural puncture (see p. 1071); fluid of any sort in excess of a milliliter or two is an abnormal finding.

**Differential Diagnosis.** Subdural hematoma must be distinguished from hydrocephalus, chronic meningitis and brain tumor, and from other fluid accumulations without the brain, notably a subdural effusion complicating meningitis.

**Treatment.** The basis of treatment for subdural hematoma at any age is removal of the abnormal fluid with as much of its surrounding membrane as possible. An immediate surgical approach results in a high fatality rate and should not be considered. Reasonably good end results can be expected from a regimen combining subdural drainage with craniotomy at a later date, if this proves necessary.

No more than a total of 30 ml. of fluid should be removed from the two sides in the initial or subsequent daily aspirations. The hemoglobin and serum protein levels should be restored by transfusion, and any infection should be treated. The infant's condition usually improves rapidly. Frequently the hematomas reduce in size and may disappear from tapping alone. If after eight to ten days of aspiration no real reduction of fluid has occurred, burr holes are placed over the vertex, and the sacs are washed clean by catheter. The fluid then often ceases to accumulate. If this occurs, it is the practice in some clinics to stop at this point. In others small flap craniotomies are performed, and as much of the adherent membrane and contained clot as possible is removed. Even after craniotomy, fluid may continue to accumulate for a time, and aspiration may still be neces-



sary, since all the membrane can seldom be removed. With this regimen mortality may be kept well below 5 per cent with complete recovery and without mental limitation in better than 50 per cent of the cases. The best prognostic sign is the condition of the brain at the time of operation; if severe atrophy exists, the prognosis is poor.

### SUBDURAL EFFUSION

In the course of pyogenic meningitis, accumulations of protein-rich, xanthochromic, sometimes encapsulated fluid occur in the subdural space. These are thought to be due to an effusion of fluid across an inflamed arachnoid or from thrombosed subdural veins into the subdural space, where the exudate stimulates encapsulation and grows by imbibition and capillary rupture, similar to a subdural hematoma. Curiously, this striking lesion was not noted in the preantibiotic era; its exact pathogenesis is still uncertain.

The lesion can occur at any age and with any of the pyogenic meningitides. *Hemophilus influenzae* is responsible for more than 50 per cent of the cases, and mainly in infants of three to eight months of age. Effusions should be suspected in chronic pyogenic meningitis, or in any treated meningitis when the fever fails to abate after three or four days of adequate therapy, when convulsions or neurologic signs appear, when cerebrospinal cultures remain positive or when the infant vomits or fails to thrive. The treatment is that of subdural hematoma, except that effusions less often have well developed membranes and more often respond to daily tapping.

### ACUTE SUBDURAL HEMATOMA, SUBDURAL HYGROMA AND CHRONIC SUBDURAL HEMATOMA IN OLDER CHILDREN

*Subdural bleeding* can be expected in most instances of severe head injury; if the condition of such a patient is worsening steadily, with deepening stupor and advancing hemiparesis, exploration and aspiration through burr holes are indicated as an emergency measure.

*Subdural hygroma*, in the strictest sense, is an accumulation of cerebrospinal fluid in the subdural space, to which it gets ingress through a valvelike rent in the arachnoid. It is always traumatic, and not clinically separable from epidural or subdural hematoma. It is rare, and many fluid accumulations so diagnosed are really effusions or leptomenin-

geal cysts containing fluid with an unusually low protein content.

*Chronic subdural hematoma in older children* is rare; the clinical syndrome is that of headache, mild hemiparesis and papilledema. At times there are vomiting and/or seizures. Visual field defects are rare; abducens palsy may appear. Angiography is often diagnostic, but the definitive procedure is exploration through a burr hole followed by appropriate craniotomy.

### EPIDURAL HEMATOMA

This is an accumulation of blood between dura and bone. The cause is trauma; the lesion accounts for about 2 per cent of pediatric hospital admissions for head trauma. One half of the cases occur before two years of age. In the older child or adult the classic course is that of head trauma with brief loss of consciousness followed in turn by a lucid interval and then by deepening stupor, homolateral pupillary dilatation, contralateral hemiparesis, slowing pulse and respiration, rising blood pressure and death within the ensuing hours. The bleeding is arterial, usually as a result of a linear fracture which lacerates the middle meningeal vessels. In the child under two years of age, loss of consciousness is less frequent, the fracture usually diastatic rather than linear, and the bleeding venous as well as arterial. The course is often slower, and the hematoma may become large enough to produce extensive blood loss, and the symptoms are those of shock rather than increasing pressure and brain stem compression.

The common signs at any age are lacerations of the scalp, drowsiness, stupor and/or coma. Pupillary dilatation or advancing oculomotor palsy is almost always homolateral, rarely contralateral; hemiparesis is almost always contralateral, rarely homolateral. The temperature is often subnormal and the pulse pressure wide. In the early stages the pupillary and hemiparetic signs, as well as the slowing pulse and respiration, may be inconspicuous if the child is kept roused by examinations. Careful, quiet observation in a private room, with regular frequent recordings of pulse and respiration, is better than repeated vigorous examination.

This condition is a surgical emergency, and when its existence is considered likely, operation should not be delayed. Roentgenographic examination is valuable if the child's condition permits; other studies and especially

lumbar puncture are best avoided. Since brisk hemorrhage is often encountered, a blood transfusion should be started before or be immediately available during operation. Survival and functional recovery depend on early, successful evacuation of the clot and arrest of bleeding.

## BRAIN ABSCESS

Focal sepsis in the brain in childhood generally occurs (1) by extension from infection in the mastoid, paranasal sinuses, scalp or skull; (2) metastatically from bronchopulmonary, pleural, cardiac or other remote sources; (3) as a complication of congenital cyanotic heart disease or pulmonary arteriovenous fistulas; or (4) rarely from penetrating wounds. In a small percentage of instances no source is found. Almost any pathogen can be responsible.

Infection from sources about the head is by direct extension or along thrombosed vessels and usually involves immediately adjacent cerebral tissue. Hematogenous spread localizes at the junction of the cortex and white matter, with slight preference for the left hemisphere. A focus of septic encephalitis is established which may enlarge rapidly and produce paralysis, coma and death. More often the lesion becomes walled off, and an abscess forms. As it expands, there is edema of the surrounding area. Extension is toward the ventricle, and secondary abscesses in the wall are common. Rupture usually occurs into the ventricle; some abscesses become sterile; the wall calcifies, and the lesion becomes static.

There are three stages. The first is characterized by focal encephalitis. The patient, already ill with a primary infection, has an elevation of temperature, is drowsy and complains of headache. He may have a convulsion, or there may be meningeal signs. Improvement occurs in a day or two, especially with antibiotic therapy. The second stage, during which the abscess is enlarging, is a relatively quiet one. For days or weeks the child is only vaguely ill, listless, occasionally feverish to 100° or 101° F., and complains of some headache, usually frontal. Neurologic signs are slight, unnoticed or absent. Eventually the tempo of illness increases, headache is worse and more localized and a seizure often occurs. Focal signs appear, the optic disks blur and the cranial sutures may separate. At any moment the child may pass into the third stage, of decompensated increased

intracranial pressure with neurologic and cardiorespiratory signs of brain stem compression, or the abscess may rupture and be evidenced by high fever, meningeal signs, seizures and a decerebrate state.

Clinical signs depend on increased pressure and on the locus of the abscess. Drowsiness, headache, vomiting, sixth nerve palsies and papilledema are early manifestations. Since most abscesses are solitary and most are supratentorial, the common localizing signs are hemiparesis, visual field defects and aphasia. The frontal abscess is notably silent; lethargy and dullness are often the only signs. A cerebellar abscess produces lateralized hypotonia, ataxia, adiadochokinesis, coarse nystagmus mainly toward the side of the abscess and skew deviations. Percussion tenderness over the abscess is one of the most valuable of all localizing signs.

Leukocytosis, present during the first stage, is absent during the second one and becomes marked only with rupture of the abscess. Anemia of infection is usually present. Roentgenograms of the skull show only sutural separation or sellar demineralization; films of the chest, long bones, sinuses or mastoids may reveal an unsuspected infective focus. The cerebrospinal fluid in the first stage is marked by pleocytosis and elevated pressure, but the fluid is sterile; in the second stage, pressure and protein content are constantly elevated, and there may be a few cells. In the third stage, pressure, protein and cells increase; high pleocytosis indicates leakage or rupture, in which case pathogens may be cultured from the fluid. The electroencephalogram is a valuable tool, since the large zone of edema often produces lateralized and sometimes sharply localized delta waves; serial electroencephalograms are of diagnostic value in the differential diagnosis.

Four to 8 per cent of all patients with cyanotic heart disease or pulmonary arteriovenous fistulas suffer brain abscess. The etiology of these abscesses is not clear. They do not arise from bacterial endocarditis and a specific focus is rarely demonstrated. Relief of cyanosis by anastomotic procedures does not protect against cerebral abscess, which occurs in any form of cyanotic congenital heart disease. Clinically, diagnosis is difficult because a definite first stage is absent, and the symptoms of headache, irritability, recurrent fever and even sudden onset of localizing signs or hemiplegia are common in cyanotic heart disease. Only constant vigilance will detect the abscesses. Since these



children tolerate prolonged anesthesia poorly, repeated aspiration is the best means of treatment.

**Treatment.** Adequate antibiotic therapy probably often heals incipient abscesses during the first stage. An established abscess must be treated surgically. Two methods are used: In one the abscess is tapped through a burr hole, aspirated and thorium dioxide instilled to outline the cavity. Repeated aspirations are performed under roentgen guidance, and antibiotic therapy is continued until the abscess disappears. In the other the initial treatment is the same, but after some days the abscess is resected in toto. The purpose is to ensure cure and to minimize the incidence of seizures; the evidence for the latter is questionable. The writer favors the first method because it is simpler and less likely to leave neurologic residuals.

Case fatality rates average about 25 per cent, a rate that is far too high. Survivors have seizures in about 45 per cent of instances and hence should be maintained on anti-convulsant therapy for at least five years.

## INCREASED INTRACRANIAL PRESSURE

### WITHOUT MASS LESIONS

#### *DURAL SINUS THROMBOSIS*

Occlusion of dural sinuses results from neighboring or remote infection, sometimes from polycythemia or hemoconcentration, anemia, blood dyscrasias, slowing of circulation, trauma or tumor invasion.

The signs and symptoms are (1) those of the primary condition, such as chills, fever, leukocytosis, otitis media and marasmic state; (2) neurologic ones stemming from the region of the brain affected by venous stasis, edema or infarction; and (3) manifestations of increased intracranial pressure. Any or all may be present, and, conversely, all may be absent and the occluded sinus discovered incidentally.

**Superior Sagittal Sinus.** The occlusion is most often nonseptic and occurs as a rule in dehydrated, marasmic or toxic infants. The onset is abrupt; convulsions and single, or sometimes double, hemiplegia indicate extension of the thrombus into the superficial cortical veins. Stupor, head retraction, bulging fontanel, dilated scalp veins, papilledema and enlargement of the head are signs of obstruction of the sinus and of increased pressure. The cerebrospinal fluid often contains some red and white blood cells. The ventricles are

initially compressed by congestion and edema, but later enlarge, and the cortex atrophies. Incomplete occlusion with lateralizing neurologic signs and less marked increase of intracranial pressure is more common than complete occlusion and is less serious. This condition must be distinguished from the stupor, convulsions and rigidity of severe hypernatremia.

**Sinus Rectus and Galenic Vein.** Occlusion here is either septic or nonseptic. Sudden onset of coma, generalized convulsions and high intracranial pressure are accompanied by initial flaccidity rapidly changing to decerebrate rigidity. The cerebrospinal fluid is grossly bloody, and the child soon dies.

**Cavernous Sinus.** Thrombosis of this sinus is almost always septic, being secondary to infections about the orbit, face, pharynx, sphenoidal sinus or the petrous apex. The chills, fever, headache and leukocytosis of the severe infection are accompanied by drowsiness, but rarely by seizures or stupor. Edema and chemosis of the eyelids, protrusion of the eyeball, thrombosis of retinal veins and later low grade papilledema are associated with a decrease in vision and with extraocular palsies. Extension across the circular sinus to involve the other eye, meningeal signs and pleocytosis of the cerebrospinal fluid may occur; there is usually increased intracranial pressure.

**Lateral Sinus Thrombosis.** Evidence of otitis media, acute or chronic, is almost always present. The onset may be abrupt with septic fever, chills, leukocytosis and a positive blood culture, or it may be insidious with only signs of increasing intracranial pressure. If the onset is abrupt, contralateral facial weakness, sometimes contralateral seizures and rarely hemiparesis indicate spread of the thrombosis upward through the cortical veins across the hemisphere. Paralysis of the ninth, tenth and eleventh cranial nerves is due to thrombosis of the jugular vein, which may become palpable in the neck. There is headache, drowsiness and papilledema in about half of the cases. Differentiation from brain abscess may require ventriculography.

**Treatment of Dural Sinus Thrombosis.** Any infection must be appropriately and vigorously treated with antibiotics and surgical drainage when indicated. Anticoagulants to limit spread of the thrombosis are of doubtful value. Increased pressure, once the diagnosis is established, is best managed by repeated lumbar punctures, but if vision is threatened, subtemporal decompression may

be used. Surgical removal of the thrombus is seldom done since the clots recanalize rapidly.

### BENIGN INCREASED INTRACRANIAL PRESSURE

(TOXIC HYDROCEPHALUS, PSEUDOTUMOR CEREBRI, QUINCKE'S OR SEROUS MENINGITIS)

This term is used to identify a syndrome resulting from increased intracranial pressure and manifested by headache, papilledema, sixth nerve palsies, sometimes vomiting and absence of other neurologic signs. Though most common in young adult women, it occurs in childhood. Some cases have been identified as "silent" lateral or longitudinal sinus thrombosis, but others seem to follow various infections or slight head injuries, and the actual etiology remains obscure. The definitive diagnostic procedure is ventriculography, which reveals small, symmetrical, unshifted ventricles (Fig. 324). Treatment is by repeated lumbar puncture, with surgical decompression if vision is threatened; attempts at chemical decompression, as with acetazolamide have not been impressive. Elevated intracranial pressure may persist for months.

### HYDROCEPHALUS

Hydrocephalus is an abnormal increase in

cerebrospinal fluid within the intracranial cavity. It is not synonymous with an enlarged head, since the latter may be due to subdural hematoma or macrocephaly, whereas hydrocephalus may or may not notably enlarge the head.

A lesion which obstructs the flow of cerebrospinal fluid anywhere from point of secretion to point of absorption is the cause in almost all cases. Overproduction of cerebrospinal fluid by a tumor of the choroid plexus is a rare cause; dural sinus thrombosis seldom causes maintained hydrocephalus. The lesions vary widely; about one third are congenital defects, such as atresia or forking of the aqueduct, the Arnold-Chiari malformation, atresia of the foramina of Luschka and Magendie, occipital encephalocele, agenesis of the corpus callosum and failure of development of subarachnoid cisterns. Inflammatory lesions, either meningitis or reaction to bleeding from birth trauma, cause aqueductal gliosis and obliteration of subarachnoid systems. Rarely, meningeal deposits, lipid-laden phagocytes in gargoyism or multiple metastases are responsible. Tumors, abscess and angiomatous malformations are other causes.

Much of the pathogenesis is simple mechanics. The fluid system dilates above the point of obstruction; e.g., obstruction at Monro's foramen dilates one or both lateral ventricles, aqueductal lesions, the third and lateral ventricles; and obstruction at the fourth ventricular foramen or in the subarachnoid space enlarges all four. The obstruction may be partial, intermittent or complete; the symptoms may be rapid or slow and steadily advancing or remittent. Atrophy of the choroid plexuses is a late event, and fluid continues to be formed in their absence. Fenestrations may develop in the septum pellucidum, the membranous walls of ventricles or other points, and spontaneous bypassing of obstructed points occurs.

Though hydrocephalus is sometimes recognized before birth, most cases become manifest in the first few weeks or months of life. The fontanels widen and are moderately tense, and the skull enlarges in all diameters. The brow bulges; the sclera becomes visible above the iris, owing rather to upper lid retraction than to pressure on the orbit; the scalp becomes shiny, and scalp veins dilate. Failure of upward gaze, strabismus, hyperactive reflexes, mild diplegia and optic atrophy are additional manifestations; papilledema in the infant is rare. Irritability, failure to thrive

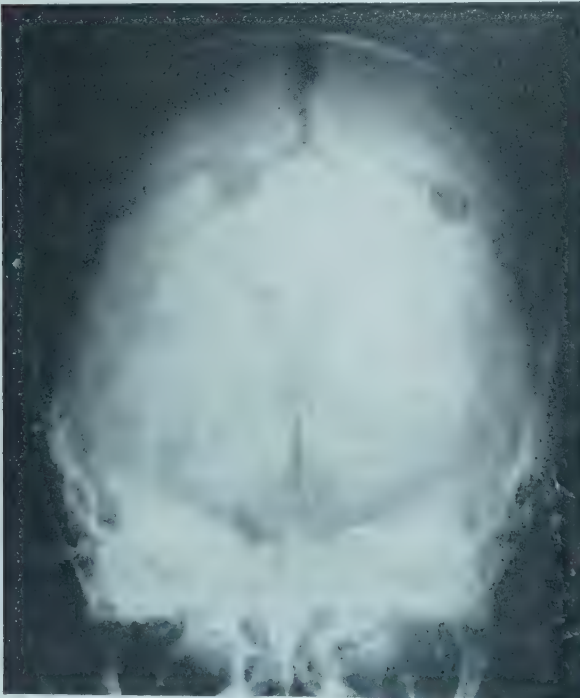


FIG. 324. Benign increased intracranial pressure or "pseudotumor" in a boy of 4 years. Sutures are separated, but ventricles are small and unshifted.



and a high-pitched cry are common. When the onset is later, or the progress less rapid, the head may enlarge much more in one plane than another, producing brachycephaly or scaphocephaly. The disproportion of the skull may help to locate the obstruction, a shallow posterior fossa suggesting aqueductal or third ventricular lesions.

If the brain is not seriously malformed, mental function remains surprisingly good; children with paper-thin cortex often have intelligence quotients within the normal range. Motor function is generally retarded, both by the weight of the head and by the actual neurologic impairment present.

The steps in management of hydrocephalus are as follows: (1) The existence of hydrocephalus must be established and its advancement proved by serial head measurement. (2) Surgically remedial lesions, particularly subdural hematoma, must be excluded. (3) The point of obstruction must be located and the child evaluated for a bypassing operation. Contraindications to operation are as follows: age under six months; cerebral cortex less than 1 cm. as shown by air study; severe mental retardation or other congenital defects, and especially absence of proved progression of the hydrocephalus. The obstructing point is located by studying the flow and absorption of phenolsulfonphthalein after its injection into the lateral ventricle during ventriculography along with a small bubble of air (large volumes of injected air are not well tolerated), and sometimes by dural sinography.

*Treatment* is not generally satisfactory. Two approaches have been attempted: (1) Reduced production of cerebrospinal fluid by plexectomy, fluid restriction, blood letting and the like; these procedures are now largely abandoned. Acetazolamide, orally in large doses, may be effective. (2) The bypass of points of obstruction with shunting of the cerebrospinal fluid to the arachnoid villi or an artificial point of absorption or excretion. In older children with previously adequate subarachnoid systems, third ventricular or aqueductal obstruction responds well to ventriculocisternostomy, either through the lamina terminalis or ambient cistern or by passing a rubber tube from the lateral ventricle to the cisterna magna. In young infants, or when the subarachnoid spaces are obliterated or incompetent, the fluid must be (1) conveyed to a new point of absorption—the lesser peritoneal space is the only satisfactory one, and that for a few months at best—or (2) conveyed from the spinal theca or ventricle to

a ureter, after nephrectomy. The latter shunt is well maintained, but in small infants the loss of cerebrospinal fluid via the urine results in a negative sodium balance and 2 to 3 gm. of sodium chloride must be given daily. Spinal ureterostomy is unaffected by growth; with ventriculo-ureterostomy, longer tubes become necessary as the child grows.

## HYDRANENCEPHALY

In this condition the cerebral cortex, except for the inferior temporal and mesial occipital lobes, is represented only by a membrane filled with clear fluid. The basal ganglia and thalamus are present, the cerebellum and brain stem are well preserved, and the aqueduct is generally obliterated. The size of the head at birth is normal. There are two theories of pathogenesis: (1) It may represent obstructive hydrocephalus in utero, the intrauterine pressure preventing enlargement of the head with resulting cortical atrophy. (2) The internal carotid arteries may be deficient or compressed, allowing only those parts of the brain supplied by the basilar artery to develop. Neither theory is proved, and the condition has been seen associated with cytomegalic inclusion disease. The infant is well formed, but obviously defective and blind, and may have poor temperature regulation. Diagnosis is readily established by transillumination of the head in a dark room (Fig. 325). There is no treatment.



FIG. 325. Hydranencephaly shown by transillumination.

## DEGENERATIVE DISEASES

The outstanding features of the degenerative disorders are functional incapacitation and/or progressive loss of nervous elements. Their etiology is not established, their clinical manifestations are so variable that exact diagnosis during life is difficult, and a satisfactory classification is almost impossible. The following is one of convenience only:

### *Lipidoses, Leukodystrophies and Progressive Encephalomyelopathies*

- A. Cerebromacular degeneration—amaurotic idiocy
- B. Cerebral von Gierke's disease
- C. Demyelinating leukodystrophies
- D. Progressive encephalomyelopathies (Schilder's disease), disseminated sclerosis and neuromyelitis optica

### *Degenerative Disease Involving Specific Fiber Tracts and/or Neural Groups*

- A. Spinocerebellar ataxias—Friedreich's disease and other spinocerebellar forms
- B. Pyramidal degenerations—familial progressive spastic paraplegia
- C. Extrapyramidal disease—dystonia musculorum deformans, Huntington's chorea, hepatolenticular degeneration
- D. Motor neuron disease—Werdnig-Hoffmann's spinal atrophy; the amyotonia congenita syndrome
- E. Neuroradicular disease—peroneal muscular atrophy
- F. Leber's familial optic atrophy

### *Degenerative Diseases of Uncertain Classification*

- A. Cerebral degeneration with myoclonus
- B. Heller's infantile dementia

## LIPIDOSES AND LEUKODYSTROPHIES

Lipidoses and leukodystrophies represent primary disorders in the metabolism of sphingolipids. One or another of these compounds, accumulating in abnormal amounts in the brain, involves the cells and gray matter in cerebromacular degenerations and the white matter with demyelination in the leukodystrophies. Whether this deranged metabolism represents overproduction, underutilization or accumulation of products of degeneration is not known.

### CEREBROMACULAR DEGENERATION

Amaurotic idiocy, or Tay-Sachs disease, is the commonest of the cerebromacular degenerations. It is a degenerative disease of in-

fancy, marked by progressive blindness, macular degeneration, spasticity, seizures, wasting, dementia and death. The lipid involved is ganglioside; one of its components, neuraminic acid, is greatly increased in the brain. The brain is firm and somewhat atrophic; the cerebellum is greatly shrunken. All neurons contain stored lipid. The condition is inherited as a recessive trait, and is most frequent among eastern European Jews. Apparently healthy at birth, the infant by about six months becomes apathetic, shows motor regression and fails to fix with his eyes. At one year he is fat, flaccid and listless, with hyperactive reflexes, and is obviously blind. The classic macular cherry-red spots, which may be black in the Negro, with surrounding gray-white retina, optic atrophy and normal vessels have appeared in the fundi. Next is a stage of intense spasticity, with greatly heightened reflexes, extensor plantar responses, decerebrate posturing and increasing dementia. The infant startles readily at slight sounds. The swallowing function is lost, and, now completely demented, he begins to waste away despite all efforts to maintain nutrition and dies usually before the third birthday. No laboratory procedure is of positive diagnostic value; the usual blood and cerebrospinal fluid determinations remain normal. Serum aldolase rises in the period of active muscular wasting, and serum glutamic-oxalacetic transaminase is elevated throughout. The only important distinction is from Niemann-Pick disease, which may show similar macular and cerebral changes; anemia, foam cells and hepatosplenomegaly distinguish it (p. 1000).

Late infantile and juvenile forms of cerebromacular degeneration also occur. Without racial preference, these are hereditary; the juvenile form is transmitted by both dominant and recessive patterns. The *infantile form* begins about three years of age, often with convulsions followed by ataxia, dementia, spasticity and blindness. There is optic atrophy with or without a red-brown macular discoloration. Death occurs within three to five years. The *juvenile form* begins at a later age with visual failure and fundus changes, including optic atrophy, "pepper and salt" pigment deposits, grayish or brownish discoloration and loss of the foveal reflex at the macula. After a year or two vision is gone or mostly so, and mental changes and seiz-



ures appear, followed by extrapyramidal disorders of gait, explosive laughing or crying, and finally extreme dementia, wasting, contractures and death. Distinction from syphilitic optic atrophy and retinitis pigmentosa is difficult in the first stage; progressive deterioration, seizures and the persistently negative serology soon clarify the situation. If real doubt exists, and the family wish information to guide them in regard to future pregnancies, cortical biopsy may be justified.

#### CEREBRAL VON GIERKE'S DISEASE

Storage of glycolipid or related material in neurons occurs in some instances of glycogen storage disease. The affected infant begins at a few weeks of age to regress in motor performance and alertness, becomes limp, has occasional cyanotic spells and vomits; tachycardia, a large heart without murmurs and thick tongue are present. Cortical blindness, apathy and death follow within the first year. The cerebral and cerebellar cortexes are usually spared, but subcortical neurons and striated (Fig. 326) and cardiac muscle contain material staining for glycogen and with some fat stains. The differential diagnosis includes amyotonia congenita, congenital heart disease, cretinism and mongolism.

#### LEUKODYSTROPHIES

A variety of conditions have been described as "diffuse sclerosis." Genetic patterns, usually recessive, are found in all varieties, and they all have certain histologic features in common. Myelin is destroyed early, and abnormal materials, free fats, cerebroside or metachromatic glycolipids accumulate; oligo-

dendroglial cells disappear and scarring by astrocytes is marked.

The *infantile* or *Krabbe type* has a familial pattern. The infant, well for the first few months, becomes fretful and rapidly apathetic or stuporous; then rigidity is followed by tonic and clonic seizures, vomiting, cortical blindness or optic atrophy or both, dysphagia and wasting. Death usually occurs within a year of the onset. The white matter contains large, globular bodies which take stains positively for glycogen or conjugated glycogen compounds. The disorder involves cerebroside metabolism.

In the *Greenfield type* the onset is in the second year of life with ataxia and loss of reflexes, followed by speech impairment, visual loss, dementia, rigidity and extensor plantar responses. Death occurs about three years of age. The brain shows rather selective destruction of the later-myelinated fiber systems, with pronounced loss of oligodendroglial nuclei and deposits of a material staining strongly for glycolipid complexes and metachromatically with aniline dyes. A later type, strongly familial, begins with disturbance of gait, then mild dementia, pyramidal signs, optic atrophy, and finally rigidity, blindness, convulsions and death, after a period of three to four years. Metachromatic material is present in the brain and kidney, as well as in the urine, where it can be demonstrated by staining with appropriate dyes, making accurate diagnosis in life a possibility.

There is no known treatment for these illnesses. Specific diagnosis is often dependent on a postmortem examination. The most that one can conclude is that dementia, fundus

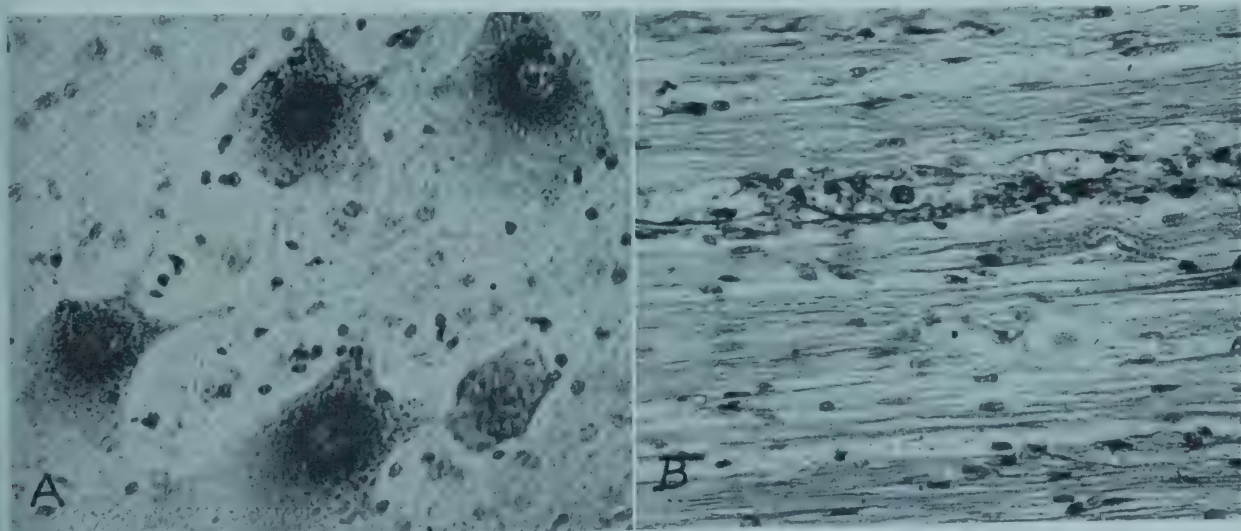


FIG. 326. Cerebral glycogen storage disease. A, Glycogen- and fat-stain positive material in motoneurons. B, Glycogen-infiltrated skeletal muscle.

changes and seizures which precede outspoken neurologic signs usually indicate disease of the gray matter, whereas milder dementia with more pronounced physical signs and a later onset of seizures suggest primary involvement of white matter.

### PROGRESSIVE ENCEPHALOMYELOPATHIES

*Encephalitis periaxialis diffusa* (*Schilder's disease*) is a progressive disease featured by bilateral spasticity, cortical blindness and deafness, optic atrophy or neuritis, dementia and death. The distinctive pathologic feature is massive destruction of myelin, largely confined to the cerebral hemispheres, with glial scarring and sometimes cavity formation. Arcuate fibers are spared, and neuronal changes are inconspicuous. The disease is hereditary; the onset is at any age, but most commonly is in later childhood. The child has often been vaguely ill, irritable or doing poorly in school for some months before the beginning of clear-cut symptoms. These are usually disorders of gait, due to spasticity, which are often initially hemiplegic, but soon become bilateral. The onset may be almost apoplectic, with either optic neuritis or papilledema; in these circumstances the child is acutely ill, and intracranial pressure may be increased and abducens palsies present. Cortical blindness and deafness (sometimes the initial symptoms) or aphasia and apraxia signify extension into the occipital, temporal and parietal lobes. Mental deterioration always ensues; convulsions may occur late or relatively early in the course. Optic atrophy is common, but cerebellar or spinal cord signs are unusual. Bronzing of the skin is a rare manifestation. The course varies from weeks to a few years.

*Disseminated sclerosis* is a slowly progressive disorder in which recurrent attacks, usually interspersed with remissions, involve various parts of the central nervous system, principally the visual, cerebellar and spinal portions. The lesions are multiple plaques in which there is destruction of myelin, relative preservation of axons, phagocytosis of the products of myelin degeneration and finally glial scarring; wallerian degeneration is inconspicuous. The disease may start as (1) attacks of retrobulbar neuritis; (2) recurrent bouts of paraplegia; or (3) cerebellar disorders with disturbances of gait. Nystagmus, ataxia of speech, emotional lability with euphoria and sphincter disturbances are common. The course is long. During attacks, the proteins of the cerebrospinal fluid, particu-

larly the gamma globulins, are increased, and a paretic gold curve and mild pleocytosis are common. No laboratory finding is diagnostic.

In this form, disseminated sclerosis is rare in childhood. Most cases so diagnosed are perhaps better described as disseminated encephalomyelitis. When it does occur, the common courses are as follows: (1) attacks of retrobulbar neuritis with sudden severe visual loss, central scotomas, loss of color vision and, rarely, swelling of the optic disks. Vision may return after several weeks or may remain permanently defective. In either case the disks become pale, temporally. One or several such attacks may occur and one or both eyes may be involved. During the course of these symptoms or after remissions of months or years, symptoms of spinal cord, cerebellar or cerebral disease appear, usually with weakness of legs, urinary urgency, frequency or incontinence, cerebellar ataxia of a limb and at times hemiparesis. (2) In other instances the onset is characterized by manifestations of partial or fairly complete transverse myelitis, and such attacks may recur repeatedly, often at or near the same site. In this clinical pattern retrobulbar neuritis may, but rarely does, appear later.

Once the course of the illness is established, diagnosis is not difficult. The initial attack of retrobulbar neuritis cannot be distinguished from retrobulbar neuritis of other causes; some believe that all unexplained retrobulbar neuritis is disseminated sclerosis. In Leber's hereditary optic atrophy the central scotomas are usually larger, the loss of vision less abrupt and a familial history usually present. Neuro-myelitis optica, whether of spinal cord or optic nerve, may be indistinguishable. The leukodystrophies are not manifest by evidences of spinal cord lesions, and their course is steadily progressive. Disseminated encephalomyelitis is usually much more violent, the child much more ill, and signs of widespread lesions are apparent.

The prognosis is unfavorable, but long periods of remission are frequent and the outlook is not hopeless. No specific treatment is available. Good nursing care, physiotherapy and especially careful attention to the bladder in acute involvement of the spinal cord are necessary.

*Neuromyelitis optica* is an illness combining visual loss due to optic neuritis with paraplegia due to transverse myelitis. The lesions typically are multiple foci of softening or necrosis in the optic nerves and chiasm and in the white and gray matter of the brain and



spinal cord; the distinction from acute disseminated sclerosis may be largely artificial. The disease occurs at any age. The onset may be with optic neuritis or transverse myelitis, or both. Fever and signs of systemic illness are generally present, especially in the myelitic onset. There is frequently pain and tenderness over the level of the cord lesion, and pain in the eyeball may precede optic neuritis. There is a pleocytosis. At times there may be complete destruction of several segments of the cord and paralysis may ascend rapidly; such patients usually have severe muscular wasting. Such cerebral signs as drowsiness, headache and convulsions are rare.

Differential diagnosis is that of disseminated sclerosis (see p. 1096), which it closely resembles. There is no specific treatment, but since good recovery, for a time at least, is possible, the best of nursing care, tidal drainage of the bladder, respirators for respiratory paralysis and early physiotherapy are indicated.

## DEGENERATIVE DISEASES INVOLVING SPECIFIC FIBER TRACTS AND/OR NEURAL GROUPS

### FRIEDREICH'S ATAXIA

This degenerative disease of unknown cause is transmitted by both dominant and recessive patterns. It is characterized by ataxia, loss of reflexes, pes cavus, kyphoscoliosis, cardiac abnormality, nystagmus and optic atrophy. There is degeneration of the dorsal columns and spinocerebellar and pyramidal tracts, in some lemniscal systems, in the cerebellum and in the optic and auditory nerves.

The majority of cases become symptomatic before puberty. Recessive strains tend to have an earlier onset than the dominant ones. Duration varies from a few to many years, possibly even to a normal life span in incomplete forms; average duration of life is about sixteen years. The first symptoms are ataxia of gait or aching, cramping pains in the limbs. Then clumsiness of hands, truncal ataxia, dysarthria, kyphoscoliosis, nystagmus and optic atrophy appear. The first sign is usually pes cavus with hammer toe deformity, which, combined with absent reflexes, constitutes the commonest pattern of the incomplete forms. The deep reflexes disappear early; distal sensory loss, affecting stereognosis, position and vibratory sense, with little decrease in cutaneous sensation, is common. Ataxia is both cerebellar and spinal in type;

the slapping, reeling gait and the compensatory movements of the trunk and limbs often suggest chorea. The intensity of the voice fluctuates, and the speech is nasal or explosive. Mental retardation is present in about 10 per cent of cases, and progressive dementia is a late event in about the same ratio.

Visceral symptomatology is of especial interest. Vomiting and other gastrointestinal disturbances occur, but the most important are the cardiac symptoms. Tachycardia and loud murmurs are common. The electrocardiogram shows abnormalities of the S-T segment or inversion of the T wave in about half of the cases. Histologically there is a peculiar interstitial myocarditis and fibrosis. Death may be due to a cardiac arrhythmia or congestive failure.

The condition is to be distinguished from other spinocerebellar ataxias and peroneal muscular atrophy with which it may be related, from disseminated sclerosis, especially in older patients, and particularly from rheumatic heart disease with chorea. The last is a common diagnostic error, owing to the ataxic movements, heart murmur, leg pains and electrocardiographic abnormalities. The orthopedic defect and congestive failure are treated symptomatically.

*A number of other forms of hereditary ataxia* have been described in children. These are initially purely cerebellar and later develop pyramidal signs, or they may combine ataxia with spasticity and hyperactive reflexes from the start. A positive family history, a slow course and frequently late visual failure and dementia are common. There is no treatment.

### HEREDITARY SPASTIC PARAPLEGIA

This is a hereditary degenerative disease, with destruction of Betz cells and pyramidal tract degeneration, most prominent farthest from the cortex. Its inheritance is variable, but it is usually recessive and sometimes sex-linked; males are more often affected than females. Symptoms begin usually in early childhood, first as stiffness and slowness in walking, then with steady development of a spastic paraplegia. The reflexes are increased, but Babinski's sign may appear late. The sensory systems, sphincters, upper extremities and the intelligence are spared. Flexion deformities, arrest of growth of the lower limbs, and sometimes late dementia, blindness or other signs occur. The strong familial history usually distinguishes it, but in sporadic cases, tumor of the cord, vertebral disease and other

degenerative or inflammatory lesions must be excluded by examination of the cerebrospinal fluid and roentgenographically with myelography. No curative treatment is known.

#### **DYSTONIA MUSCULORUM DEFORMANS**

Torsion spasm and dystonic movements may occur in several disease processes, such as postencephalitic syndromes and Wilson's disease. There is, however, a fairly distinct clinical entity of maintained torsion of limbs and/or of the trunk of unknown etiology, which occurs mainly in Russian Jews. Pathologically, there is a loss of cells, especially of the large ones, in the basal ganglia. The illness begins before puberty, usually about eight to ten years, without sex preference, but at times with a definite familial pattern. The first sign is a fixed posturing of one leg, the foot extended and held in pes cavus with the toes flexed. Soon the thigh flexes and adducts and the knee bends; then the other leg becomes involved and the child walks on tiptoe. Extreme lumbar lordosis appears early. After some years the arms rotate internally, adduct, extend at the elbows and flex at the wrists. Finally strong involuntary torsion movements appear, which are really a powerful exaggeration of the posturing of legs, trunk and arms; any movement, particularly walking, brings on fantastic writhing. These movements, absent in sleep, are greatly worsened by emotion, suggestive of hysteria, but psychotherapy is not helpful. Reflexes, sensation, sphincters, vision, speech, swallowing and movements of the fingers are not impaired. The condition is distinguished from double athetosis, hepatolenticular degeneration and postencephalitic states by the bizarre picture described, the Jewish parentage, family history and the absence of hepatic involvement or of a history of encephalitis. The course is long, the disease ultimately confining the patient to bed. There is no effective treatment, though pallidotomy has been suggested.

#### **HUNTINGTON'S CHOREA**

This is a degenerative disease of genetic origin (dominant) and is characterized by progressive choreic movements, dementia and death. The brain is atrophic, particularly the frontal lobes; the ventricles are enlarged and there is a widespread, slow degeneration of neurons, greatest in the putamen and in the caudate nuclei. Unaffected members of families have an unusually high incidence of psychopathic or psychotic behavior and suicide. The onset

is usually in the fourth decade, but may occur in children as early as six years, with death by ten years. The first symptom in the child may be an emotional disturbance, choreic movements or seizures. The choreic movements affect the face, trunk and arms at first, the large joints being more involved than the small ones. The movements initially are exaggerations of voluntary ones and tend to remain a crude parody of willed motions. Reflexes are normal or heightened; the cranial nerves at first are intact, but pseudobulbar palsy and swallowing difficulties finally appear. Progressive dementia and the violence of the movements ultimately confine the patient.

Huntington's chorea is distinguished from Sydenham's chorea and congenital chorea principally by its progressive course, dementia and family history; the first and second are, of course, not initially apparent, and the third may be carefully concealed. Hepatolenticular degeneration is excluded by its corneal ring, hepatic involvement and tremor. There is no known treatment, though large doses of rauwolfia derivatives are currently used for reduction of chorea.

#### **HEPATOLENTICULAR DEGENERATION**

##### **(WILSON'S DISEASE)**

This is an inborn metabolic defect, apparently inherited as an autosomal recessive. The symptoms are tremor, dysarthria, hypertonus and dementia, combined with hepatic cirrhosis and corneal pigmentation. Primary failure of formation of ceruloplasmin disturbs copper metabolism; the intestinal absorption and tissue deposition of copper, particularly in the brain and liver, are increased. Plasma copper is decreased and urinary copper increased. The principal anatomic lesions are shrinkage, discoloration or cavitation of the lentiform nuclei and hepatic cirrhosis.

Familial incidence is common. The age at onset is probably determined by the time required for enough copper to accumulate in the brain or liver to produce symptoms; it may vary from seven years to the fourth decade. The duration is usually several years. Indistinct, dysarthric or explosive speech, a fixed unblinking stare, drooling of saliva, tremor at rest and in motion, beginning in a hand but soon involving the entire body, generalized hypertonus, seizures late in the course and dementia are the principal clinical features. Reflexes are altered only by rigidity; sensation remains intact. The characteristic



Kayser-Fleischer ring, usually of golden-brown discoloration at the corneal limbus, and the palpable liver are important signs.

If hepatic symptoms are associated with the neurologic signs, no diagnostic problem exists; if not, Wilson's disease must be distinguished from double athetosis, which is of congenital onset and without real tremor, from dystonia (p. 1098) and from post-encephalitic syndromes. The corneal ring should be looked for with a slit lamp. High urinary and low plasma copper and especially low plasma ceruloplasmin, which otherwise is found only in the newborn or in the nephrotic syndrome, are diagnostic laboratory findings.

Treatment with chelating agents sometimes gives partial, but usually poorly maintained, relief; BAL, Versene and penicillamine have all been tried. Low copper diets, perhaps combined with such agents, may prove to be more effective. Siblings and every case of unexplained cirrhosis or jaundice should be examined carefully to detect early cases.

#### WERDNIG-HOFFMANN DISEASE

This is a progressive hypotonia and wasting of skeletal muscle in infancy and childhood, which is due to degeneration of motor neurons. There is no evidence of other involvement of the nervous system and the condition usually terminates fatally at an early age.

The etiology is unknown. The essential pathologic lesion is progressive loss of motor neurons, with little reaction in the surrounding tissue (Fig. 327, C), beginning or most severe at the caudal end of the spinal cord, extending cranially and finally involving cranial nerve motor nuclei. The anterior roots are thin and pale (Fig. 327, B). The skeletal muscle shows atrophy of denervation as manifest by narrowed fibers, increased sarcolem-

mal nuclei, preserved cross striations and replacement by fibrous tissue (Fig. 327, A). Cerebellar defects and absence or underdevelopment of Betz cells in the motor cortex have been described.

The condition is familial in at least half the cases and may occur in successive generations; its inheritance is not clearly understood, and sexes are equally affected. Fetal movements are often feeble or absent. The infant is born limp, flaccid and areflexic, but sensation, the cranial nerves, sphincter functions and intelligence are adequate. The infant lies in a froglike position and can be folded or doubled into almost any grotesque posture. The muscles are thin, soft and hard to palpate; the only limb movements are feeble flickers of the digits. Side-to-side movements of the head are usually preserved. The intercostal muscles are paralyzed before the diaphragm, resulting in sternocostal retraction and respiratory difficulty. Fibrillations of the tongue appear, sucking is lost and the infant usually dies of respiratory infection by eight to twelve months of age.

Variations in the time of onset or the rate of progression are common. *Arthrogryposis multiplex congenita* may represent an incomplete form which has run its course in utero. By contrast, fetal movements may have been present, and the infant at birth appears to be normal, only to manifest the illness in the first few days or weeks. In other instances the symptoms may not appear for several months or even a year or two. Sometimes the progress is slow, growth for a time outstrips degeneration, and the infant slowly makes some developmental progress; a few may live for years, but seldom to puberty.

Werdnig-Hoffmann disease is one of the many entities comprising the *amyotonia congenita syndrome*, which in actuality only im-

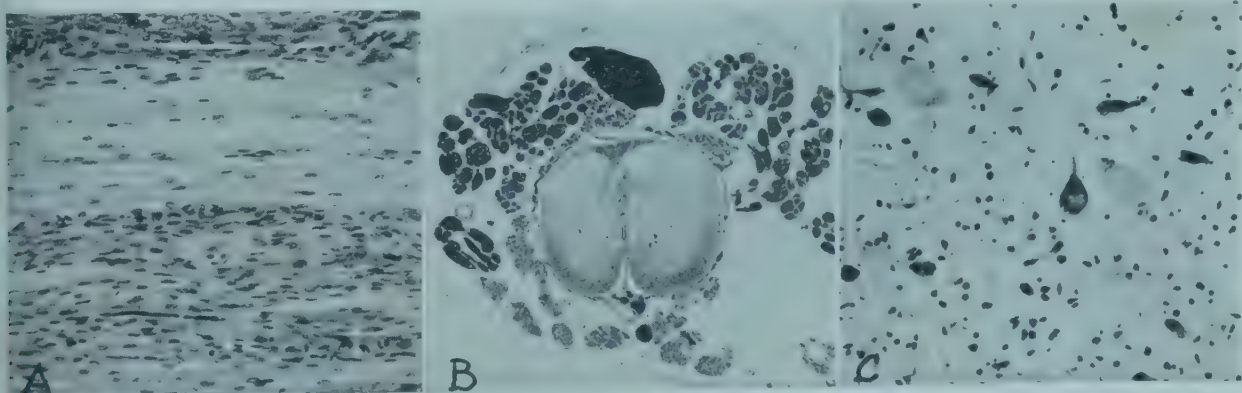


FIG. 327. Werdnig-Hoffmann disease. A, Fascicular atrophy of muscle. B, Pallor of ventral roots. C, Degenerating motoneurons.

plies extreme hypotonia in an infant. Other causes include the following:

1. Diseases of the central nervous system or neuromotor unit
  - Atonic diplegia
  - Cerebral lipidosis
  - Cerebral von Gierke's disease
  - Kernicterus
  - Neonatal poliomyelitis
  - Infantile polyneuritis
  - Spinal cord lesion birth injury or congenital tumor
  - Congenital or neonatal myasthenia gravis
  - Congenital myopathies
  - Polymyositis
2. Non-neurologic diseases
  - Deficiency states such as rickets and scurvy
  - Chronic infection
  - Malnutrition
  - Congenital defects, such as arachnodactyly
3. Benign congenital hypotonia

*Differential diagnosis* of the syndrome can be difficult. The diagnosis of Werdnig-Hoffmann disease depends on (1) a history of familial incidence and diminished or absent fetal movements; (2) the presence of extreme hypotonia and areflexia in an otherwise normal infant at or soon after birth or development of weakness and hypotonia in an infant or young child; (3) generally normal laboratory studies, except for muscle biopsy and perhaps electromyography. The infant with atonic diplegia may be exceedingly limp, but the reflexes are retained; there is often a history of abnormal pregnancy and labor, the infant makes powerful spontaneous movements at intervals, and signs of mental retardation soon become obvious. The cerebral degenerative diseases, lipidoses and cerebral von Gierke's disease may parallel Werdnig-Hoffmann's disease in time of onset and general flaccidity, but the reflexes are retained and the progressive loss of vision and dementia are distinctive. A history of unusual neonatal jaundice and early athetoid movements distinguishes kernicterus. Neonatal poliomyelitis is best excluded by serologic studies, and infantile polyneuritis by an onset following intestinal or respiratory infection and by a maintained high cerebrospinal fluid protein level. Birth injury of the spinal cord regularly complicates breech delivery; the segmental pattern of motor and sensory paralysis, sphincter involvement and loss of sweating in the involved area are characteristic; a segmental level of paralysis may also be due to a congenital spinal cord tumor. Neonatal myasthenia affects only the infant of a myasthenic mother; as in congenital myasthenia

there is early involvement of ocular and bulbar muscles and a diagnostic response to Prostigmin. Congenital myopathies or polymyositis may require muscle biopsy to distinguish them.

Of the non-neurologic diseases, the pseudo-paralysis of scurvy may superficially resemble Werdnig-Hoffmann disease, but distinction is not difficult (p. 368) as is the case with rickets (p. 375). The infant with arachnodactyly may have hypotonia, but other features are diagnostic (p. 1243).

The most important differential diagnosis is with the syndrome of *benign congenital hypotonia*, which at times is familial. The infant usually has moved well in utero; some tendon reflexes can always be obtained, and no other neurologic signs are present. Despite striking hypotonia and hypermobility of joints, the child occasionally makes strong movements. Sternocostal retraction and respiratory distress occur, but evidence of progression or fibrillations of the tongue do not appear. Physical milestones are passed slowly, few walk before eighteen and twenty-four months of age, and many not until three to five years. Ultimately all are able to get about and about half of them are quite normal by eight or nine years of age. In others the muscles remain feeble, and then may develop contractures, but the joints always remain hypermobile. Muscle biopsy reveals no abnormalities. Treatment is limited to orthopedic assistance in the avoidance of contractures.

#### PERONEAL MUSCULAR ATROPHY

##### (CHARCOT-MARIE-TOOTH'S DISEASE)

Peroneal muscular atrophy is a hereditary disease characterized by distal wasting, weakness, and loss of reflexes in the extremities.

Pathologically, there is degeneration, apparently first in the motor nerves, then in the roots with some loss of motor cells. Similar changes appear later in the sensory nerves and dorsal root ganglia, and secondary degeneration extends up the dorsal columns. The muscles involved show atrophy of denervation.

The disease is strongly hereditary by dominant, recessive or sex-linked recessive patterns. Symptoms generally begin in late childhood or adolescence; progress is slow, and the disease is compatible with long life. Wasting, first of the extensors, evertors and intrinsic muscles of the feet, produces the dropped foot and equinovarus deformity; the peroneal, tibial and finally the calf muscles are involved, but wasting seldom goes much above



the knee, thus producing the characteristic storklike leg. Loss of muscular strength parallels loss of bulk, and fasciculations are usually present. The ankle reflexes disappear, but the patellars persist. Cramps and paresthesias may be present early, but sensory loss is slight, involving mostly positional and vibratory senses. Similarly, wasting and sensory and reflex losses later involve the forearms. Sphincters are not often affected; optic atrophy may occur late. The extremities are cyanotic, cold and mottled; after years, atrophy of bones and perforating ulcer of the foot appear. Incomplete forms, especially claw foot with absent ankle jerks, are common.

The cerebrospinal fluid is usually unchanged, and no laboratory finding is diagnostic. Familial incidence, slow course and absence of muscle tenderness distinguish it from chronic polyneuritis; absence of ataxia, nystagmus, widespread reflex loss and cardiac findings, from Friedreich's disease. Interstitial hypertrophic polyneuritis is characterized by miotic, fixed pupils, increased cerebrospinal fluid protein, and palpable peripheral nerves, none of which are present in peroneal atrophy. The disability is surprisingly slight in view of the wasting. Braces and fusion of ankle joints keep the patient ambulatory.

#### HEREDITARY OPTIC ATROPHY

##### (LEBER'S DISEASE)

Leber's disease is a hereditary degeneration of the retina and papillomacular bundle with serious loss of vision; at times there are associated neurologic symptoms. The ganglionic and, to a less extent, the inner nuclear layers of the retina are degenerated, and the axons and myelin sheaths of the papillomacular bundle are destroyed without inflammatory response, whereas the peripheral fibers are partially spared. There is transneuronal degeneration in the lateral geniculate bodies and in the optic radiation. The remainder of the brain is normal.

The condition is usually inherited as a sex-linked recessive, appearing in males, but dominant strains and occurrence in females are known. The onset is usually in the late teens, but may be in childhood or adult life. Rapid loss of vision—sometimes beginning in one eye, but soon becoming bilateral—large, absolute central scotomas and relative peripheral scotomas accompany mild swelling of the disks, which is replaced by pallor in a few weeks. The rest of the fundus is normal. Vision fails rapidly for a few weeks, then be-

comes stationary and remains so for years. Complete blindness is rare. Associated neurologic manifestations, such as epilepsy, ataxia, club feet, mental deficiency and sphincter involvement, are not uncommon. The family history, rate of onset, bilateral visual loss and large scotomas usually distinguish it from retrobulbar or optic neuritis. There is no treatment.

#### DEGENERATIVE DISEASES OF UNCERTAIN CLASSIFICATION

##### HELLER'S DISEASE

This singular illness is a progressive dementia without other signs of organic neurologic disease. Pathologic data are scanty; sclerotic, irregularly arranged cortical neurons, lipid deposits, meningeal fibrosis and multinucleated giant glial cells have been described, though none is completely convincing. The onset of illness is in the third or fourth year of life. A child, previously well or perhaps after an infection, first becomes irritable and disobedient, has temper tantrums, and then begins to regress in speech and signs of mentation. Within a year he is mute, pays no attention to speech, may have tics, is incontinent and often has to be fed. All observers stress the intelligent expression which is said to persist, though the behavior is that of extreme dementia. The patients survive for years. It is still uncertain whether this is an organic disease in the strictest sense, or a form of schizophrenia in childhood (see Autism). No treatment has been effective.

#### THE SYNDROME OF EPILEPSY, CEREBRAL DEGENERATION AND MYOCLONUS

The association of seizures, myoclonic jerks and cerebral degeneration is not uncommon in childhood. Two forms are recognizable and may represent the same disease.

In the first, often familial and probably hereditary, lesions consist in degeneration and necrosis in the middle and outer cortical layers, producing status spongiosus and some gliosis. The deeper cortex and white matter are spared, but similar lesions are present in the thalamus, lentiform nuclei and the dentate and olivary nuclei. Infantile and juvenile types occur. In infancy the onset is with head-dropping spells, myoclonic jerks of trunk

and arms, and generalized seizures (see also p. 1119). Rigidity and some ataxia appear, the child demented rapidly, seizures begin to occur in bouts, and myoclonic jerking is almost constant. Cortical deafness and blindness without optic atrophy appear early. The child dies in status epilepticus after one or two years. The *juvenile form* begins in early childhood, the child sometimes having been previously retarded. The progress of signs and symptoms, though slower, is like that of the infantile form; choreo-athetosis and cerebellar signs are usually more conspicuous. Death in status epilepticus occurs after several years.

The second form, *Unverricht's myoclonus epilepsy*, is a hereditary disease, probably recessive, characterized by convulsions, massive myoclonic jerks, ataxia or choreo-athetosis and dementia. Intracytoplasmic inclusion bodies in neurons and degeneration and gliosis of the outer cortical layers are charac-

teristic pathologic features. The onset is prepuberal, and the first symptom is a convulsion. Minimal cerebellar ataxia or extrapyramidal signs and myoclonic jerks are usually present, but often overlooked. In succeeding years the child becomes irritable and regresses mentally. As dementia slowly increases, the convulsions disappear and are replaced by massive myoclonic jerks involving the shoulders, trunk and proximal parts of the limbs. They are so violent that they prevent walking, ultimately confine the patient to bed and may conceal the evolution of cerebellar and extrapyramidal signs.

The family history, progression, frequency of extrapyramidal or cerebellar signs, myoclonus and replacement of seizures by massive myoclonus separate these illnesses from the common occurrence of myoclonic jerking in epileptics. No treatment is known other than the use of anticonvulsants for symptomatic relief.

## NEUROLOGIC SYNDROMES PECULIAR TO CHILDHOOD

The following illnesses seem the almost exclusive property of childhood. Syndromes rather than diseases, they are encountered frequently enough to deserve mention.

### SPASMUS NUTANS

This condition, also called nodding spasms, which is found mainly in infants, combines irregular movements of one or both eyes, head-nodding and deviations of the head. The etiology is unknown. Vitamin A or D deficiency, wasting illness and in particular poor lighting of nurseries, which might delay development of optic fixation, have all been suggested. The disease is more common in the low-income group, and symptoms usually begin in the winter, but convincing evidence for any of the supposed etiologies is wanting.

The onset may be as early as a few weeks or as late as three years, but most often is between four and twelve months of age. There is no sex preference; more than one sibling may be affected. The three cardinal symptoms are head-nodding, irregular eye movements and deviation of the head. Movements of the head or eye may be the first or the only symptoms. Head movement occurs

in about 80 per cent of cases and perhaps is the most common initial symptom. It is slow, inconstant and irregular and occurs in any direction; it disappears during sleep or when the child lies down. Eye movements, which also occur in about 80 per cent of cases, usually begin in one eye and are almost always more pronounced in one than in the other. They are rapid, inconstant, irregular jerkings of small amplitude in any direction and without definite components. They disappear when the eyes are covered or the child sleeps, but are instigated or made worse by holding the head still. Deviations of the head, which occur in about one third of cases, are in any direction and do not lead to contractures; they may help the child to focus. Nonparalytic strabismus occurs at times; there are no other ocular or neurologic signs. The condition clears spontaneously, usually within several months. At times there are temporary exacerbations.

*Congenital nystagmus* is differentiated from spasmus nutans by the family history, early onset, compensatory head movements and failure to improve. No treatment of spasmus nutans is necessary beyond ensuring adequate light and nutrition and reassuring the parents.



## ACUTE CEREBELLAR ATAXIA

Cerebellar syndromes after infections are not uncommon; measles and chickenpox are known precursors. Many cases of acute ataxia in childhood, however, have no apparent cause, and, since they are seldom fatal, the pathologic lesions are not known. The syndrome is commonest in young children who have begun to walk, usually between two and four years of age. There may be no history of previous illness, or only a slight cold. The onset is usually rather sudden. The child may vomit occasionally for a day or so; the principal feature is the evolution over a few hours to three or four days of a decided unsteadiness of gait; the child often refuses to walk or even to lift his head. Some irritability or change in personality is present, but convulsions, stupor or signs of systemic illness are usually absent. Physical signs include unsteadiness, wide-based gait, cerebellar ataxia, heightened or depressed reflexes, hypotonia and fugitive extensor plantar responses. Irregular or rapid jerking of the eyes, when the child attempts to fix, is common. The cerebrospinal fluid at the onset is normal or contains a few lymphocytes; after days or weeks the protein may rise to 200 mg. per 100 ml. or more. Beyond a mild peripheral leukocytosis and variable electroencephalographic abnormalities in about half the cases, no other laboratory tests are abnormal. The unsteadiness and irritability may persist for weeks or months, but usually disappear completely; residual disability is rare.

Such cases must be differentiated from brain tumor, cerebral degenerative diseases, poliomyelitis and the early stages of polyneuritis. Absence of increased intracranial pressure and the course of the illness are the most valuable differential points. Tumor or degenerative disease inevitably advances, the former with signs of increased intracranial pressure, localizing signs or both. Facial diplegia, distal sensory loss and usually complete areflexia distinguish polyneuritis. There is a possibility that the condition represents cerebellar involvement by any of the various encephalitic viruses or perhaps by a variety of toxic agents. The treatment is entirely symptomatic.

## ACUTE INFANTILE HEMIPLEGIA

(POLIO-ENCEPHALITIS OF MARIE-STRÜMPPELL)

This syndrome of hemiplegia with lateralized seizures and usually severe neurologic re-

siduals has a sudden onset. The etiology is almost certainly manifold. Thrombosis on subintimal plaques in cerebral arteries, thrombosis of the carotid artery, embolism of unidentified source, intracerebral rupture of vascular anomalies and cortical thrombophlebitis are all possibilities.

In the classic form a child of one to two years of age, previously well except perhaps for a slight cold, begins his illness with the apoplectic onset of lateralized seizures, often with a jacksonian type of progression. Between seizures the affected limbs are flaccid and hemiplegic. The child is comatose and soon has fever and some leukocytosis. Meningeal signs are absent and there are usually no changes in the cerebrospinal fluid at this time. The electroencephalogram shows principally voltage depression or absence over the affected hemisphere. No pathogens are consistently cultured.

Coma persists for hours or days, but the child seldom dies. Cells appear in the cerebrospinal fluid after some days, probably as a reaction to necrotic tissue. Movement slowly returns to the affected side, first in the extremity last involved by seizures. Walking and, especially with right hemiplegias, talking must be learned again. The neurologic residuals include (1) hemiparesis, in about three quarters of the cases, with growth arrest and often choreo-athetoid movements of the affected side; (2) recurrent lateralized seizures in about two thirds—they may worsen the hemiparetic signs transitorily; (3) intellectual disturbances in about three quarters, ranging from learning disorders to severe mental deficiency. Hemianopsia is infrequent. Second attacks are almost unknown.

In the acute stage, pneumoencephalography may show swelling of the affected hemisphere and shift of the ventricles; later there is obvious dilatation of the involved lateral ventricle and lateralized cortical atrophy. The skull grows asymmetrically, the vault on the affected side smaller, the bone thicker, the petrous ridge higher and the frontal sinus larger than those on the unaffected side.

This condition must be distinguished from meningitis, encephalitis and hemorrhagic encephalopathies by persistent lateralization of the signs and normality of the cerebrospinal fluid in the early stage. Tumors and abscess lack such apoplectic onset and cause increased intracranial pressure. Occasionally a severe bout of convulsions may call attention to or worsen a hemiparesis of congenital

origin, previously undetected, and cause some confusion.

In infants, usually under one year of age, hemiplegias and seizures occasionally occur during severe respiratory and intestinal infections. These infants are gravely ill; it will often be found that their signs are bilateral, but more notable on one side. Pleocytosis of the cerebrospinal fluid appears early. These cases probably represent cortical thrombophlebitis or extensions of thrombosis from dural sinus occlusions into the cortical veins. In older children the onset may be slower with recurring attacks of numbness or weakness of an arm, leg or entire side over a period of hours or days before a persisting hemiplegia develops. Some of these have been proved to be due to thrombosis of the carotid artery in the neck.

**Treatment.** In the acute state, treatment consists in sedation or rectal anesthesia to control seizures, fluids, treatment of any infection present, avoidance of secondary infection and possibly hypothermia. Since endarterectomy may improve the prognosis for carotid thrombosis, any atypical case should have arteriograms performed within the first few hours; if obstruction is found, immediate surgical removal of the clot should be attempted.

In chronic cases physiotherapy and special schooling for the handicapped are necessary. Seizures are so frequently a residual that an anticonvulsant drug should be given routinely. Rarely, intractable seizures or behavior disorders at later ages may benefit by hemispherectomy.

## CRANIOCEREBRAL AND SPINAL TRAUMA

The symptoms of a blow on the head are due mainly to differential movement of the brain and skull. Brief loss of consciousness is caused either by the effect of a sudden shift of intracranial contents on the hypothalamus and periaqueductal gray matter or by less-understood direct effects on nerve cells. At points where shifting of the brain brings it against the skull, multiple hemorrhagic foci or wedges of cortical necrosis appear; these lesions, with some swelling of the brain, may produce moderately prolonged unconsciousness and mild neurologic signs. Severe swelling of the brain or intracerebral hematoma compresses large vessels, damages widely distant parts of the brain and causes prolonged unconsciousness and localizing neurologic signs.

In open head injuries the skull and dura are lacerated. The child is usually unconscious and in shock, with localizing signs. Such an injury is a grave surgical emergency, requiring immediate treatment of shock and débridement of the wound. Most head injuries of childhood are closed ones with or without fractures; operation is indicated only when there is suspicion of epidural, subdural or intracerebral hematoma (p. 1087).

**Mild Closed Injury.** The usual history is that after a fall the child was unconscious for a few seconds, then seemed pale and shaken or screamed lustily, and two to four hours later became sleepy and vomited. He was irritable and drowsy and his pulse was

a little slow, but neurologic signs were absent. The management is careful, repeated observation of vital and neurologic signs to detect possible development of intracranial hypertension. A roentgenogram of the skull should be obtained, if convenient, and the child put in a quiet room where pulse, respirations, blood pressure, state of consciousness, size and reactivity of pupils and appearance of any neurologic signs are recorded every half-hour for four hours. If no change occurs, observation of pulse, respirations and state of consciousness is continued at home, the child being awakened at least every two hours to make sure that he is not drifting into stupor. Recovery is usually complete in twelve to twenty-four hours.

**Severe Closed Injury.** The child is usually stuporous or unconscious, though seldom in deep shock, which, if present, should lead to search for other injuries. A patent airway should be ensured at once by tracheotomy, if necessary, and shock, if present, should be treated. A sequential record is begun of vital signs, state of consciousness, pupillary size and reactions and such lateralizing neurologic signs as diminution of spontaneous or induced movement and appearance of Babinski's sign. Since such signs often fluctuate, it is the establishment of a trend in one or another direction, rather than isolated observations, that is important. Rising blood pressure, slowing pulse and respiration and deepening stupor mean increasing pressure; if



lateralized pupillary dilatation or motor signs appear, intracranial hematoma must be sought for.

Intravenous fluids should be given cautiously, glucose in 0.45 per cent saline solution being safest; oral or stomach tube feeding should be started as soon as possible. Fever, often due to the injury alone, responds to aspirin, sponging, and cooling by fans or air conditioners. Lumbar puncture is not generally advisable, but may help to control restlessness, for which paraldehyde rectally is also valuable. Opiates and mydriatics should not be used. Infection or suspicion of a basal fracture is an indication for antibiotic therapy.

Controlled hypothermia, the child being cooled to 90° to 92° F. and so maintained for about five days, is now frequently used; it may have some benefit.

The presence or absence of *skull fracture* seldom changes the management. A linear fracture across a suture or a diastatic fracture in the infant increases the possibility of epidural hematoma. A depressed fracture in a newborn infant should be elevated as soon as discovered; in older children elevation is deferred until edema subsides. A basal fracture is probably present if there is (1) bleeding from the nose, ears, pharynx or bilaterally into the orbits; (2) a peripheral facial palsy; or (3) escape of cerebrospinal fluid from the nose or ear. Antibiotics should be given to such patients routinely, and the meningeal fistula closed surgically.

*Post-traumatic syndromes* include epilepsy, psychotic states and neuroses. Epilepsy follows closed head injury in about 3 per cent of cases, open head injury in as many as 50 per cent; it appears to be related to the site and nature of the injury. Its onset cannot be predicted by post-traumatic electroencephalographic abnormalities unless they become paroxysmal. The seizures are almost always controllable by drugs. The child recovering from an open injury or a severe closed one should be maintained on anticonvulsant therapy for at least one year.

Postacute psychotic states are rarely per-

sistent. Neuroses, headache, giddiness, fatigability, poor concentration and behavior disorders are not uncommon. Malingering, unless fostered by parents, is rare. Encouragement, reassurance and optimism on the part of the physician and parents are the best prevention and therapy.

**Injury of the Spinal Cord.** Much rarer, but more crippling than head injury, spinal cord trauma is almost always associated with fracture or dislocation of vertebrae. In breech delivery excessive traction on the trunk before the aftercoming head is delivered is a cause of severe injury; a distinct snap may be heard. The lesion is a fusiform, central hemorrhagic necrosis in the lower cervical and upper thoracic cord; at times there is actual severance. The infant is paraplegic below the lesion, and there is urinary retention. Roentgenograms of the vertebral column usually show no lesion. Such an injury may be confused with congenital defects of the cord or with amyotonia congenita. The mortality is high. In those who survive, recovery of function is insignificant, and arrest of growth occurs below the lesion. Only supportive treatment is possible.

In the older child falls, blows or diving accidents are common causes of cord lesions; the usual sites are C 5–6 and T 12–L 1. Paraplegia is usually complete at first with sensory, motor and sphincter paralysis; tendon reflexes below the lesion are absent for some days. Physical and roentgen signs of fracture or dislocation are usually present. The child should be immobilized, from the moment of injury if possible, to prevent further injury; all movement of the vertebral column should be carefully avoided. Casts, hyperextension and traction are used for simple and compressed fractures; laminectomy is indicated only for comminuted fractures. High cervical lesions may require a respirator; tidal drainage of the bladder maintained until voluntary or automatic control returns and scrupulous care of the skin are essential. The return of function is usually poor.

## DISEASES OF THE SPINAL CORD

The spinal cord suffers with the rest of the nervous system in most neurologic disease. A few conditions, however, require special mention. Nuclear aplasias and localized developmental defects may affect any motor

nucleus, in which case the muscle supplied is small or absent. Nuclei for the anterior abdominal muscles and for parts of the pectoral muscle and, in the brain stem, the facial and abducens nuclei are common sites. Defective

development of preganglionic autonomic centers or more widespread congenital malformations may be associated.

In *syringomyelia* a tubelike cavity develops within the spinal cord, initially in the lower cervical portion, from which it extends downward or upward. A similar slitlike cavity in the lower brain stem is termed *syringobulbia*. The process of cavity formation destroys parts of the anterior and posterior horns, commissures and fiber tracts. The cause is unknown, but faulty fusion of alar and basal plates or trauma from repeated neck bending may be contributing factors. *Platybasia*, *dolichocephaly*, sternal deformity, *spina bifida*, *kyphoscoliosis* and spinal cord tumors may coexist.

Symptoms begin in the second or third decade. Weakness and wasting of the hands or arms, lack of cognizance of burns or other trauma to the arms and shoulders, shooting pains in the upper limbs, stiffness of gait and finally urinary urgency and frequency are common. The signs are wasting and loss of reflexes of the hands and forearms, spasticity and pyramidal signs in the legs and varying degrees of sensory loss over the involved dermatomes; incomplete syndromes are frequent. *Syringobulbia* produces lower cranial nerve palsies and facial and corneal analgesia.

The cavity, if under tension, may erode vertebral pedicles or cause spinal block. A spinal cord tumor must be excluded for which laminectomy or a myelogram may be necessary. There is no satisfactory treatment; decompression of the cavity and roentgen therapy are thought to check its progress, which is usually slow and may arrest spontaneously.

Symptoms of *compressing lesions of the spinal cord* depend partly on the rate of development of pressure. Slowly advancing pressure produces spasticity, weakness and faulty gait with pyramidal signs; sensory loss and urinary urgency and incontinence come later. Rapidly advancing pressure causes sudden paraplegia, with urinary retention and areflexia. Stiff back or neck, radiating root pain, which is worse after lying down or on coughing, percussion tenderness over the site of the lesion and local muscular atrophy are other signs. Lesions of the cauda equina and conus produce overflow incontinence from the start.

Common causes of spinal compression are congenital vertebral defects, collapse of vertebral bodies from metastases or osteomyelitis

or expanding lesions such as cysts, abscess or tumor. Young children with severe pharyngitis may have severe stiffness of the neck and mild paraplegia; hyperemia and softening of supporting ligaments may permit spontaneous dislocation of the cervical vertebrae without osteomyelitis. Intervertebral disk protrusion is rare in childhood and follows direct trauma.

*Intraspinal abscess*, almost always epidural, may be secondary to a remote infection or may be a direct infection through a dermal sinus or from a neighboring osteomyelitis. Spinal cord compression develops rapidly, and percussion tenderness over the lesion is exquisite, but signs of infection need not be present. Immediate surgical decompression is indicated to relieve the spinal block. Careful attention to the bladder and the paralyzed extremities is imperative, since recovery is usually possible when the pressure is relieved early and urinary tract infection or trophic sores avoided.

*Spinal cord tumors*, about one fifth as common as intracranial ones, include epidermoids, lipoma, teratoma, ependymoma, neurofibromas on roots or centrally placed, and metastases usually from lymphomas or medulloblastomas. The symptoms are those of slow spinal cord compression with stiff back, root pain and localizing signs; the clinical course may be irregular and rapid. Papilledema is a rare and unexplained sign. Myelography will usually establish the diagnosis. All such lesions should be explored.

*Cysts* are either dermoids or epidural; the latter, in adolescent boys, may produce the syndrome of *kyphosis dorsalis juvenilis*.

*Transverse myelopathy* is a syndrome which may be part of a demyelinating disease or result from vascular occlusion or from rupture of vascular anomalies. It may occur in association with infections or immunizations, when it is probably due to vasculitis as a manifestation of hypersensitivity. The illness usually starts with fever, stiff neck and pains in the back or extremities; the signs of a transverse lesion of the cord evolve over hours to a few days. Cerebrospinal fluid protein is increased, pleocytosis may be present, but spinal block is rare. All degrees of severity may occur. Poliomyelitis is excluded by sensory loss and sphincter involvement; epidural abscess, by absence of spinal block. Recovery may be complete, or there may be any degree of residual paralysis. There is no specific treatment. Skilled nursing care is essential. Corticosteroid therapy has been used.



# DISEASES OF THE AUTONOMIC NERVOUS SYSTEM

Symptoms of abnormal autonomic function are common to many neurologic diseases, but proved primary dysfunction of the autonomic system is rare. Congenital defects occur in Hirschsprung's disease, in which the intrinsic plexuses of the gastrointestinal tract are aplastic, and possibly in some congenital defects of the urinary tract; autonomic centers in the spinal cord, as well as in peripheral ganglia, may be defective.

*Familial dysautonomia*, the Riley-Day syndrome, occurs mostly in Jews. The constant features are defective or absent lacrimation and corneal sensory impairment leading to corneal ulceration; episodic hypertension and postural hypotension; blotchy skin and hyperhidrosis; generalized indifference to pain; mental and physical retardation; impaired

temperature regulation and feeding problems in infancy. The children are small, emotionally unstable, hypotonic, hyporeflexic or areflexic and poorly coordinated. They swallow poorly, salivate excessively, drool, and have urinary frequency. Recurrent respiratory infection is common. No adequate pathologic basis is known, though disseminated lesions in the reticular formation of the brain stem are described. The diagnosis is a clinical one, based on the signs and symptoms described. Treatment is limited to supportive therapy during hypertensive or vomiting crises, protection of the cornea, use of sedative and ataractic drugs and efforts to maintain a good emotional equilibrium. Some children may reach adult life.

## NEURITIS AND NEUROPATHIES

Degenerative changes in peripheral nerve, plexus or root have many etiologies. Mechanical injury usually involves single nerves or parts of plexuses; chemical, metabolic or toxi-infective substances are more likely to cause generalized damage. The pathology in most cases is similar, comprising breakdown of myelin sheath, proliferation of sheath cells, some invasion by phagocytes and often degenerative change or disruption of axons; true inflammatory changes are slight. In recovery axons remaining intact reinvest with myelin, while those actually degenerated must proliferate from the proximal stump; regeneration is always more complete if physical continuity of the nerve trunk is maintained.

### CHRONIC POLYNEURITIS

This is a syndrome with a clinical pattern like that of acute infective polyneuritis (Guilain-Barré syndrome, p. 525), except that it may continue for several years. Occurring in infancy, it is frequently mistaken for Werdnig-Hoffmann disease, from which it is distinguished by a high cerebrospinal fluid protein content, a mild sensory loss and protracted recovery over years.

### POLYNEURITIS DUE TO CHEMICAL, METABOLIC AND TOXI-INFECTIVE AGENTS

Polyneuritis due to heavy metals, such as lead and thallium, is rare in childhood and usually accompanied by an encephalopathy which dominates the picture. Serum sickness following the injection of almost any foreign protein may cause a generalized polyneuritis or an isolated lesion of a peripheral nerve or plexus, usually of the fifth and sixth cervical roots. These lesions are independent of the site of the injection. Muscular atrophy may be severe and permanent, though the prognosis is usually good. Deficiency states, pellagra, porphyria, primary amyloidosis and certain drugs are also occasional causes.

Polyneuritic and sometimes mononeuritic manifestations occur in many infections of childhood, notably in scarlet fever, typhoid fever, dysentery and mumps. In diphtheria neuritic signs tend to appear in three stages: palato-pharyngo-laryngeal paralysis in the second week of the disease, paralysis of accommodation in the third week and, in the second month, generalized polyneuritis. The last reaches its peak after eight to ten days and recedes slowly over several months.

**TRAUMATIC NEURITIDES**

These are due to direct injury to nerve trunks or to transmitted injury through pressure, edema or scarring. Almost any nerve may be affected; the common groups are (1) obstetric palsies; (2) neonatal facial palsy, and Bell's palsy; (3) palsy due to pressure, laceration or to trauma from injection; (4) palsies due to neoplastic invasion.

**OBSTETRIC PALSY**

See page 318.

**NEONATAL FACIAL PALSY**

See page 320.

**BELL'S PALSY**

Sudden peripheral facial palsy in childhood is identical with that in the adult, weakness being preceded frequently by otitis or exposure to cold; the side of the face is often numb or prickly for a day before paralysis ensues. Pathologically, swelling, congestion and constriction of the nerve in the facial canal are the principal findings.

Bell's palsy is sometimes confused with the early development of facial diplegia in polyneuritis, with bulbar poliomyelitis or other viral involvement of the facial nucleus or with herpetic lesions of the geniculate ganglion. True Bell's palsy is rare under two years of age; facial palsy in this age group should rouse suspicion of one of the above or, more ominously, of tumor of the brain stem.

More than 80 per cent of patients with Bell's palsy make a good recovery if an existing otitis is adequately treated; no other treatment is indicated except for protection of the cornea and perhaps adhesive strapping of the face to avoid stretching of facial muscles during recovery. Corticosteroids, started within the first forty-eight hours, are thought by some to reduce edema and improve recovery. Almost all patients maintain some slight asymmetry throughout life and may have persistent misregenerative movements: blinking the eye when the lips are smacked or twitching the corner of the mouth when the eyes are blinked.

**PALSIES DUE TO PRESSURE OR LACERATION**

Maintained pressure on a nerve trunk interrupts function and ultimately continuity of axons. A poorly placed cast or intravenous board, careless positioning of limbs in anesthetized children and pressure of knapsack straps are common causes. Recovery from such palsies is spontaneous and complete, usually requiring one to four months. Simple pressure

palsies need only support of the involved limb in the position of rest and passive exercise. Lacerations or severances, caused by cuts or at fracture sites, require careful surgical suture. Unless the original cut was a clean one, reparative surgery is best delayed four to eight weeks, since the full extent of destroyed nerve is usually greater than it originally appears. Premature suture may end in ineffective regeneration and formation of a neuroma.

Palsies due to injection of serums and antibiotics deserve special attention. Sciatic and radial nerves are usually involved. Damage is due apparently to direct trauma and to pressure from secondary scarring, rather than to specific toxicity of the injected material. Complete wrist drop usually marks the radial palsy; in sciatic lesions the peroneal division suffers most, and foot drop and peroneal sensory loss are often the only signs. Sharp pain is instantaneous, but weakness may occasionally be delayed for some days; both are often overlooked in the young infant. A fair degree of recovery is the rule, but sciatic injuries in young infants usually arrest growth of the foot. Surgical dissection of scar from the nerve may be of some avail, though its beneficial effect is not proved.

Signs of isolated or multiple root or nerve lesions may be caused by a neoplasm, especially of the pelvis or abdomen. Unexplained persistent weakness, pain, sensory loss or decreased reflexes in the legs should provoke search for such a neoplasm. Another singular variety is a transient radial palsy caused by an overlying mass of subcutaneous fat necrosis in a newborn infant.

DAVID B. CLARK

**REFERENCES***General*

- Epstein, B., and Davidoff, L. M.: *An Atlas of Skull Roentgenograms*. Philadelphia, Lea & Febiger, 1953.
- Ford, F. R.: *Diseases of the Nervous System in Infancy, Childhood and Adolescence*. 3rd ed. Springfield, Ill., Charles C Thomas, 1952.
- Greenfield, J. G.: *Neuropathology*. Baltimore, Williams & Wilkins Company, 1958.
- Ingraham, F. D., and Matson, D. D.: *Neurosurgery of Infancy and Childhood*. Springfield, Ill., Charles C Thomas, 1954.
- Merritt, H. H., and Fremont-Smith, F.: *The Cerebro-spinal Fluid*. Philadelphia, W. B. Saunders Company, 1937.
- Monrad-Krohn, G. H.: *The Clinical Examination of the Nervous System*. 10th ed. New York, Paul B. Hoeber, Inc., 1955.
- Robertson, E. G.: *Pneumoencephalography*. Springfield, Ill., Charles C Thomas, 1957.



- Walsh, F. B.: *Clinical Neuro-ophthalmology*. 2nd ed. Baltimore, Williams & Wilkins Company, 1957.
- Wartenberg, R.: *Diagnostic Tests in Neurology*. Chicago, Yearbook Publishers, Inc., 1953.
- Wilson, S. A. K., and Bruce, A. N.: *Neurology*. 1st ed. Baltimore, Williams & Wilkins Company, 1940.
- Static and Developmental Lesions, Ectodermal Dysplasias and Congenital Vascular Malformations*
- Barry, A., Patten, B. H., and Stewart, B. H.: Possible Factors in the Arnold-Chiari Malformation. *J. Neurosurg.*, 14:285, 1957.
- Benda, C. E.: *Developmental Disorders of Mentation and Cerebral Palsies*. New York, Grune & Stratton, Inc., 1952.
- Bobath, K., and Bobath, B.: The Diagnosis of Cerebral Palsy in Infancy. *Arch. Dis. Childhood*, 31:408, 1956.
- Borberg, A.: *Clinical and Genetic Investigations into Tuberculous Sclerosis and Recklinghausen's Neurofibromatosis*. Copenhagen, Ejnar Munksgaard, 1951.
- Crowe, F. W., Schull, W. J., and Neel, J. V.: Multiple Neurofibromatosis. Springfield, Ill., Charles C Thomas, 1956.
- Evans, P. R., and Polani, P. E.: Neurological Sequelae of Rh Sensitization. *Quart. J. Med.*, 19: 129, 1950.
- Hamby, W. B.: *Intracranial Aneurysms*. Springfield, Ill., Charles C Thomas, 1952.
- Krabbe, K. H.: Facial and Meningeal Angiomatosis Associated with Calcifications of the Brain. A Clinical and Anatomic-pathological Contribution. *Arch. Neurol. & Psychiat.*, 32:737, 1934.
- Kurland, L. T.: Definitions of Cerebral Palsy and Their Role in Epidemiological Research. *Neurology*, 7:641, 1957.
- Masland, R.: The Prevention of Mental Retardation. *A.M.A. Am. J. Dis. Child.*, 95:3, 1958.
- Norman, R. M.: Malformations of the Nervous System, Birth Injury, and Diseases of Early Life; in Greenfield, J. G., and others: *Neuropathology*. Baltimore, Williams & Wilkins Company, 1958.
- Expanding Lesions and Increased Intracranial Pressure*
- Bailey, P., Buchanan, D. N., and Bucy, P. C.: *Intracranial Tumors of Infancy and Childhood*. Chicago, Univ. of Chicago Press, 1939.
- Campbell, J. B., and Cohen, J.: Epidural Hemorrhage and the Skull of Children. *Surg., Gynec. & Obst.*, 92:257, 1951.
- Foley, J.: Benign Forms of Intracranial Hypertension—"Toxic" and "Otitic" Hydrocephalus. *Brain*, 78:1, 1955.
- Foley, J.: Physiology of Increased Intracranial Pressure; in Williams, D.: *Modern Trends in Neurology*. New York, Paul B. Hoeber, Inc., 1957.
- Johnson, R. T.: Patterns of Mid-Brain Deformity in Expanding Intracranial Lesions; in Williams, D.: *Modern Trends in Neurology*. New York, Paul B. Hoeber, Inc., 1957.
- Pennybacker, J.: Abscess of the Brain; in Feiling, A.: *Modern Trends in Neurology*. London, Butterworth and Co., 1951.
- Russell, D. S.: Observations on the Pathology of Hydrocephalus. Special Report 265, The Medical Research Council. London, H. M. Stationery Office, 1949.
- Sweet, W. H.: Formation, Absorption, and Flow of Cerebrospinal Fluid; in Williams, D.: *Modern Trends in Neurology*. New York, Paul B. Hoeber, Inc., 1957.
- Symonds, C. P.: Hydrocephalic and Focal Cerebral Symptoms in Relation to Thrombophlebitis of the Dural Sinuses and Cerebral Veins. *Brain*, 60:531, 1937.
- Degenerative Diseases*
- Aronson, S. M., Saifer, A., Kanof, A. A., and Volk, B.: Progress of Amaurotic Family Idiocy as Reflected by Serum and Cerebrospinal Fluid Changes. *Am. J. Med.*, 24:390, 1958.
- Austin, J. H.: The Metachromatic Form of Diffuse Sclerosis. I. Diagnosis during Life by Urine Sediment Examination. *Neurology*, 7:415, 1957.
- Bell, J.: *Treasury of Human Inheritance*. Part I. Cambridge University Press, 1934.
- Brandt, S.: Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy. Copenhagen, E. Munksgaard, 1950.
- Denny-Brown, D.: *Diseases of the Basal Ganglia and Subthalamic Nuclei*. New York, Oxford Loose-Leaf Medicine, Oxford University Press, 1945.
- Gall, J. C., Hayles, A. B., Siebert, R. G., and Kuth, H. M.: Multiple Sclerosis in Children. *Pediatrics*, 21:703, 1958.
- Greenfield, J. G.: *The Spino-cerebellar Degenerations*. Springfield, Ill., Charles C Thomas, 1954.
- Scheinberg, I. H.: Relation of Ceruloplasmin and Plasma Copper to Hepatolenticular Degeneration; in *Neurochemistry*. Korey, S. A., and Nurnberger, J. I.: New York, Paul B. Hoeber, Inc., 1956.
- van Bogaert, L., Cumings, J. N., and Lowenthal, A.: *Cerebral Lipidoses. A Symposium*. Springfield, Ill., Charles C Thomas, 1957, p. 212.
- Walton, J. N.: The Limp Child. *J. Neurol., Neurosurg. & Psych.*, 20:144, 1957.
- Neurologic Syndromes Peculiar to Childhood*
- Cottom, D. G.: Acute Cerebellar Ataxia. *Arch. Dis. Childhood*, 32:181, 1957.
- Ford, F. R., and Schaffer, A. J.: The Etiology of Infantile (Acquired) Hemiplegia. *Arch. Neurol. & Psychiat.*, 18:323, 1927.
- Cranio-cerebral and Spinal Trauma*
- Brock, S., ed.: *Injuries of the Skull, Brain, and Spinal Cord*. Baltimore, Williams & Wilkins Company, 1940.
- Crothers, B., and Putnam, M. C.: Obstetrical Injuries of the Spinal Cord. *Medicine*, 6:41, 1923.
- Trauma of the Nervous System. *Proc. A. Res. Nerv. & Ment. Dis.*, 24:1943.
- Diseases of the Spinal Cord and Autonomic Nervous System*
- Paine, R. S., and Byers, R. K.: Transverse Myelopathy in Childhood. *Am. J. Dis. Child.*, 85:151, 1953.
- Riley, C. M.: Familial Dysautonomia. *J.A.M.A.*, 149: 1532, 1952.

# Tetany

Tetany is a syndrome whose principal manifestations result from a state of increased neuromuscular irritability. Because of its occurrence in a number of unrelated conditions, it has seemed expedient to describe the more important types under their respective designations. They are brought together here as an aid in the differential diagnosis of the various conditions in which tetany may be one of the manifestations. The differential data are summarized in Table 108.

The clinical forms of tetany can be divided into two groups: those caused by a decrease in serum calcium, and those associated with a state of alkalosis. Tetany has also been attributed to certain intoxicants, notably guanidine.

Tetany can be produced experimentally in animals by intravenous administration of phosphate. Serum calcium is lowered after injection of either the acid or the alkaline salt, but tetany occurs only after administration of the alkaline phosphate. It is assumed that the acid salt increases the relative concentration of the ionized calcium, whereas the alkaline salt reduces it. It is estimated that under usual conditions slightly more than 50 per cent of the serum calcium is in a diffusible state and that the remainder is non-diffusible, being bound to serum protein. Practically all the diffusible calcium is ionized; only a small fraction is present in the form of a citrate-like compound.

It is the increase or decrease of the diffusible or ionized serum calcium which is responsible, respectively, for the symptoms of hypercalcemia or hypocalcemia. Thus for a proper evaluation of a serum calcium determination the serum protein level should also be known, since, even when the total serum calcium is within the normal range, the ionized fraction may be increased or decreased, depending upon the level of the serum protein. Nephrosis provides an example. Owing to the low serum protein levels, total serum calcium may be reduced below the tetany level of 6 to 7.5 mg. per 100 ml. without clinical manifestations of tetany be-

cause there remains an adequate concentration of ionized calcium. Conversely, the serum ionized calcium could be so increased in such a case by hyperactivity of the parathyroids or administration of parathyroid hormone that the relative increase in ionized calcium would actually constitute hypercalcemia, even though the total serum calcium was not above the normal range.

Tetany may also be produced experimentally in animals by feeding them diets deficient in magnesium. In such instances the serum magnesium is lowered, but the calcium and phosphorus are within normal limits. Though a few isolated cases of tetany in the human subject have been attributed to magnesium deficiency, only one case has been reported in which the data are sufficiently impressive to suggest that this type of tetany may occur in man (Miller).

**Clinical Forms. Hypocalcemic tetany.** Serum calcium may be reduced by a number of factors, but, whatever the cause, when the total concentration falls below 7 or 7.5 mg. per 100 ml., symptoms of tetany are likely to occur. In *tetany of the newborn* (p. 342) it is postulated that there is temporary hypofunction of the parathyroid glands and that the serum calcium may be further lowered by too heavy initial feeding of cow's milk with its relatively high phosphorus content. After the first four weeks of life vitamin D deficiency (p. 378) and celiac disease (p. 723) are the most frequent causes of hypocalcemic tetany. Infrequently in children, hypoparathyroidism (p. 1175) is a factor.

**Tetany of alkalosis.** The mechanism of the tetany of alkalosis is not entirely understood; it is not associated with changes in the serum levels of calcium and phosphorus. It has been suggested that the shift of the acid-base balance of the blood to the alkaline side reduces the amount of ionized calcium without reducing the total serum calcium concentration. Though this concept is not completely substantiated, the fact that the symptoms of tetany can be abolished by acid salts or other factors which decrease the pH of the



blood without altering the level of the serum calcium or phosphorus can be accepted as evidence in favor of it. Clinically, the tetany of alkalosis may be observed in conditions responsible for excessive overbreathing (hyperventilation tetany), loss of chloride (gastric tetany) or excessive intake of bicarbonate (bicarbonate tetany).

In *hyperventilation tetany* there is an excessive loss of plasma carbonic acid with a lesser loss of bicarbonate. The pH of the blood is elevated, but the carbon dioxide content is decreased (respiratory alkalosis, p. 179). Overbreathing may be due to hysteria or high altitude or to irritation of the central nervous system by infectious or toxic agents.

Table 108. Differential Data of Various Types of Tetany\*

Type of Tetany	Usual Age Distribution	Serum Calcium	Serum Phosphorus	Bicarbonate of Blood	pH of Blood	Serum Phosphatase	Excretion during Low Calcium Diet			
							Urine		Feces	
							Ca	P	Ca	P
Tetany of the newborn	First 2-3 weeks of life	Low	High			Normal				
Hypocalcemic Tetany										
Vitamin D deficiency—rickets (infantile tetany)	3 months -3 years	Low	Low or normal	Normal	Normal	High	Low	Low	Low	Low
Celiac disease	Infancy and childhood	Low	Low or normal	Normal	Normal	Normal or slight increase	Low	High	High	Normal
Hypoparathyroidism: traumatic; idiopathic surgical	Children and young adults Young adults	Low	High	Normal	Normal	Normal	Low	Low	Normal	Normal
Pseudohypoparathyroidism (Albright)	Any	Low	High							
Tetany of Alkalosis										
Hyperventilation	Any	Normal	Normal	Low	High					
Gastric (vomiting)	Any	Normal	Normal	High	High					
Bicarbonate	Any	Normal	Normal	High	High					
Other and Experimental Types of Tetany										
Phosphate		Low	High	Normal	Normal or high					
Magnesium deficiency		Normal	Low or normal							
Guanidine		Normal or slightly lower	Normal or slight increase							

\* Adapted from Aub; Best and Taylor; and Shelling.



FIG. 328. Carpal spasm in tetany.

*Gastric tetany* follows loss of chloride ions from excessive vomiting, repeated gastric lavage or gastric retention. It is occasionally observed in pyloric stenosis and in high intestinal obstruction. The chloride of the serum is reduced and the bicarbonate elevated. The carbon dioxide content and the pH of the blood are increased.

*Bicarbonate tetany* occasionally results from ingestion or intravenous administration of sodium bicarbonate. Both the carbon dioxide content and the pH of the blood are elevated. The danger of administration of bicarbonate in the presence of vomiting or renal insufficiency cannot be overemphasized.

**Clinical Manifestations.** The symptoms of tetany are essentially the same, irrespective of the etiology, and reflect a state of increased neuromuscular irritability. There are, of course, clinical manifestations peculiar to each of the various disturbances with which tetany is associated. The manifestations of tetany may be divided into two phases, latent and manifest.

**Latent tetany.** In the latent phase there are no spontaneous manifestations, but increased neuromuscular excitability may be elicited by the mechanical or electrical means described below. The diagnosis is confirmed in hypocalcemic tetany by a low serum calcium level.

**CHVOSTEK'S SIGN.** This is a unilateral

contraction of the facial muscles about the mouth, nose and eye when the area in front of the auditory meatus, where the facial nerve approaches the surface, is tapped. It cannot be obtained while the infant is crying. A positive Chvostek's sign is normal in the newborn infant and is obtained frequently in healthy children over five years of age, but in the age range of vitamin D-deficient tetany, three months to three years, it is strong presumptive evidence in favor of tetany.

**PERONEAL SIGN.** This is elicited by tapping the peroneal nerve just below the head of the fibula while the knee is relaxed and slightly flexed. A positive response consists in dorsal flexion and abduction of the foot.

**TROUSSEAU'S SIGN.** This is based on the production of carpal spasm. It is elicited by maintaining firm constriction of the upper arm for two or three minutes after the hand has become blanched. When the test is positive, the hand assumes the position of carpal spasm, which is described below under Carpopedal Spasm.

**ERB'S SIGN.** This is obtained by measuring the amount of galvanic current required to elicit a muscular contraction and is based on the greater muscular irritability of the patient with tetany. It is the most sensitive of the various tests, but requires skill for its performance and interpretation. The current required to obtain anodal and cathodal contractions is measured on a milliammeter. The electrodes are moistened in saline solution; the indifferent one is placed on the abdomen, and the stimulating one over the nerve to be tested. The peroneal nerve is usually used. The average electrical thresholds for the various ages are shown in Table 109. More current is required to elicit a response in an infant than in an older child. The response to the cathodal opening contraction (C.O.C.) is considered to be most significant; when this is obtained in children under five years of age with less than 5 milliamperes of current, it is pathognomonic of tetany. An anodal opening contraction (A.O.C.) obtained with less current than the anodal closing contrac-

Table 109. Typical Electrical Thresholds (in Milliampères) in Normal Persons at Different Ages\*

Age	C.C.C.	A.C.C.	C.O.C.	A.O.C.	
Under 6 months.....	3.5	7.0	10.0	9.0	A.O.C. > A.C.C.
About 1 year.....	2.5	5.0	8.0	6.0	A.O.C. > A.C.C.
Over 5 years.....	1.8	4.0	6.5	3.5	A.O.C. < A.C.C.

\* From Shelling: The Parathyroids in Health and Disease. C. V. Mosby Company.





FIG. 329. Pedal spasm.

tion (A.C.C.) and with less than 5 milliamperes of current during the first six months of life or with less than 2 milliamperes from the age of four to five years is also considered characteristic of tetany.

**Manifest tetany.** This phase is characterized by spontaneous muscular twitchings and spasms, laryngospasm and convulsions.

**CARPOPEDAL SPASM.** This is perhaps the most characteristic feature of tetany. The thumb is drawn into the cupped palm, the hands are abducted and the wrists flexed, and the fingers are flexed at the metacarpophalangeal joints, but extended at the more distal ones (Fig. 328). The foot is extended in the position of talipes equinus or equinovarus, the toes flexed, and the sole cupped (Fig. 329). Both the arms and the legs may be rigidly flexed and adducted.

**LARYNGOSPASM.** This is a relatively common manifestation and may be characterized simply by an inspiratory, high-pitched crowing sound, but in extremely severe cases there is such spasm that respirations may cease for an uncomfortable interval and the infant become quite cyanotic. Rarely intubation is required for relief, and occasionally an infant has died during such an attack.

**CONVULSIONS.** These do not differ from other generalized seizures, except as there may be carpopedal spasm.

**Diagnosis.** The diagnosis is based on the clinical manifestations and the laboratory data. Of the latter, the important measurements are the serum calcium in hypocalcemic

tetany and the pH of the blood in the tetany of alkalosis. These and other data are detailed in Table 108.

In the differential diagnosis other causes of convulsions must be considered (p. 1115), as must other conditions which may be responsible for laryngospasm or stridor. *Congenital stridor* is eliminated as a possibility, since it is present from birth. The laryngospasm of *pertussis* has been confused with that of tetany. The characteristic cough of *pertussis*, with absence of other signs of tetany, should establish the diagnosis, which, in many instances, may be confirmed bacteriologically. *Acute laryngeal infections* are characterized by fever and other evidences of infection. Breath-holding spells may be confused with tetany, but a history of previous episodes, the relation to fits of temper and the absence of other signs of tetany are differential factors.

**Treatment.** Treatment of the various hypocalcemic tetanies is considered under their respective headings. In tetany due to alkalosis primary attention should be directed to relieving the cause. In hyperventilation tetany, rebreathing into a paper bag and inhalation of carbon dioxide are helpful procedures. Carefully controlled sedation is usually indicated to decrease the hyperpnea. In gastric tetany the underlying disturbance should be controlled, if possible, and generous amounts of physiologic saline solution should be administered parenterally. Acid salts such as ammonium chloride or calcium lactate may be administered orally if vomiting is controlled.

WALDO E. NELSON

## REFERENCES

- Aub, J. C.: Diseases of the Parathyroid Glands, in Cecil, R. L., ed.: *Textbook of Medicine*, 8th ed. Philadelphia, W. B. Saunders Company, 1951.
- Guild, H. G.: Infantile Tetany; in Brennemann, J., ed.: *Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 1, Chap. 37.
- McLean, E. C., and Hastings, A. B.: The State of Calcium in the Fluids of the Body; The Conditions Affecting the Ionization of Calcium. *J. Biol. Chem.*, 108:285, 1935.
- Miller, J. L.: Tetany Due to Deficiency in Magnesium. *Am. J. Dis. Child.*, 67:117, 1944.
- Shelling, D. H.: *The Parathyroids in Health and in Disease*. St. Louis, C. V. Mosby Company, 1935.

# Convulsive Disorders

Convulsive phenomena are common symptoms in children and occur with a wide variety of disorders of the central nervous system. Seizures may be classified according to (1) their etiology or pathogenesis (see Table 110), (2) their clinical manifestations, and (3) their electroencephalographic pattern.

**Incidence at Various Ages.** In clinical practice consideration of the relative incidence of the various etiologic factors at different ages (Fig. 330) is frequently helpful in arriving at a correct diagnosis and in evaluating prognosis.

Convulsions are far more common during the first two years than at any other period of life. Intracranial birth injuries, including the effects of anoxia and hemorrhage and congenital defects of the brain, are the most

frequent causes of convulsions in very young infants. In the latter part of infancy and in early childhood acute infections (extracranial and intracranial) are the most frequent causes. Far less frequent causes in infants are tetany, idiopathic epilepsy, spontaneous hypoglycemia, brain tumors, renal insufficiency, poisoning, asphyxia, spontaneous intracranial hemorrhage and thrombosis, postnatal trauma and others listed in Table 110. By midchildhood acute extracranial infections have become an infrequent cause of convulsions, whereas idiopathic epilepsy, first appearing as an important cause of convulsions about the third year of life, is the most common etiologic factor.

Other causes of convulsive seizures in the postinfancy period are congenital defects of the brain, residual cerebral damage from

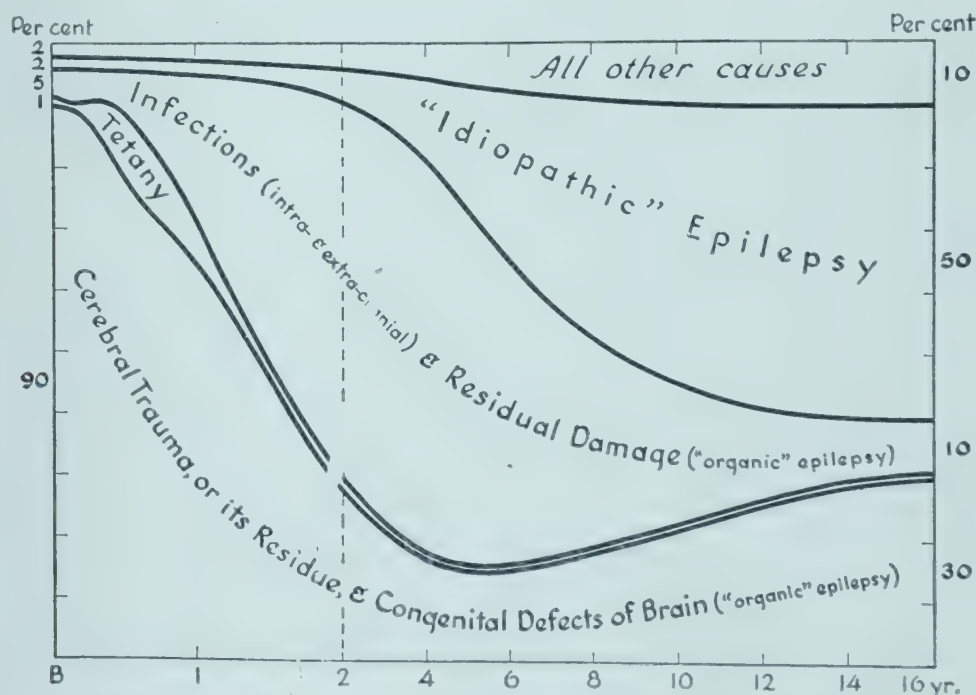


FIG. 330. Comparative incidence of different causes of convulsions at different ages from birth to the sixteenth year of life. The data used in the construction of this chart are representative of pediatric experience in children's clinics in the northern part of the United States, covering the period between 1925 and 1940. It is likely that there are some variations in the percentage distribution of causes of convulsions at various ages at present. In particular there is probably a significant decrease in those due to tetany of vitamin D deficiency.



earlier trauma, infection, lead poisoning, phritis and certain degenerative diseases of brain tumors, acute or chronic glomerulone- the brain.

*Table 110. Etiologic Classification of Convulsive Disorders*

<i>I. Acute or Nonrecurrent Forms</i>	
"Febrile convulsions" (e.g., at onset of acute extracranial infections; in association with high environmental temperatures)	
Intracranial infections (e.g., acute meningitis, encephalitis, sinus thrombophlebitis, cerebral abscess, tetanus, malaria, typhus fever)	
Intracranial hemorrhage (e.g., from birth or other trauma, hemorrhagic disease, rupture of defective vessels)	
Toxic:	
1. Convulsant drugs (e.g., camphor, thujone, Metrazol, strychnine)	
2. Kernicterus	
3. Lead encephalopathy	
Anoxic (e.g., sudden severe asphyxia, inhalation anesthesia)	
Metabolic or nutritional (e.g., acute hypocalcemic tetany, alkalosis, therapeutic hypoglycemia, pyridoxine deficiency)	
Acute cerebral edema (e.g., in acute glomerular nephritis or allergic edema of the brain)	
Brain tumor	
Miscellaneous	
<i>II. Chronic or Recurrent Forms</i>	
Epilepsy:	
1. Idiopathic (primary, cryptogenic, essential or genuine epilepsy)	
(a) Hereditary or genetic type	
(b) Nongenetic or acquired idiopathic type (?)	
2. Organic (secondary or symptomatic epilepsy—with residual brain damage from previous focal or diffuse injuries)	
(a) Post-traumatic (e.g., from direct laceration of brain tissue)	
(b) Posthemorrhagic (e.g., from injury at birth or later, from hemorrhagic diseases, pachymeningitis, rupture of miliary aneurysm)	
(c) Postanoxic (e.g., from severe asphyxia neonatorum)	
(d) Postinfectious (e.g., following encephalitis, meningitis, sinus thrombophlebitis or abscess)	
(e) Post-toxic (e.g., kernicterus, encephalopathy following lead, arsenic or other chronic poisoning)	
(f) Degenerative (e.g., "idiopathic atrophy," cerebromacular degeneration, encephalitis periaxialis diffusa, intracranial neurofibromatosis)	
(g) Congenital (e.g., cerebral aplasia, porencephaly, tuberous sclerosis, hydrocephalus, vascular anomalies such as the Sturge-Weber type and arteriovenous aneurysms)	
(h) Parasitic brain disease (cysticercosis, toxoplasmosis, syphilis)	
(j) Posthypoglycemic injury	
Epilepsy-simulating states:	
Narcolepsy and cataplexy	
Hysteria ("psychogenic epilepsy")	
Tetany	
1. Hypocalcemic (e.g., idiopathic, postoperative, neonatal, vitamin D deficiency, deficient intestinal absorption)	
2. Of alkalosis (e.g., vomiting, administration of bicarbonate, hyperventilation)	
Hypoglycemic states	
1. Hyperinsulinism (e.g., tumor or hyperplasia of islets of Langerhans)	
2. Hypopituitarism (e.g., deficiency of adrenocorticotrophic, thyrotropic and growth hormones)	
3. Adrenal cortical insufficiency	
4. Hypothyroidism (e.g., cretinism)	
5. Hepatic disorders (e.g., von Gierke's disease)	
6. Miscellaneous (e.g., familial type, idiopathic)	
Uremia	
"Cerebral" allergy	
Cardiovascular dysfunction or syncopal attacks (e.g., simple fainting attacks, Stokes-Adams syndrome, hyperactive carotid sinus reflex)	
Migraine	

## ACUTE OR NONRECURRENT CONVULSIVE DISORDERS

The causes of acute convulsive attacks in children are extremely varied (Table 110). Any type of seizure may occur as a transient manifestation of acute disease involving the brain, but generalized tonic and clonic convulsions similar to the grand mal attack of epilepsy are by far the most common. Practically all seizures resulting from extracranial disorders are of this type.

Approximately 6 to 8 per cent of all children have "febrile convulsions," most of which occur after the first six months of life, but within the first two to three years. The incidence decreases progressively up to six to eight years of age, after which such seizures are exceedingly rare. Males are more often affected than females, and there appears to be an increased susceptibility in some families.

**Diagnosis.** Though most of the convulsions which occur in the latter part of infancy and in the first few years of childhood merely represent an initial symptom of an acute febrile illness, each child who has had a convulsion should be examined for the possibility of some other cause. Such disorders as tetany, lead encephalopathy, intracranial injury, hemorrhage or tumor, poisoning with a convulsant drug, hypoglycemia, asphyxia, cerebral sinus thrombosis (associated with cyanotic congenital heart disease and cachexia), acute nephritis and epilepsy should be considered. Figure 330 indicates the importance of considering the age factor as an aid to diagnosis.

A carefully taken history of previous attacks, of immediately preceding symptoms such as hyperirritability, fever, muscular cramps, headache, vomiting or dizziness, of a possible dietary deficiency, of poisoning of any kind, of cranial injury, of a hemorrhagic tendency, of exposure to infection or of a hereditary predisposition to seizures is invaluable for orientation.

A complete physical examination, including a thorough neurologic appraisal, is essential. Inspection of the eyegrounds may give the first clue to the nature of the primary illness by revealing an optic neuritis or choking of the disks. These may occur in the presence of an expanding intracranial lesion (tumor, cyst, hemorrhage or abscess), acute hydrocephalus or severe encephalitis. Such examination may also reveal the presence of

retinal hemorrhages, suggesting intracranial bleeding from trauma or a blood dyscrasia. Albuminuric retinitis may furnish the first clue to the presence of subacute or chronic nephritis. There may be slight choking of the optic disks in acute nephritis with arterial hypertension. The chorioretinitis of toxoplasmosis, the reddish areas of degeneration in the macular region in cerebromacular degenerative disease, and the choroidal tubercles of miliary tuberculosis are highly characteristic.

Determinations of the calcium and inorganic phosphorus of the serum, of the sugar and urea nitrogen of the whole blood will aid in the diagnosis of hypocalcemic tetany, hypoglycemia and acute nephritis, respectively. Coexisting hypertension, albuminuria and cylindruria are evidences of nephritis. Roentgenographic examinations may show the "lead line" of lead poisoning in the long bones, or thinning of the skull and separation of the sutures in the presence of an expanding intracranial lesion.

If the primary disease is infectious, it should be ascertained whether the infection is extracranial ("febrile" or "prefebrile" convulsions) or intracranial. It is necessary to determine whether an intracranial infection is meningitis, encephalitis, abscess, sinus thrombophlebitis or tetanus. Certain other infectious diseases, such as typhus fever and malaria, which produce local lesions in the brain may occasionally cause convulsions; in some instances the convulsions are related to disturbances of water and electrolyte balance.

**Treatment.** For the control of "febrile" convulsions which occasionally occur at the onset of acute extracranial infections a sedative dose of phenobarbital (3 mg. per kilogram of body weight) and reduction of the elevated body temperature usually suffice.

If the convulsion is prolonged or if the child has a second convulsion before he recovers fully from the first, more vigorous anticonvulsant treatment is indicated (see p. 1117). The appropriate treatment for other conditions which may be responsible for acute convulsive seizures is detailed elsewhere.

Seizures secondary to electrolyte disturbances require special therapy (see p. 192). After other causes for seizures have been excluded as well as it is possible to do so a



clinical trial of pyridoxine may be indicated in young infants (see p. 110).

**Prognosis.** When a seizure is a result of some physical or metabolic disturbance, the prevention of recurrent convulsions is dependent upon the eradication or control of the underlying disease.

After a single "febrile" seizure the family can be reassured that the probability of chronic epilepsy is not great. The occurrence of more than one "febrile" seizure increases the probability of subsequent spontaneous nonfebrile convulsions. According to Livingston, there is a relatively high probability that idiopathic epilepsy will develop in children who have more than five "febrile" convulsions in a twelve-month period, single seizures which last for more than one hour, or persistent electroencephalographic abnormalities. However, the electroencephalogram of a child who has had a febrile convulsion may be abnormal as long as a week afterward. Approximately 25 per cent of epileptic children do not have a history of "febrile" seizures.

Present evidence seems to indicate that daily anticonvulsant therapy does not reduce the number or duration of "febrile" convulsions. Therefore, as long as the physician feels that a child has "febrile" convulsions, such therapy is not indicated. When convulsions recur with little or no evidence of infection or if the electroencephalogram is significantly abnormal two weeks or more after the last seizure, a therapeutic trial of daily anticonvulsant therapy may be indicated.

An infant or young child who has had one or more "febrile" seizures is entitled to more prompt antipyretic measures, such as aspirin or tepid sponges, and *anti-infectious* therapy than might otherwise seem indicated. Some physicians give phenobarbital prophylactically to such infants during a febrile episode. If anti-infectious or anticonvulsant therapy is prescribed, the physician must observe the child closely for the possibility that such serious infections as meningitis may be masked.

## CHRONIC OR RECURRENT CONVULSIONS

### EPILEPSY

The terms *epilepsy* (from the Greek *epilēpsia*, a seizure) and *recurrent convulsive disorder* can be used interchangeably. These terms designate a variable symptom complex characterized by recurrent, paroxysmal attacks of unconsciousness or impaired consciousness, usually with a succession of tonic or clonic muscular spasms or other abnormal behavior. If a cause of the patient's seizures cannot be found, he may be said to have *idiopathic* or *cryptogenic epilepsy*; if a cerebral abnormality is demonstrable, *organic* or *symptomatic* epilepsy.

Because many persons, from prejudice or ignorance, feel that a person with epilepsy will somehow fail to make an adequate social adjustment, some physicians are reluctant to use the term "epilepsy" in discussing the problem with parents. Although its use without a previous explanation of its meaning may be potentially harmful, an affected family should know the term and how it applies to them. This is part of the physician's responsibility as he educates the family toward living more comfortably with a chronic ill-

ness. There is considerable variation in a family's ability and desire to acquire information about a chronic illness. Too much information on a single visit is undesirable (see p. 1122). Orientation should be a continuing process, especially during the early period of medical supervision.

**Idiopathic Epilepsy.** Approximately 60 per cent of children who have a recurrent convulsive disorder before fourteen years of age have idiopathic epilepsy. The onset is between the ages of four and eight years in about 50 per cent; less than 2 per cent of them have a convulsion before the age of two years (Fig. 330). In most instances there is no significant degree of mental retardation and no significant physical defect. Acceptable prophylactic control of the seizures is possible in at least 85 per cent of such patients.

The underlying cause of the convulsions has not been determined. It is possible that a specific genetic defect in cerebral metabolism is responsible in most instances.

Electroencephalographic tracings, particularly during sleep, show definite generalized abnormalities in 90 per cent of children with

idiopathic seizures. Rarely there are focal electroencephalographic abnormalities; on repeated examinations a focus often migrates from one area to another. Lennox has pointed out that electroencephalographic abnormalities (cerebral dysrhythmias) are more likely to be found in parents and siblings of affected children than in the population at large. However, a hereditary factor is usually not clinically demonstrable.

**Organic Epilepsy.** A variety of genetically determined conditions (Table 110) are associated with seizures. These disorders have abnormalities demonstrable anatomically (congenital ectodermoses) or biochemically (phenylketonuria). In addition, convulsions may occur after cerebral damage acquired in the prenatal, natal or postnatal period. Neurologic examination of such children frequently shows a motor handicap of central nervous system origin (cerebral palsy) and mental retardation. These patients almost always have electroencephalographic abnormalities.

The recognition of genetically determined conditions is important for several reasons: (1) Cerebral damage in younger siblings of affected patients may be prevented in certain instances by prompt and effective therapy (congenital hypoglycemia, phenylketonuria, kernicterus). (2) Less characteristic signs and symptoms in siblings may be more readily recognized (tuberous sclerosis, lipochondrodystrophy, neurofibromatosis). (3) Identification of an organic etiology of the seizures is important prognostically; in general, control of such seizures is less good and social adjustment of the child less adequate than in children with the idiopathic form.

**Clinical Manifestations.** *Grand mal seizures.* These seizures may be preceded by a momentary aura, but fewer than a third of epileptic children can give a definite description of such an experience. In some cases a preliminary, localized spasm or twitching of muscles may precede a generalized seizure. This is often referred to as a "motor aura," or warning. Vague prodromal symptoms or signs, such as irritability, digestive disturbances, headache and mental dullness, may forewarn patients or their parents of impending motor seizures. The period intervening is usually short, but may be hours or even a day or two.

Grand mal seizures are generalized convulsions, usually with tonic and clonic phases of the muscular spasms. The onset of the paroxysm is abrupt, and the tonic spasm may occur simultaneously with loss of conscious-

ness. The patient, if sitting or standing, falls to the ground. His face suddenly becomes pale, the pupils dilate, the conjunctivas become insensitive to touch, the eyeballs roll upward or to one side, the face is distorted, the glottis is closed, the head may be thrown backward or be twisted forcibly to one side, the abdominal and chest muscles are held rigidly, and the limbs are contracted irregularly or stiffen out. As the air is forced out of the lungs through the glottis by sudden contraction of the diaphragm and the intercostal muscles, a short, startling cry may be heard. The tongue may be severely bitten as a result of the rapid contraction of the jaw muscles. Micturition and less frequently defecation may follow the sudden forceful contraction of the abdominal muscles. As the tonic phase of the seizure continues, facial pallor is quickly followed by suffusion and this in turn by cyanosis, occasionally severe, due to arrest of all respiratory movements. At the end of this phase, which usually lasts not more than twenty to forty seconds, the clonic phase sets in, and lasts for variable periods of time.

The patient may awake from his postconvulsive sleep with a severe, generalized headache and in a state of confusion. He may go about in a semidazed or stuporous state in which he may perform more or less automatic acts without being able to recollect what he has experienced. These postparoxysmal or postictal reactions are interpreted as malfunctioning of neurons which have not yet recovered from the effects of the seizure. These may be so severe as to result in prolonged automatism, transient paresis or, more rarely, in hemiplegia or other paralytic manifestations of focal injury or hemorrhage.

A grand mal seizure may occur at night (nocturnal epilepsy) without the patient's being aware of it. A bitten tongue or lip, headache, blood on his pillow or a bed wet with urine may be the only clue. Generalized motor seizures tend to be predominantly tonic during infancy, although the clonic feature is always present to some degree.

So-called secondary symptomatology, which pertains chiefly to personality traits such as egocentricity, shallowness, religiosity and chronic negativism and which is considered by some to be characteristic of epilepsy, is much less prominent in children than in adult patients. When such personality traits are manifest, they usually represent the patient's response, over a long time, to psychogenically injurious attitudes of other people toward him and his disability. These traits are not



to be attributed to the disease per se or confused with the transient behavior disturbances of psychomotor attacks. Similar personality disturbances develop frequently for the same general reasons in victims of any chronic handicapping condition.

**Petit mal seizures.** These seizures consist in a transient loss of consciousness. There may be such minor manifestations as an upward rolling of the eyes, moving of the lips, drooping or rhythmic nodding of the head, or slight quivering of the trunk and limb muscles. Clinical evidence of petit mal rarely appears before three years of age, and frequently disappears by the time of puberty. Girls are more often affected than boys. Intellectual development is rarely impaired in children who have only simple, staring petit mal seizures. Attacks of this type last less than thirty seconds and are most frequently described by parents or other associates of the child as "dizzy spells," "absences," "lapses" or "fainting turns." The patient rarely falls, but usually drops articles which he may have in his hand or mouth at the time. If performing an act such as writing or reading at the time of onset, he will suddenly discontinue it, and then resume it when the seizure is ended. He may not be aware of having had a convulsion. Such seizures vary in frequency from one or two a month to as many as several hundred a day. Individual petit mal seizures may, in rare instances, become progressively prolonged and gradually resemble a mild form of grand mal. Prolonged episodes of confusion, inappropriate action and loss of ability to speak or understand (petit mal status) are rare and can be distinguished from psychomotor seizures only by an electroencephalogram during the attack.

**Pyknolepsy.** Pyknolepsy (pyknoepilepsy, "myriad spells") is the designation used by Adie to describe a clinical state in which mild petit mal seizures suddenly appear in great numbers in otherwise normal children between the ages of three and ten years. Such episodes recur over a period of months or years, then cease spontaneously and permanently without impairment of the victim's mentality. The electroencephalograms of such patients are typical of petit mal epilepsy. There appears to be little justification for setting this condition apart as a separate clinical entity.

**Psychomotor seizures.** Psychomotor seizures are the most difficult to recognize and, except for infantile myoclonic spasms, to control. They consist in purposeful but inap-

propriate motor acts, which are repetitive and often complicated. Most frequently a slight aura may manifest itself in a young child by a shrill cry or an attempt to run for help. Often the child is drowsy or sleeps for a short time after the spell. The seizure itself often consists in a gradual loss of postural tone. For example, the child may extend one arm and make a slow half-turn to one side while falling slowly to the ground. He often has vasomotor changes, such as circumoral pallor. After a one- to five-minute episode of unconsciousness the child may resume his normal activity or may sleep. There are usually no tonic or clonic movements. Fugue states or episodes of confusion, which may resemble petit mal status, are rarely noted in children. A normal electroencephalogram, except at the time of a psychomotor seizure, is not uncommon. Treatment is similar to that of grand mal seizures.

**Focal seizures.** These seizures may be sensory or motor in type (jacksonian epilepsy), depending upon the location of the focal area of abnormal neuronal discharge. Localized sensory attacks which give rise to a variety of symptoms are rare in children. Focal seizures, either sensory or motor, may occasionally occur in the absence of organic lesions. Although they are not infrequently preceded by a brief tonic phase, unilateral motor or jacksonian attacks are typically clonic, indicating their origin in the motor cortex. The muscles most frequently involved in a jacksonian seizure are those most specialized for voluntary purposes—most frequently those of the hand, face or tongue and less often of the foot and trunk.

As might be expected from the relationship of the areas of representation of the various muscle groups in the precentral gyrus, a focal motor seizure beginning in one member spreads or extends to others according to a fixed pattern, e.g., from thumb to fingers, to wrists, to arm, to face and then to the leg on the same side ("jacksonian march" of muscle spasms). When such an attack is of brief duration and remains localized to one area, consciousness may not be disturbed. When its spread is extensive and rapid, however, consciousness is lost, and a generalized convulsion follows, indistinguishable from a typical grand mal seizure.

**Infantile myoclonic seizures.** This term describes a type of convulsive seizure in infants which is also variously termed "infantile spasm," "lightening major" and "jack-knife epilepsy." Unlike true petit mal seizures,

these episodes occur before two years of age and involve more than a single group of muscles. The most common type of mass myoclonus consists in a sudden dropping of the head and flexion of the arms. The attack may be repeated several hundred times a day. The electroencephalographic changes suggest a diffuse, disorganized state and consist of random high voltage slow waves and spikes (hypsarrhythmia). It is one of the most characteristic encephalographic patterns. An underlying defect in cerebral metabolism appears to be responsible. Although the convulsive manifestation tends to disappear after the second or third year of life, most children with this condition are seriously retarded mentally and may later have grand mal seizures.

Unless a specific cause such as phenylketonuria can be discovered, control of the seizures has been generally unsatisfactory. For infants who developed normally before the onset of seizures, Sorel has suggested therapy with corticotropin. His plan of therapy consists of 5 units of ACTH gel daily in conjunction with Thorazine (5 mg. three times a day) and Mysoline (125 mg. twice a day) for fifteen days. If electroencephalographic abnormalities were present eight days later, the course of therapy was repeated. Infants who had had seizures for less than two months prior to therapy were said to have recovered completely; those with illness of longer duration continued to be mentally retarded. This form of therapy requires further evaluation.

**Myoclonic and akinetic seizures.** Occasionally children with or without other clinical manifestations of epilepsy have myoclonic jerks or involuntary muscular contractions with or without loss of consciousness. A single group of muscles is usually affected. A patient may have a normal electroencephalogram while he is having myoclonic jerks involving one side or one extremity. The origin of the seizure is presumed to be subcortical in such instances.

An akinetic seizure is associated with a sudden generalized loss of postural tone and therefore differs from single or repeated myoclonic jerks. These seizures in young children may resemble infantile myoclonic seizures and are sometimes called motor petit mal, jackknife or akinetic seizures. The electroencephalogram usually reveals spike and wave pattern of less than 3 per second.

Minor motor seizures are often associated with a degenerative disease, mental retarda-

tion or other central nervous system disorders and may be difficult to control.

**Diagnosis. Electroencephalography.** In practically all instances an electroencephalogram should be obtained when there is clinical evidence of a convulsive disorder. An exception may be made in a child with an obvious clinical diagnosis of the staring type of petit mal seizure, since the characteristic three per second spike and wave pattern is almost invariably present.

Three types of rhythms have been described in the electroencephalogram of the normal human adult. The most common one, the alpha rhythm, consists of regular sinusoidal waves occurring at frequencies of eight to twelve per second, with a voltage of 20 to 60 microvolts when recorded from the scalp. The second most common, or the beta rhythm, is most prominent in the frontal cortex. It has a lower amplitude, and a frequency of thirteen to thirty-two per second. The least common, or gamma rhythm, arises from the frontal lobes and consists of a more rapid, thirty-three to fifty-five, rate per second with waves of extremely low voltage. Slower waves (theta, five to seven per second, and delta, one to four per second) are not present in normal adults during the waking state.

The interpretation of the electroencephalogram of infants and children is more difficult than that of adults because of the presence of slow rhythms (three to eight per second) in normal children. Cortical rhythm is poorly developed in the newborn. As the infant matures, the electroencephalogram shows random three to seven per second waves and some low voltage faster activity. Gradually the basic rhythm becomes more regular, and by six years of age the pattern is made up principally of five to seven per second waves, and by ten years alpha waves, eight to twelve per second, predominate. During adolescence some slow wave activity, four to eight per second, is not uncommon and may be incorrectly interpreted if adult standards are used.

Sleep, without the use of a hypnotic, hyperventilation for two minutes, Metrazol, artificially induced fever, the Pitressin test and a flickering light serve to bring out latent abnormalities in the electroencephalogram and may on occasion produce a seizure. Of these, sleep and hyperventilation are most frequently used in cooperative subjects.

**ABNORMAL WAVES.** Most patients with frequent grand mal seizures have definite



abnormalities in their electroencephalograms in the intervals between seizures. These consist of random spike discharges, diffuse high voltage slow waves or a pattern not consistent with the child's chronologic age. An electroencephalogram obtained during a grand mal seizure shows multiple high voltage spike discharges. After the seizure there are asymmetries between the two hemispheres and diffuse slowing.

Patients with seizures other than grand mal have a variety of electroencephalographic abnormalities. The most easily recognized one is that of infantile myoclonic seizures with its high voltage, one to two per second, spike and wave pattern, the so-called hypsarrhythmia (hyps=mountainous). The record gives the impression of complete disorganization.

During petit mal attacks there is a three per second spike and wave pattern with a well developed basic rhythm interrupted by spike and wave activity.

Spike discharges, particularly in the temporal area, are usually associated with clinical abnormalities. In the anterior temporal areas, older children with psychomotor seizures may show intermittent bursts of six to fourteen per second spikes. A constant asymmetry of one area compared to its counterpart on the opposite side may be significant, especially if the electrical activity shows phase reversal of slow waves. Shifting foci are more common in children than in adults and indicate a functional disturbance rather than an anatomic lesion. Absence of electrical activity over an area suggests a large lesion such as a subdural collection of fluid or an abscess. Serial electroencephalograms of children with hydrocephalus show a disturbance of function as the process progresses. After cerebral insults such as trauma, encephalitis, cerebral thrombosis and prolonged seizures, electrical activity may be slow for a variable time and may be roughly correlated to the child's clinical course.

Metabolic disorders, such as hypoglycemia, hyperthyroidism and adrenal insufficiency, alter cortical activity; the clinical significance of these changes is not clear.

Various types of cerebral dysrhythmia may occur for short times between clinical seizures. The occurrence of abnormal discharges of short duration, such as a single wave and spike formation or a short series of spikes similar to those in grand mal seizures, without clinical manifestations has given rise to the designation of subclinical or larval sei-

zures. These subclinical bursts may at times foretell the onset of clinical seizures.

**Roentgenography.** A roentgen examination of the skull is considered an essential part of the diagnostic appraisal in search for such abnormalities as intracranial calcifications, erosion of the base or increased densities as causes of organically determined seizures. A hammered-silver pattern of the cranium is

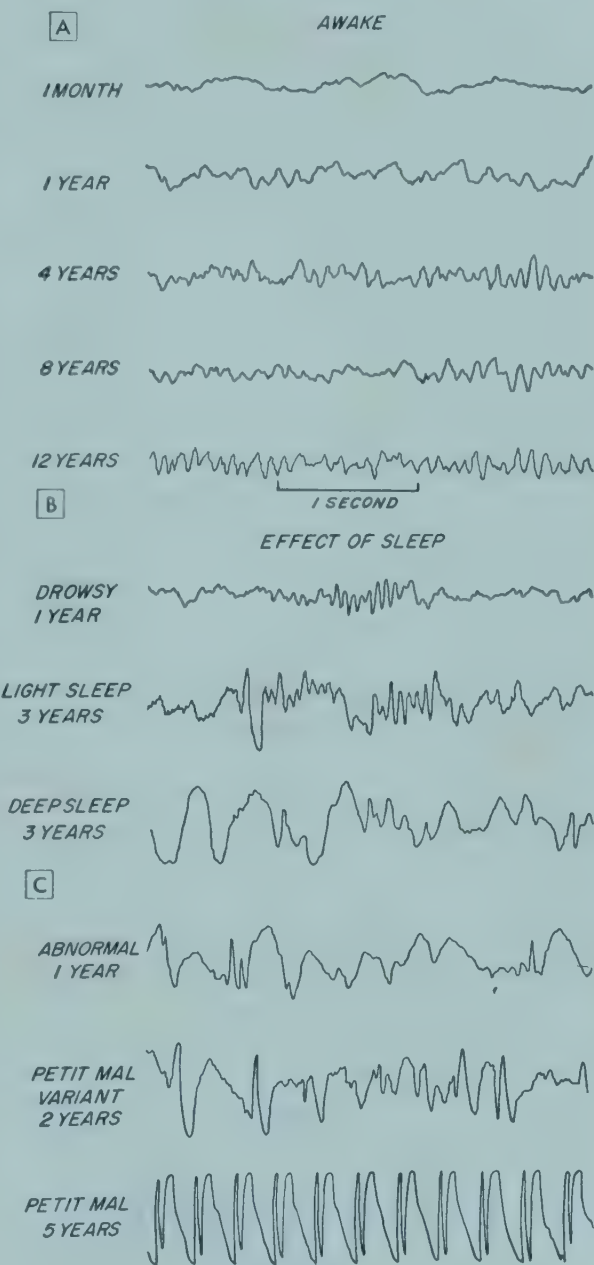


FIG. 331. Electroencephalograms of infants and children. A, These tracings were obtained from comparable areas of the scalp and represent electrical activity in the motor cortex. The variations of rhythm with age during a quiet phase just prior to sleep. B, The effect of sleep, variations of patterns in normal children; compare with tracings in A and C. C, Abnormal waves.

present so commonly that by itself it is not considered abnormal. Routine pneumoencephalography in the epileptic child is not considered necessary, since space-filling lesions without localizing peripheral neurologic changes which justify surgical exploration are an uncommon cause of convulsions in children.

The decision concerning additional laboratory examinations other than the routine urinalysis, blood cell count and tuberculin test should be based on leads obtained from the medical history, the physical examination and the clinical course. Examination of the cerebrospinal fluid need not be routine, but it may provide additional information when lead poisoning, certain instances of mental deterioration and encephalitis are considered diagnostically.

When hypoglycemia (p. 1215), nephritis (p. 1038) and tetany (p. 1110) are considered possible causes of convulsions, appropriate diagnostic steps are obviously indicated.

**Treatment. Management of the individual seizure.** Practically all that can be done for a patient during an attack is to protect him from bodily injury. This necessitates constant supervision in severe cases, especially when warning auras are absent before the attack. At the beginning of a major seizure clothing about the neck should be loosened. The patient should then be turned on his side so that he does not aspirate his pooled secretions. He should be observed carefully for changes in color; administration of oxygen is indicated during prolonged convulsions. As injury to the mouth and tongue frequently happens at the onset of the convulsion, the time-honored custom of placing a stick or other object in the mouth of the convulsive patient is potentially harmful and does little to improve the patency of the airway.

**Status epilepticus.** If a series of grand mal convulsions occurs before the patient has fully recovered, the prolonged seizure is termed status epilepticus. The intervals between individual convulsions may be so short that the seizures are virtually continuous. During status the muscular contractions may appear to be one-sided or to shift from one group of muscles to another. This does not constitute a true focal (jacksonian) seizure. Drug treatment of status consists in prompt administration of phenobarbital sodium intramuscularly (average doses, 60 mg. at six months of age to 120 mg. at two to three years, or 5 to 6 mg. per kilogram of body weight); if the convulsion is not controlled within twenty

minutes, the initial dose should be repeated. If the convulsion has been only partially controlled by this time, one-half the initial dose should be given. Subsequent administrations may be necessary. The rhythmic contraction of a single group of muscles following a severe convulsion does not require additional therapy. Sedative therapy should be limited to a single agent.

The dangers of intravenously administered barbiturates and of inhalation anesthesia are similar to those of anesthetizing an excited child. Such procedures are rarely necessary and, when indicated, should be performed by an experienced anesthesiologist. Laryngeal spasm and even sudden death may occur if treatment is too vigorous.

Administration of oxygen is indicated during prolonged convulsions, and administration of small amounts of 5 per cent glucose in 0.45 per cent saline solution intravenously may shorten the recovery time.

A quiet and otherwise calm atmosphere and reassurance and avoidance of unnecessary annoyance to the patient are important factors in general management, especially during the recovery phase.

**Continuous therapy of the epileptic child.** The aims of treatment are to reduce the number of seizures, to promote the acceptance of the child at home and in the community on the basis of his capabilities, and to encourage his functioning at a level commensurate with his natural endowment. For example, five grand mal seizures in the course of a year may be considered acceptable control in many instances.

The important therapeutic considerations include physical, emotional and mental hygiene, psychotherapy, anticonvulsant drugs and, rarely, a dietary regimen. The degree of success that can be anticipated depends upon a number of limiting conditions, such as the duration and severity of symptoms, the kind of seizures, the presence of a genetic factor, the presence of complicating cerebral lesions, and the capacity of the patient and his family to cooperate. Causative factors should be eradicated or alleviated whenever possible.

Initially the physician must secure the confidence and understanding of the child and his family. In the first few visits they should become aware of the nature of the disturbance, of what can be done to bring it under control and of what constitutes control. They need to know that the seizures of idiopathic epilepsy are not in themselves catastrophic and need not interfere with nor-



mal growth and development. The principal dangers are the attitudes of the child's family and his social contacts toward the disease. The child should attend school and participate in activities to which he is naturally inclined.

Parents, teachers, companions and especially the patient himself are usually only vaguely aware of the close relation between emotional or mental stresses and the occurrence of seizures. In older children a careful survey of the social relationships and a search for contributory emotional factors should be made from time to time with the hope of eliminating or avoiding mental conflicts and unnecessary anxiety. In hospital or clinic practice a social service worker can often render valuable assistance in ferreting out significant social factors which might otherwise be unknown. When the personality and the mental and emotional factors are complex, the co-operation of an experienced child psychiatrist is indicated.

Home and school surroundings which are not congenial and work requirements or responsibilities which are beyond the capacities or outside the interests of the patient may account for his failure to respond to therapy. Idleness and boredom have an especially deleterious effect on the epileptic child. In addition to a constructive program in school, he should be encouraged to occupy his spare time with interesting hobbies through which he can achieve favorable distinction. Self-confidence can thereby be sustained. The epileptic child is better off in his own home and in public school than in a special institution if his mental and emotional capacities permit it.

It is the duty of the physician, the nurse and the social worker who are acquainted with the problem to do everything possible to improve the attitude of the public toward the epileptic patient and his disease. Nearly every intelligent epileptic child sooner or later encounters attitudes toward him of pity and oversolicitousness or disgust and horror. These are likely to be a source of constant anxiety unless he is able to acquire an adequate philosophy.

**Drugs.** Since the introduction of bromides for the treatment of epilepsy by Leacock in 1858, drug therapy has been the choice and usually the only form of treatment. The tendency to rely upon medication alone was encouraged by the introduction of phenobarbital in 1912. Subsequently dietotherapy came into use when it was discovered that

fasting, the ketogenic diet and reduction of the water intake all tended to prevent epileptic seizures. Since the demonstration by Putnam and Merritt in 1937 that Dilantin (sodium diphenyl hydantoinate) was effective in the control of some patients not controlled by phenobarbital, the tendency to depend mainly upon drug therapy has again increased.

The successful management of the epileptic child requires determination of the most appropriate anticonvulsant drug or combination of drugs for him as well as the most appropriate dosages of them. To achieve this result, a systematic program for a trial of the various anticonvulsant drugs is necessary; a suggested schedule to determine an adequate therapeutic program is shown in Table 111. A change in the dose of a medication or from one medication to another should usually not be made more frequently than every two weeks.

*Phenobarbital* is the drug of choice for prolonged use in the average patient with grand mal epilepsy. Its virtues are its relative effectiveness, its comparative harmlessness in therapeutic doses for a prolonged time, its ease of administration and its low cost. Doses range from 8 mg. ( $\frac{1}{8}$  grain) one to three times daily for an infant to 100 mg. ( $1\frac{1}{2}$  grains) one to three times daily for an older child with a severe form of the disease. It may also be prescribed on a weight basis with an initial dose of 3 mg. per kilogram of body weight per day in two to four divided doses, with gradual increases to the required maintenance dose. More than 6 mg. per kilogram per day may result in drowsiness.

Occasionally a child will have an idiosyncrasy to phenobarbital. A maculopapular eruption on the skin and mucous membranes, excessive drowsiness and fever may be signs of sensitivity or overdosage. These soon disappear without permanent harm if the dose is reduced or if the drug is withdrawn. Rarely a patient, particularly one whose attacks are primarily petit mal, appears to be made worse by phenobarbital and has petit mal variants or psychomotor attacks. In such an event Dilantin may also be administered. Discontinuation of medication, which should always be done gradually, and substitution of another drug are rarely necessary.

**MEBARAL.** Mebaral (mephobarbital) is a barbiturate which is of value in some cases. The dose is approximately double that recommended for phenobarbital.

**DILANTIN.** The only drugs which rival the

Table 111. Schedule for Determination of Adequate Therapeutic Program in Epilepsy

	<i>Grand Mal</i>	<i>Psychomotor</i>	<i>Petit Mal</i> ( <i>Simple Staring</i> )	<i>Petit Mal</i> with <i>Motor Component</i>	<i>Infantile</i> <i>Myoclonic</i>
Phenobarbital					
3 mg./kg./day.....	1	1	1	1	1
5 mg./kg./day.....	2	2	2	2	2
Dilantin					
3 mg./kg./day.....	3	3		3	3
5 mg./kg./day.....	4	4		4	4
8 mg./kg./day.....	5	5		5	5
Mysoline					
(Not more than 250 mg. q.i.d.)					
125 mg. HS.....	6	6			6
250 mg. HS.....	7	7			7
250 mg. b.i.d.....	8	8			8
Tridione					
(Not more than 900 mg. q.i.d.)					
20 mg./kg./day.....			3	6	
40 mg./kg./day.....			4	7	
60 mg./kg./day.....			5	8	

In this plan of therapy phenobarbital is given initially at the lower dose (1) and increased if necessary to the larger dose (2). It is prescribed and continued for all types of convulsions except as there are untoward reactions to it. If additional therapy is considered necessary, Dilantin is added. The dose is increased as deemed necessary as indicated above. Changes in medication or dosage are not made more frequently than two weeks. Mysoline is not used except as a supplement to Dilantin and phenobarbital. Mebaral may be used instead of phenobarbital, but at twice its calculated dose. The dose of Mysoline may also be calculated on the basis of body weight (15-25 mg. kg. day). Usually it is necessary to reduce the amount of phenobarbital by one third when Mysoline is added. The medications are given in divided doses 2-3 times each day.

barbiturates in the control of grand mal seizures are certain hydantoin compounds, such as diphenylhydantoin sodium, U.S.P., also known as phenytoin sodium (Dilantin). They are administered to older children in capsules and to younger ones in powder form mixed with a little food or fruit juice. Doses range from 15 mg. ( $\frac{1}{4}$  grain) two or three times daily in infants to 100 mg. ( $1\frac{1}{2}$  grains) one to four times daily in older children. The drug may also be prescribed on a weight basis with an initial dose of 3 mg. per kilogram of body weight per day in two to four divided doses, with gradual increases to the required maintenance dose. More than 8 mg. per kilogram per day may result in toxic manifestations. The chief advantage of hydantoin compounds over the barbiturates is that they act as efficient anticonvulsants without producing excessive drowsiness. One of these should be given a trial, therefore, whenever grand mal seizures are not adequately controlled by phenobarbital alone in nondepressing doses. Replacement should be made gradually, however, since sudden changes may result in increased convulsive reactivity.

The occurrence of nonpainful, nonhemorrhagic hypertrophy of the gums usually follows the administration of Dilantin. It usu-

ally requires no special treatment other than good dental hygiene. If it becomes unattractive cosmetically, another drug should be substituted.

Ataxia and drowsiness may occur if the initial dose is too large, if the dose is increased too rapidly or if the total daily dose exceeds about 8 mg. per kilogram per day. Serious toxic reactions such as nausea or vomiting, erythema or a morbilliform eruption, nervous manifestations such as tremor of the hands, ataxia, diplopia with nystagmus, paralytic manifestations and mild psychoses are uncommon. These disappear after reduction of the dose, usually to about two thirds of its former level.

TRIDIONE. Trimethadione or Tridione (3,5,5-trimethyloxazolidine 2,4-dione) is an effective drug for the treatment of petit mal epilepsy in doses of 0.3 gm. (5 grains) one to four times daily. The drug may also be prescribed on a weight basis with an initial dose of 25 mg. per kilogram per day in two to four divided doses, which may be gradually increased if necessary to 80 mg. per kilogram per day. Tridione may increase the occurrence of grand mal attacks if they also exist, and the additional administration of a barbiturate or hydantoin is indicated. Exces-



sive doses or prolonged use of Tridione may result in photophobia, hemeralopia, drowsiness, nausea, skin eruptions or nephrosis. Such manifestations tend to disappear promptly after withdrawal of the drug. Several fatalities from aplastic anemia and agranulocytosis have been reported in patients receiving Tridione regularly for several months. When it is given for more than a short time, periodic blood cell counts should be obtained, and the drug discontinued if any abnormality is found.

**PARADIONE.** Paradione is less toxic than Tridione, but also less effective. The dosage is similar to that of Tridione.

**MYSOLINE.** Mysoline or primidone (5-phenyl-5-ethyl-hexahydropyrimidine-4:6-dione) is used in the treatment of grand mal and psychomotor seizures. It may be used alone or in combination with other drugs and does not depress hemopoietic activity. The chief side effects, drowsiness, ataxia and dermatitis, can be minimized by starting with small amounts (125 mg.) at bedtime and by increasing the dose slowly at seven- to ten-day intervals to a maximum dose of 250 mg., three times daily.

**Special diet therapy.** Fasting causes cessation of grand mal seizures in a majority of epileptic children, the effect usually manifesting itself shortly after ketosis has appeared on the third day. A strongly *ketogenic diet* has a comparable anticonvulsive effect after ketosis has developed. Stringent restriction of the water intake, even when the diet is nonketogenic, results in cessation of grand mal seizures in most of those patients who respond favorably to fasting or the ketogenic diet. Establishment of a negative water balance, by restricting the intake or increasing the output, intensifies the anticonvulsive effects of the ketogenic regimen. Administration of alkaline salts in sufficient amounts to neutralize the acidogenic effect of fasting or of the ketogenic diet abolishes the anticonvulsive action, whereas administration of inorganic acids or acid-forming salts fortifies or intensifies such action. The ketogenic diet is beneficial for both petit mal and grand mal epilepsy.

The value of fasting is that it can be used to determine in a short time whether a patient with severe epilepsy is likely to respond favorably to a ketogenic diet. If the incidence and severity of seizures are not sharply reduced after three to five days of fasting and moderate restriction of the water intake, it is improbable that the patient will be benefited

by the ketogenic diet. If the diet is to be prescribed after a favorable fasting test, it is advantageous to start it immediately to ensure continuance of the ketosis.

It is necessary to supplement the diet with vitamin concentrates (p. 107), and at least 1 gm. of calcium should be included in the daily intake. Between 1.5 and 2 gm. of protein per kilogram of body weight per day should also be provided.

Dietary treatment is usually more successful if it is initiated for a week or two in a well regulated hospital. Intelligent older children and the parents can be taught the details of the dietary management and the technique of determining the presence of acetoacetic acid in the urine and the urinary specific gravity. Dietotherapy is most likely to succeed when the specific gravity of the urine is made to range above 1.020 and the urine turns a dark brown to deep burgundy red on addition of an excess of 10 per cent ferric chloride solution. It is essential that the various constituents of the diet be weighed carefully at first if success is to be expected. The diet should be made palatable and varied as much as possible.

Calculation of trial diets is facilitated by use of the following formulas:

1. *For Children of Preschool Age (or Body Weight up to 19 Kg.):*

Total	
water	.. 30 to 50 cc. per kg. of body weight
Protein	.. 2 gm. per kg. of body weight
Carbohy-	
drate	.. 0.7 gm. per kg. of body weight
Fat (gm.)=	$\frac{60 \times \text{kg. of body weight}}{9}$

2. *For Children between the Ages of 6 and 10 Years (or 20 to 32 Kg. Body Weight):*

Total	
water	.. 25 to 40 cc. per kg. of body weight
Protein	.. 1.5 gm. per kg. of body weight
Carbohy-	
drate	.. 0.5 gm. per kg. of body weight
Fat (gm.)=	$\frac{50 \times \text{kg. of body weight}}{9}$

3. *For Children above the Age of 10 Years (or above 33 Kg. Body Weight):*

Total	
water	.. 20 to 30 cc. per kg. of body weight
Protein	.. 1.5 gm. per kg. of body weight
Carbohy-	
drate	.. 0.4 gm. per kg. of body weight
Fat (gm.)=	$\frac{40 \times \text{kg. of body weight}}{9}$

The basic physiologic water requirement must always be provided, but this varies so

greatly with muscular activity and changes in clothing and environmental temperature that only an approximate estimate can be made at first, final adjustments being made empirically. Impairment of renal function, acute infection, vomiting or diarrhea contraindicates restriction of the water intake. If the patient's caloric needs are too greatly exceeded by the contents of the diet offered, loss of appetite or nausea will interfere with the success of this form of treatment. If, after the first few months, the diet is gradually made less strongly ketogenic, it is compatible with normal health for a long time.

The use of the ketogenic diet is limited because of the practical difficulties of adhering consistently to a restricted dietary intake and because of the possibility of attendant emotional disturbances. It may be helpful for children who have frequent seizures which are not controlled by moderate doses of one or more of the anticonvulsant drugs, and then often in conjunction with them. The child and his family must be willing and able to accept the dietary regimen without emotional conflict.

**Prognosis.** Among the pertinent questions asked of the physician after the diagnosis of epilepsy has been established are these: What of the child's future? Is his mental development likely to be retarded by the disease? Will mental deterioration occur? Will his life be shortened by it? Should he attend school? Should he marry and have children? Such questions are probably best answered over a period of time rather than at the first visit. Usually the parents can be assured that the frequency of the seizures, especially those of the grand mal variety, can be reduced to a point at which they will not interfere seriously with the child's activity. By encouraging the parents to treat the child exactly as they would if he did not have the seizures, the personality changes can be largely avoided. Prognosis depends upon any coexisting mental retardation, physical handicaps, possible organic disease, and the adequacy of management, both medical and environmental.

Good control is difficult to define because it includes the child's social adjustment as well as reduction of the number of seizures. It is probably better for a child to have five or so major seizures a year and to be otherwise well adjusted at home and in school than to have only one a year, but to be so restricted in his activities that he becomes a social misfit. For example, parents may so restrict a child's activities that he makes few decisions

outside of their presence, and as he grows older his dependence on them continues.

The tendency to repeated seizures, with or without organic cause, is found in some families. A question by the parents or older children concerning the possibility of a convulsive disorder occurring in other children or in the offspring of affected persons is virtually impossible to answer accurately. In a general discussion of the problem it may be helpful to comment upon both the rare residual effect of a convulsion and the observation of Yannet that children who had parents with a history of a convulsive disorder were better adjusted and had fewer seizures than those children whose parents had not had seizures. Possibly such parents understand the problem more clearly.

Although it is probable that a severe prolonged seizure of one or more hours may deplete available stores of glucose and interfere with oxygenation and thus cause secondary cerebral changes, there is reason to believe that the usual convulsive episode does not cause irreversible damage. Convulsions followed by permanent hemiplegia are probably more often the result of a vascular accident which occurred before the seizure rather than during it. In such instances there are likely to be recurrent convulsions which are more difficult to control than those of idiopathic epilepsy.

Epileptic patients who are otherwise normal seldom die or sustain serious injuries as a result of their convulsive disorder.

Though the course of the disease varies in different patients, the tendency is for seizures to become more numerous unless the course is modified by therapy. A number of patients with unquestioned idiopathic grand mal epilepsy appear to undergo spontaneous cessation of seizures after adequate treatment. Patients who are well controlled medically rarely have seizures during their participation in athletic activities. The results of therapy are rarely satisfactory in infants and young children with infantile myoclonic seizures.

The prognosis for mental development in young epileptic patients or for mental deterioration in older patients has until recent years been gloomy, chiefly because opinion was based largely upon experiences with the more severe cases in public institutions. Collins and Lennox found the intelligence quotients of 100 children and 200 adults in private practice to average 109 with a range of 52 to 153 for the former and 47 to 139 for the latter. The intelligence quotient of those with evi-



dence of cerebral damage before the first seizure averaged 10 points lower than of those with idiopathic epilepsy. The highest scores were found in those with essentially normal electroencephalograms and in those with typical petit mal activity, the lowest in those having both grand mal and psychomotor attacks. With proper treatment most epileptic patients with normal mentality can be expected to maintain it.

## CHRONIC PAROXYSMAL DISORDERS

### SIMULATING EPILEPSY

#### NARCOLEPSY

Narcolepsy is a symptom complex characterized by recurrent diurnal attacks of irrepressible sleep, usually precipitated by a sudden emotional change. It is rare in children and is said to be more frequent in boys than in girls.

Narcolepsy has been classified according to etiology into "idiopathic" and "symptomatic" groups. Wilson has further subdivided the latter group into six categories: (1) toxic-infective, e.g., postencephalitic, (2) circulatory, (3) post-traumatic, (4) endocrine, (5) neoplastic, and (6) psychopathologic.

The attacks resemble those of epilepsy in their brevity, in the abruptness of their onset and in their paroxysmal and involuntary nature. The overpowering sleep of narcolepsy may come on suddenly while the patient is engaged in some activity such as talking, walking or driving. He then ceases what he is doing and falls "in a heap." The "sleep" is usually shallow, and the patient is easily aroused. The disturbance apparently has no relation to the physiologic need for sleep. Regular nocturnal sleep is normal. The patient exhibits mental alertness rather than somnolence after he has been aroused.

**Prognosis and Treatment.** The disorder tends to be chronic, but spontaneous improvement and cure are more common than in epilepsy. The amphetamines have proved much more effective than ephedrine. Dosage for a child should be established on the basis of the minimal amount which will produce the desired effect.

#### BREATH-HOLDING

See page 78. These spells, comparatively common in early childhood, are sometimes complicated by convulsions.

#### HYSTERICAL FITS

These can resemble true epileptic seizures in a superficial way. They are fairly easily dis-

tinguished by a number of characteristics. There is usually a typical neurotic background. Between attacks the patient may exhibit motor or sensory disturbances which do not follow the true neural patterns, and the gag reflex may be absent. Dilatation of the pupils and pallor of the skin and mucous membranes rarely accompany an attack. Loss of consciousness is superficial and variable. Sphincter control is not lost, and bodily injury from the seizure does not occur. Crying, moaning and disconnected talk throughout the attack, which may last half an hour or longer, are common. Hysterical patients, like other neurotic children with behavior problems, frequently show some abnormalities in the electroencephalogram. The treatment of hysterical seizures is that of the underlying psychogenic disorder.

#### SYNCOPE

Syncopal attacks of various types due chiefly to transient cerebral anemia are frequently complicated by slight tonic and clonic convulsive reactions of short duration confined mostly to the face and upper extremities. The most common form seen in early life is the *simple fainting spell*, which is brought on reflexly in certain children by a simple procedure such as removal of a sliver or insertion of a needle into the skin, or by a sudden fright or a painful stimulus while in a standing or sitting posture. The susceptibility to fainting in such children appears to be related to defective reflex regulation of the vascular system, which manifests itself as a sudden relaxation of the visceral venous system with bradycardia and a fall in blood pressure. Placing the patient in a horizontal position or with the head tilted downward at a 45-degree angle will tend to shorten the period of unconsciousness. When it is necessary to subject a child known to faint easily to some painful test or treatment, it is advisable to have him lie on a table during the procedure. Vigorous crying before and during a procedure, such as taking a blood sample, tends to prevent fainting. In an older child active gripping of some object and voluntary contraction of the abdominal muscles have the same effect.

In the *Stokes-Adams syndrome*, which occurs in heart block (p. 887), a short convulsive reaction often accompanies the syncopal attack. The latter appears within ten to twenty seconds after the onset of asystole. Syncopal attacks of a similar sort have been reported in patients as a result of *paroxysmal*

*tachycardia*, and attacks occur fairly frequently after muscular effort in young children with certain congenital anomalies of the heart, such as the tetralogy of Fallot.

A *hyperactive carotid sinus reflex* manifests itself by episodes of unconsciousness with or without brief tonic and clonic convulsive attacks. Fortunately this condition is extremely rare in children and is not more common among epileptic than among nonepileptic patients. Pressure over the carotid sinuses in the anterior cervical region causes a slowing or temporary arrest of the pulse in persons subject to attacks. Associated with the asystole are symptoms of faintness, weakness, loss of consciousness and finally the convulsive reaction.

## MIGRAINE

### (HEMICRANIA)

See also page 88. Migraine has long been regarded as being akin in some respects to epilepsy. The two frequently occur in the same family. Occasionally attacks of migraine are replaced by typical epileptic seizures in the same patient. Its paroxysmal character, its chronicity and its genetic features make migraine resemble idiopathic epilepsy. This has given rise to the unfortunate use of the designation "sensory epilepsy" as a synonym for migraine. In true visual seizures of epileptic patients the eye symptoms are much shorter in duration than they are in migraine and are bilateral.

IRVINE McQUARRIE  
HENRY W. BAIRD, III

## REFERENCES

- Aass, F., Kaada, B. R., and Torp, K. H.: The Diagnostic and Prognostic Value of the Initial Electroencephalogram in Children with Convulsions. *Acta paediat.*, 45:335, 1956.
- Baird, H. W., III, and Borofsky, L. G.: Infantile Myoclonic Seizures. *J. Pediat.*, 50:332, 1957.
- Baird, H. W., III, and Garfunkel, J. M.: Electroencephalographic Changes in Children with Artificially Induced Hyperthermia. *J. Pediat.*, 48:28, 1956.
- Berger, H.: Ueber das Elektrenkephalogram des Menschen. *Arch. f. Psychiat.*, 87:527, 1929.
- Collins, A. L., and Lennox, W. G.: The Intelligence of 300 Private Epileptic Patients. *Epilepsia*, 3: 223, 1947.
- Frame, B., and Carter, S.: Pseudohypoparathyroidism. *Neurology*, 5:297, 1955.
- Gibbs, F. A., and Gibbs, E. L.: *Atlas of Electroencephalography*. 2nd ed. Cambridge, Mass., Addison-Wesley Press, Inc., 1952, Vol. 2.
- Henry, C. E.: *Electroencephalograms of Normal Children*. Washington, D.C., Society for Research in Child Development, National Research Council, 1944.
- Jasper, H. H.: *Electroencephalography in Child Neurology and Psychiatry*. *Pediatrics*, 3:783, 1949.
- Knobloch, H., Sayers, M. P., and Howard, W. H. R.: The Relationship between Findings in Pneumoencephalograms and Clinical Behavior. *Pediatrics*, 22:13, 1957.
- Lennox, W. G., and Davis, J. P.: Clinical Correlates of the Fast and Slow Spike-Wave Electroencephalogram. *Pediatrics*, 5:626, 1950.
- Livingston, S.: *The Diagnosis and Treatment of Convulsive Disorders in Children*. Springfield, Ill., Charles C Thomas, 1954.
- Malamud, N., and Garoutte, B.: Pneumoencephalography in Children with Mental Defect and/or Cerebral Palsy. *Am. J. Dis. Child.*, 87:16, 1954.
- McQuarrie, I.: Idiopathic Spontaneously Occurring Hypoglycemia in Infants. *Am. J. Dis. Child.*, 87: 399, 1954.
- McQuarrie, I., and Peeler, D. B.: Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children; Diagnostic and Etiologic Study. *J. Clin. Investigation*, 10:915, 1931.
- Merritt, H. H., and Putnam, T. J.: Sodium Diphenylhydantoinate in Treatment of Convulsive Disorders. *J.A.M.A.*, 111:1068, 1938.
- Peterman, M. G.: Convulsives in Childhood; 20 Year Study of 2,500 Cases. *Am. J. Dis. Child.*, 72:399, 1946.
- Yannet, H.: *The Treatment and Prognosis of Convulsive Disorders in Children*. Bull. New York Acad. Med., 27:466, 1951.



# Mental Deficiency

Mental deficiency can be defined as inadequate mental development which may be expected to result in incapacity for independent social adaptation. It is a symptom of cerebral malfunction, many cases being associated with recognizable pathologic changes of the central nervous system. Though the subject will be treated here largely from the medical viewpoint, one must not lose sight of the fact that mental deficiency is a social as well as a biologic problem.

There are no comprehensive surveys to indicate the incidence of mental deficiency. In the United States there have been many large school surveys in which the estimated incidence of mental deficiency varied from 2 to 5 per cent. The number of institutionalized mentally defective persons in the United States approximates 120,000 (National Institute of Mental Health, 1947).

## PSYCHOLOGIC CONSIDERATIONS

Intelligence is not the result of a single mental process, but is made up of many different abilities, including abstract thinking, visual and auditory memory, causal reasoning, verbal expression, manipulative capacities, spatial comprehension and probably many others. This multifactor concept has been implied in the development of mental testing since Binet and the subsequent elaboration of the many varieties of psychologic tests. The present practice of quantitatively describing intelligence in terms of mental age, or intelligence quotient (I.Q.), which is the ratio of mental age to chronologic age, supplies an average of the composite attainments of most of these mental abilities. The practical success achieved by this method of grading intelligence results in great part from the fact that in the course of normal intellectual growth there is, as a general rule, a close correlation between the various mental processes. The degree, however, of intellectual defect associated with arrested or inadequate mental development is only rarely equally manifest

in each of the intellectual spheres. Frequently, especially in the less seriously retarded children, some of the mental functions may be well within normal limits. The importance of this concept in relation to diagnosis of mental deficiency becomes apparent when it is realized that the various mental abilities do not play an equal role in influencing subsequent social adjustment. Thus normal progress in academic schooling in the main depends on adequate development of such factors as visual and auditory memory, verbal facility and abstract reasoning. Other aspects of intelligence obviously play an important role in school progress, but defects of these are not nearly so much a handicap as are minor defects in the former. On the other hand, reasonable success in adjusting to many of the simple industrial disciplines in later life depends much more on aspects of intelligence related to visuo-manual coordination, spatial relationship, causal reasoning and other factors as well as to satisfactory personality characteristics. The relative value of comprehensive psychologic examinations must depend more on the broader concepts of the multiple factors in intelligence and its interpretation in terms of future social adaptability than simply on an estimate of average mental age.

For academic and administrative purposes the intelligence quotient is useful for classifying mentally defective children in regard to the degree of defect:

- I.Q. 51-75: moron, high grade or educable
- I.Q. 21-50: imbecile, middle grade or trainable
- I.Q. 0-20: idiot, low grade.

The proportionate distribution of these categories in the general defective population in England was estimated in the Wood Report as 75, 20, 5 for the moron, imbecile and idiot, respectively.

## CLINICAL CLASSIFICATION

The classification which follows is based on etiology and includes the most common recog-

nizable conditions in which mental deficiency is invariably present or occurs sufficiently often to rule out the possibility of random occurrence. The clinical conditions are grouped by the age periods in which the etiologic factors appear to be operative, namely, prenatal, natal and postnatal.

- I. Prenatal
  - A. Hereditary
    - 1. Familial mental deficiency
    - 2. Hereditary idiocy
    - 3. Phenylpyruvic oligophrenia
    - 4. Congenital ectodermoses (tuberous sclerosis, neurofibromatosis, cerebral angiomas)
    - 5. Heredo-degenerative cerebral diseases (see p. 1094)
    - 6. Cranial anomalies (primary microcephaly, craniostenoses, hypertelorism, congenital hydrocephalus)
  - B. Infection
    - 1. Congenital syphilis
    - 2. Toxoplasma encephalitis
    - 3. German measles
  - C. Maternal irradiation
  - D. Encephalopathy associated with kernicterus
    - 1. Rh, ABO maternal iso-immunization
    - 2. Nonspecific
  - E. Etiology not definitely established, or variable
    - 1. Mongolism
    - 2. Cretinism
    - 3. Congenital cerebral palsy
    - 4. Undifferentiated or primary amentia
- II. Birth trauma (anoxia, vascular injuries, phlebotaxis, and so on)
- III. Postnatal
  - 1. Central nervous system infections
  - 2. Cerebral trauma
  - 3. Cerebral vascular disorders
  - 4. Poisonings
  - 5. Recurrent convulsions

It is not within the scope of this section to discuss exhaustively all these conditions. Some are described elsewhere, and, for more complete descriptions of others, suitable references will be given.

FAMILIAL MENTAL DEFICIENCY

This category, from a sociologic viewpoint, represents the most important component of the mentally defective population. Numerically it is the largest group, comprising 35 to 45 per cent of all institutionalized defectives and probably about 60 to 70 per cent of all mental defectives in the community.

The diagnosis is relatively simple, depending on the presence of defective or inferior intelligence in one or both parents and in practically all the siblings, and on failure to find evidence in the history or physical ex-

amination of other causative factors. The mental status is almost invariably in the moron classification. There are no distinguishing physical characteristics, and the neurologic examination is essentially negative. The intellectual defect is most apparent in tests and situations involving verbal facility and abstract learning. The performance is on a much higher level in tests and situations dependent on manual dexterity and visuomotor coordination than would be expected from the verbal scores. Though this psychologic pattern is fairly characteristic of the familial type, it is by no means pathognomonic.

The nature of the hereditary transmission and genetic distribution is best described by reference to the following data from Halperin: Practically all the offspring resulting from a mating of two mentally defective parents of this category have defective or inferior intelligence. As the intellectual level of

PARENTS	NUM- BER OF CHILD- REN	DISTRIBUTION OF MENTAL STATUS OF SIBLINGS		
		Defec- tive	Infe- rior	Aver- age
Defective × defective	111	57%	39%	4%
Defective × inferior . .	81	35%	55%	10%
Inferior × inferior . . .	274	15%	57%	28%
Inferior ± average . . .	93	3%	33%	64%

From Halperin; Am. J. Ment. Def., Vol. 51.

either parent approaches the average, the proportion of children with defective and inferior intelligence tends to decrease. It is apparent that this type of hereditary transmission must depend on many independent genetic determinants whose effects are cumulative, rather than on a single abnormal gene as in most hereditary conditions.

These intellectually inferior individuals inherit the polygenic factors which determine their position in the lowest levels of the normal distribution curve of intelligence. In this sense these genetic factors may be considered "physiologic," in that they represent a part of the genetic pool which determines the hereditary transmission of normal intelligence. These individuals represent our intellectually marginal population, and their ability to maintain an adequate social adjustment will depend, in great part, on the nature, complexity and economic status of the environment in which they live.



# HEREDITARY IDIOCY

This category includes a number of genetically determined conditions that cannot be categorized on the basis of associated clinical symptomatology or laboratory observations as is true with the other genetic diseases to be described. Their recognition as a possible genetically determined condition must, therefore, rest on the birth of a sibling similarly affected for which no other adequate explanation is evident.

Genetically, the conditions are presumably transmitted recessively, since in all instances the parents have average intelligence. Consanguinity is occasionally present. As the designation implies, the mental level is usually low grade. The incidence of the condition cannot be estimated, since single cases in families cannot at present be recognized as belonging to this category.

## PHENYLPYRUVIC OLIGOPHRENIA (see also p. 259)

In 1934 Folling demonstrated phenylpyruvic acid in the urine of ten mentally defective patients. The incidence of the condition is difficult to determine. It occurs in about 1 per cent of institutional mental defectives. About 85 per cent of the persons with this metabolic defect have severe mental deficiency, being idiots or low imbeciles; practically all others are in the high imbecile or moron category. Rarely persons with average intelligence excrete this acid in their urine.

The enzymatic defect involves failure in the hydroxylation of phenylalanine to tyrosine. This results in accumulation of phenylalanine in the body fluids, which, after deamination, appears in the urine as phenylpyruvic acid. The amount of phenylpyruvic acid excreted seems to be related directly to the intake of phenylalanine. Since phenylpyruvic acid is excreted in fairly large amounts (0.5 to 2.5 gm.) with the ordinary diet, a random urine specimen is satisfactory for examination. When the acid is present, the addition of 5 to 10 drops of a 10 per cent ferric chloride solution to 5 ml. of urine produces a dark bluish-green color.

About 80 per cent of affected persons are blue-eyed and blonde, and many have eczematous lesions. Physical examination reveals no characteristic lesion of the central nervous system.

The inheritance of the condition depends on a recessive gene. Special diets with greatly reduced phenylalanine content have recently given some promise for preventing or mini-

mizing the cerebral damage in children with this condition, if started early in life.

## CONGENITAL ECTODERMOSSES (p. 1079)

This group, which includes tuberous sclerosis, neurofibromatosis and cerebral angiomas, has in common the presence of neoplasia or dysplasia in the central or peripheral nervous system and in other organs, as well as various skin manifestations. This group accounts for about 0.3 to 0.5 per cent of institutionalized mental defectives.

As a cause of mental deficiency, *tuberous sclerosis* (see also p. 1079) is the most important member of this group. The mental defect is not characteristic. The children are either of low imbecile or idiot classification. In infancy serious delay in mental development may be the only clinical manifestation, since other clinical features, namely, sebaceous adenomas, convulsive phenomena, cutaneous fibromas, shagreen skin, retinal lesions and extracerebral neoplasms, may be delayed in appearance or may not appear at any time. The disease may be suggested in a severely retarded child by the presence of circumscribed calcification in roentgenograms of the skull, usually in the periventricular areas. Retinal lesions are also important in infancy, since they may be the only physical manifestation of the disease. The most common one is the slightly elevated mulberry-like tumor mass, which is about twice the diameter of the optic disk and has a glistening, yellowish-white color. Convulsions are a fairly constant manifestation and often begin during the first year of life. They respond reasonably well to anticonvulsive drugs.

Genetically, the disease seems to be transmitted as a dominant character, since it is common to find incomplete forms in one of the parents, unassociated with mental defects.

Mental deficiency is an infrequent manifestation of *neurofibromatosis* (see also p. 1079), which is inherited as a dominant character. Neurofibromas may involve any nerve and vary in size from the smallest bead to grotesque overgrowth in extremities, resulting in symptomatic elephantiasis. Peculiar pigmentary lesions are seen in the skin, and there may be characteristic osseous defects. The type of mental defect varies from that of moron level to gross idiocy.

*Cerebral angiomas* (see *Sturge-Weber Syndrome*, p. 1080) is a rare cause of mental deficiency, which is usually of mild degree. This disturbance is hereditary, but the type of genetic transmission is not clear. Clin-

ically, it is characterized by cutaneous heman-  
giomas, especially of the face and forehead,  
associated with angiomatous neoplasia of the  
cerebral cortex. On the roentgenogram of the  
skull cerebral lesions have a characteristic  
type of curvilinear calcification. Convulsions  
eventually occur in most instances and are  
often difficult to control.

#### **CONGENITAL SYPHILIS** (p. 472)

Congenital syphilis is an uncommon cause  
of mental deficiency. In one institutional sur-  
vey less than two per 1000 inmates had  
definite evidence of central nervous system  
syphilis. The mental level is usually in the  
moron classification. Practically all cases show  
additional signs of neurologic abnormality in  
the form of spastic paralysis, incoordination,  
pupillary changes, and deafness. The cere-  
brospinal fluid in untreated cases is almost  
always abnormal.

#### **GERMAN MEASLES**

The importance of German measles in the  
mother during the first three months of preg-  
nancy as a cause of congenital cataracts,  
cardiac abnormalities, microphthalmos and  
deaf-mutism in the child is established. One  
of the less common developmental anomalies  
is microcephaly associated with severe mental  
retardation without microcephaly have also  
been reported.

Whether other types of viral diseases in the  
mother during the early months of pregnancy  
can injure the fetus so as to produce cerebral  
defects has not been established.

#### **IRRADIATION** (see p. 1371)

Pelvic irradiation of the mother during the  
early months of pregnancy may cause serious  
developmental malformations in the fetus.  
The severe mental retardation which occurs  
is usually in association with microcephaly.

#### **ISO-IMMUNIZATION** (pp. 335, 958, 1077)

The term "kernicterus" has been commonly  
used to designate the central nervous system  
lesions which occur as a complication of the  
hyperbilirubinemia associated with hemolytic  
disease of the fetus and newborn.

The pathologic and clinical manifestations  
of kernicterus are not confined to Rh or  
ABO iso-immunization. A variety of presum-  
ably unrelated etiologic factors in the neo-  
natal period are capable of producing the  
basic cerebral injury. These include severe

infections, dehydration and intestinal obstruc-  
tion. Prematurity greatly increases the likeli-  
hood of cerebral involvement. In all instances  
there is a definite elevation in the level of  
indirect serum bilirubin; the prophylactic  
value of exchange transfusion is related to  
reduction of it.

The term "kernicterus" indicates the strik-  
ing involvement of the nuclear masses of the  
basal ganglia; in most instances there is also  
involvement, however, either as yellow pig-  
mentation in the acute cases or as destructive  
changes in the chronic cases, of the medul-  
lary nuclei, optic nerves, fiber tracts in the  
spinal cord, dentate nuclei of the cerebellum,  
the hippocampus and the white and gray mat-  
ter of various cortical areas. Most children  
with kernicterus do not survive the neonatal  
period; those who do may exhibit a variety  
of clinical symptoms, including various mani-  
festations of cerebral palsy, mental deficiency,  
cranial nerve abnormalities particularly in-  
volving the optic and oculomotor nerves, con-  
vulsive disorders and aphasias. Mental de-  
ficiency, when severe, is usually associated  
with motor defects which may be hypertonic  
or hypotonic. Asymmetric spastic quadriplegia  
with athetosis is the most common pattern.  
Mental deficiency may rarely be the sole  
manifestation.

#### **MONGOLISM**

Mongolism is one of the most common of  
the classifiable categories of mental defect;  
Benda estimates an incidence of two to three  
cases per 1000 births. This category accounts  
for about 7 to 10 per cent of institutionalized  
mental defectives.

The cause is unknown, but two facts are  
definitely established. Although mothers of  
any age, including the very young, may give  
birth to a mongolian infant, the average ma-  
ternal age for such births is almost ten years  
greater than for random ones. Secondly,  
when mongolism is associated with twinning,  
both identical twins are almost always af-  
fected, and only rarely are both nonidentical  
twins. This fact, in addition to other observa-  
tions, suggests a dual etiology which includes  
both environmental and genetic factors. As-  
sociated noncerebral developmental defects,  
as in the heart, eye, external ear, distal  
parts of extremities and elsewhere, suggest  
that the disturbances in development in mon-  
golism are initiated between the sixth and  
eighth weeks of gestation.

Diagnosis depends on the presence of  
severe mental retardation associated with cer-





A

B

C

FIG. 332. A, The typical broad, spadelike hand of mongolism in a 12-year-old boy. Note the shortness of all fingers, especially the fifth. The presence of a single transverse palmar crease, instead of the 2 creases normally seen, is well shown. B, Roentgenogram of the hand of a 7-year-old girl with mongolism. Note the maldevelopment of the second phalanx of the fifth finger responsible for the shortening and incurving. The metacarpal bones and remaining phalanges also tend to be short and broad. C, The typical broad flat foot of mongolism in a 12-year-old boy. Note the wide space between the first and second toes.

tain pathognomonic clinical features resulting from a disordered growth of the skeletal system, especially of the skull and long bones. Findings resulting from defective development of other tissues and organs are frequently present. The disorder in the growth of the skull bones gives rise to most of the characteristic features. The skull is small, being usually in the tenth to twentieth percentile. It tends to be flattened anteriorly and posteriorly. The osseous orbits, as shown roentgenographically, are smaller than normal. There is a lateral upward slope of the eyes. An epicanthus (epicanthal fold) is present in the younger child which differs from that of Asiatic races by being confined

to the inner angle, rather than including most of the upper lid. The epicanthus tends to disappear after the tenth year of life. Chronic inflammatory changes involving the conjunctivas and lid margins are frequent. Cataracts appear in about 5 to 8 per cent of cases. Strabismus is common, as are developmental anomalies of the external ears. The tongue is usually protruded, owing as a rule to the smallness of the oral cavity. Sucking of it usually results in fissuring and furrowing (scrotal tongue) which does not become evident until about six months of age. The nose is short, with a flat bridge resulting from underdevelopment of the nasal bone. The teeth are delayed in eruption, small and ab-



A

B

FIG. 333. A, Roentgenogram of pelvis and hips of a normal infant at 9 months of age. B, Roentgenogram of pelvis and hips of an infant with mongolism at 7 months of age. The acetabular roofs are almost horizontal, and there is flaring of the ilia. These abnormalities may be measured as illustrated and as described by Caffey.



FIG. 334. Typical facial configuration of mongolism in a 7-year-old girl.

normally aligned as a rule. The neck is short and broad, and there is laxity of the skin at the lateral aspects. In the young child the abdomen is prominent, owing to hypotonia of the abdominal muscles. The extremities are shortened, especially the phalanges, so that the hands and feet tend to be broad, flat and square. The fifth finger is proportionately small, and tends to curve inward. Roentgenographic examination demonstrates that the second phalanx of the fifth finger is rudimentary in about 40 per cent of mongoloid children. The spaces between the first and second fingers and toes are increased. In the foot this is associated with a prominent skin crease. The genitals are poorly developed, and the secondary sex characteristics are delayed. An interesting observation is the straight, rather silky quality of the pubic hair. Alterations in the bony pelvis, recognizable radiographically in early infancy, have been described by Caffey. The ilia are broad, the acetabular angles are small, and the ischia are elongated.

The most frequently associated developmental anomalies are those of the eyes and heart; defects of the interventricular septum are the most common cardiac anomalies. Generalized hypotonia of the skeletal musculature is present, but wanes as the child becomes older.

Laboratory studies have not indicated any significant endocrine or metabolic abnormality.

The mental status is usually in the imbecile range, infrequently in that of idiocy or the moron level.

The emotional development of mongolian children is extremely simple. They are easily

Table 112. Differential Factors in Mongolism and Cretinism

	<i>Mongolism</i>	<i>Cretinism</i>
Recognizable . . .	At birth	After 2-3 months
Body growth . . .	Retarded	Retarded
Head . . . . .	Brachycephalic	Normal size
Eyes . . . . .	Upward, outward slant	Puffy
Osseous orbits . .	Smaller than normal	Normal
Epicanthus . . .	Present at inner angle	Not present
Nose . . . . .	Small; bridge underdeveloped	Normal
Tongue . . . . .	Scrotal; may protrude	Thick, large; protrudes
Hands . . . . .	Short; incurved 5th finger	Short; square
Feet . . . . .	1st and 2nd toes widely spaced	Short; square
Skin . . . . .	Occasionally dry	Very dry, pale, coarse
Hair . . . . .	Variable	Very dry and coarse
Muscle tone . . .	Poor; marked joint laxity	Unchanged
Constipation . .	Uncommon	Marked
Congenital anomalies . . .	Frequent: heart and eyes	Umbilical hernia
Ossification . . .	Slight or no delay	Marked delay
B.M.R. . . . .	Normal	Decreased
Serum iodine . .	Normal	Decreased
Cholesterol . . .	Normal	Increased

regimented and institutionalized. They are usually pleasant and affectionate, and rarely exhibit temper tantrums or behavior disorders. In the absence of serious extracerebral and cardiac defects, and when given reasonably good medical care, their life span need not be greatly shortened. Probably owing to the dryness of the skin and frequent fissuring and cracking of it during cold weather, erysipelas and furunculosis are more common than in normal children. The mongolian child is also more susceptible to infection of the upper respiratory tract, including the sinuses and middle ears, than is the average child, possibly because the abnormal skull development adversely affects drainage from these areas. There is, however, the usual response to antibiotic drugs. The incidence of convulsive disorders is about the same as in the general population.

The pathologic changes in the brain and spinal cord are not characteristic. Grossly, minor fissural and gyral deviations are noted. Histologically, there are minor changes in the ganglion cells, especially a reduction in number, as well as spotty areas of defective myelin formation. As in most conditions as-



sociated with mental deficiency, there is little correlation between mental capacity and pathologic observations.

The diagnosis of mongolism in the older child is relatively simple, but may present significant difficulties in the early weeks of life when most of the signs are not too obvious. The abnormal configuration of the skull, however, is established at birth, and the peculiar formation of the orbits and palpebral fissures are frequently the only specific findings on which a diagnosis can be based. Restraint in making a definite diagnosis during the first few months of life is wise, since occasionally facial appearances suggestive of mongolism occur in infants of normal intelligence.

The only clinical condition which may give some difficulty in *differential diagnosis* is cretinism (see Table 112), which usually is not manifest at birth.

There is no evidence that the *course* of mongolism is benefited in any way by the use of endocrine or other medications.

#### UNDIFFERENTIATED OR PRIMARY AMENTIA

This group includes patients with mental deficiency resulting from congenital cerebral abnormalities not classifiable in any of the recognized categories, either clinically or etiologically. Its relative importance is indicated by the fact that, in an institution admitting all types of mental defectives, this diagnosis was made in 6.5 per cent of the morons, 32 per cent of the imbeciles and 60 per cent of the idiots.

There are no characteristic physical abnormalities. There is frequently some increase in motor tone without palsy; the deep reflexes are hyperactive but equal; occasionally the Babinski responses are extensor, and extra-cerebral malformations occur in about 10 per cent of this group, the anomalies being located principally in the eyes and the skeletal system. Convulsive disorders occur in about 10 to 15 per cent of this group. The central nervous system at autopsy shows a wide variety of developmental defects, including malformations of gyri, distorted cellular architecture, absence or imperfect development of various cerebral structures, generalized or focal hypoplasias, and the like.

*Diagnosis* is made by exclusion of identifiable forms of mental deficiency.

#### BIRTH TRAUMA (p. 315)

Birth trauma is a relatively uncommon cause of mental deficiency; among 2000 admis-

sions to an institution caring for all types of mental defectives, only fifty-eight children (3 per cent) were considered to be defective as a result of birth injury. Most of them were in the imbecile and idiot categories, and about one third showed associated motor defects. Since the type of mental defect and of the motor defect when present are not characteristic, the diagnosis of birth injury depends on a careful birth and neonatal history.

#### CENTRAL NERVOUS SYSTEM INFECTIONS

(Nonsuppurative encephalitides, p. 546, purulent meningitides, p. 424; tuberculous meningitis, p. 469). Such infections account for almost 5 per cent of the admissions to institutions for mental defectives. There are all degrees of intellectual impairment, and associated neurologic abnormalities are frequent. A striking finding in those with minimal intellectual impairment is the relative frequency of severe behavior disorders, which often prevent adequate social adjustment and necessitate institutionalization.

#### RECURRENT CONVULSIONS (p. 1117)

Convulsive disorders are common among the various categories of mental defectives. In most instances the convulsions are an associated manifestation of the underlying cerebral pathology. Convulsions per se, however, recurring over a period of many years may *infrequently* be responsible for intellectual impairment. The mental status is usually in the moron category. The pathogenesis of the mental defect is not clear. In some cases frequent head trauma as a result of falls is considered significant. Continued exposure to adverse psychogenic factors with resulting psychotic deterioration undoubtedly also plays a role. Circulatory changes and other physiochemical abnormalities associated with the cerebral dysrhythmia have also been suggested as etiologic factors.

#### TREATMENT

A variety of organic methods to stimulate or accelerate the development of intelligence have been suggested. These have included glutamic acid, vitamin B<sub>12</sub>, various hormones and a surgical procedure for increasing cerebral blood flow. There is no agreement that any of them is significantly effective.

The care of the mental defective must be considered a joint responsibility of the home, school, community and state. Since these four

factors will obviously vary greatly from case to case, the subject can be discussed only in general terms. It is the responsibility of the physician, however, to translate these generalities into specific recommendations for the individual child. Defectives may be divided into (1) a trainable group, which includes most of the moron group and those of the upper imbecile level; and (2) a permanently custodial group.

**Trainable Group.** Except when there are serious emotional disturbances, most high grade mental defectives are educable and trainable for social adjustment to a partial or complete extent. The scholastic attainment should not be expected to exceed the fourth or fifth grade level. Specialized educational techniques are necessary for optimal development of limited abilities. Similarly, occupational training can be expected to result in definite but limited skills. As a rule, it is not the purpose of these specialized training programs to produce full-fledged employable artisans. Levels beyond the apprentice stage are rarely reached. The degree of occupational skill attained is not of primary importance, however. More useful is the inculcation of proper work habits, occupational interests and personality factors that make for cooperation with and trainability by future employers.

Training and education are best handled in the home and community, if possible. For most morons, community care will be successful under the following conditions: (1) The family accepts and appreciates the implications of the diagnosis of mental defect and the necessity for relatively long-term supervision. Someone in the family is willing to make the sacrifices the additional supervision requires. (2) There are facilities available in the community for the specialized types of education, training and recreation required by these children. Though these facilities, as a rule, are a part of the public school system, they are available in some private schools. The presence of associated motor defects, such as cerebral palsy or manifestations of convulsive disorders, will complicate the problem. However, the main consideration determining disposition of the case should be the intellectual impairment.

Institutionalization of mentally defective children should be resorted to only after home care has proved unsuccessful. It should rarely be necessary to remove the trainable defective from the community before early adolescence except to prevent the develop-

ment of serious emotional and behavior disorders resulting from inadequate home conditions. Under these circumstances foster homes, preferably in another community, should be considered.

**Custodial Group.** In the idiot child and those of the lower imbecile group, the problem is simply one of supplying satisfactory custodial care. The question of institutionalization, and when it should occur, is basically a parental decision, and only rarely the physician's responsibility. It will depend on such factors as (1) the economic status of the family and availability of space in a state-supported institution; (2) the presence of other children in the family; and (3) the emotional stability of the parents, especially the mother. The care required for a low grade defective infant is no more complicated or time consuming than that for a normal baby, and is frequently less. Other factors being suitable, it is poor judgment to recommend that these children be removed from their home during early life if the expense of institutionalization imposes a serious economic burden on the family. The presence of other children in the family, especially if they are relatively young, is not in itself an indication for immediate removal of the idiot child. Emotional disturbances of a significant degree rarely develop in normal children in families who continue to care for a low grade infant during the early years of his life if the parents are well oriented and emotionally adjusted. However, the emotional make-up of some parents, especially some mothers, is such that it is virtually impossible to care for a low grade defective infant in the home. The capacity of the family in this respect can usually be determined after a short trial period. As a rule, practically all mentally defective children of a low grade will eventually require institutional care, and provision should be made for it in most instances before the fifth or sixth year of life.

**Sterilization** represents an indispensable adjunct to a complete program of social care for the mentally defective. The place of sterilization in the over-all program should be clearly understood. Two distinct indications have been recommended for sterilization. One has to do with eugenic considerations. The other is primarily of social hygienic importance, based on the fact that, as a rule, the mentally defective person is unable to undertake the responsibilities of rearing a family. Although it is unlikely that the practice of sterilization will become widespread



enough to change significantly the incidence of defective genes, its value in the family with a hereditary type of defect is obvious and should be recommended. It is for social hygienic considerations that sterilization has its greatest value. Its use in this respect is generally confined to the high grade, moron female of childbearing age who does, or will, live in the community under reasonable supervision. State permissive laws vary widely, and a clear understanding of the legal aspects is necessary before the procedure is recommended. There is no evidence that the measure in any way leads to sexual promiscuity.

HERMAN YANNET

## REFERENCES

### General

- Benda, C. E.: *Developmental Disorders of Mentation and Cerebral Palsies*. New York, Grune & Stratton, Inc., 1952.
- Ford, F. R.: *Diseases of Nervous System in Infancy, Childhood and Adolescence*. Springfield, Ill., Charles C Thomas, 1946.
- Gates, R. R.: *Human Genetics*. New York, Macmillan Company, 1946.
- Penrose, L. S.: *Biology of Mental Defect*. New York, Grune & Stratton, Inc., 1949.
- Yannet, H.: *Mental Deficiency*. *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1956, Vol. 8, p. 217.

### Mongolism

- Benda, C. E.: *Mongolism and Cretinism*. New York, Grune & Stratton, Inc., 1949.
- Caffey, J., and Ross, S.: *Mongolism (Mongoloid Deficiency) During Early Infancy—Some Newly*

- Recognized Diagnostic Changes in the Pelvic Bones*. *Pediatrics*, 17:642, 1956.
- Ingalls, T. H.: *Pathogenesis of Mongolism*. *Am. J. Dis. Child.*, 73:279, 1947.
- : *Etiology of Mongolism: Epidemiologic and Teratologic Implications*. *Am. J. Dis. Child.*, 74:147, 1947.
- Jervis, G. A.: *A Note on the Etiology of Mongolism*. *Quart. Rev. Pediat.*, 8:126, 1953.

### Familial Moron

- Halperin, S. L.: *Human Heredity and Mental Deficiency*. *Am. J. Ment. Def.*, 51:153, 1946.
- Penrose, L. S.: *A Study in the Inheritance of Intelligence. The Analysis of 100 Families Containing Subcultural Mental Defectives*. *Brit. J. Psychol.*, 24:1, 1933.

### Phenylpyruvic Oligophrenia

- Knox, W. E., and Hsia, D. Y.: *Pathogenetic Problems in Phenylketonuria*. *Am. J. Med.*, 22:687, 1957.
- Tyler, F. H., and Armstrong, M. D.: *Diseases of the Nervous System*. *Ann. Rev. Med.*, 5:207, 1954.
- Wright, S. W., and Tarjan, G.: *Phenylketonuria*. *A.M.A. Am. J. Dis. Child.*, 93:405, 1957.

### Kernicterus

- Allen, F. H., and Diamond, L. K.: *Prevention of Kernicterus*. *J.A.M.A.*, 155:1209, 1954.
- Crosse, V. M., Meyer, T. C., and Gerrard, J. W.: *Kernicterus and Prematurity*. *Arch. Dis. Childhood*, 30:501, 1955.
- Yannet, H., and Lieberman, R.: *Central Nervous System Complications Associated with Kernicterus*. *J.A.M.A.*, 130:335, 1946.
- : *Mother-Child ABO Incompatibility*. *Am. J. Dis. Child.*, 76:176, 1948.
- Zuelzer, W. W.: *Kernicterus*. *Pediatrics*, 6:452, 1950.

# Cerebral Palsy

The term "cerebral palsy" as currently used includes a group of nonprogressive disorders resulting from malfunction of the motor centers of the brain, characterized by paralysis, weakness, incoordination or other aberrations of motor function, which have their origin prenatally, during birth or in the first year or two of life. Cerebral palsy encompasses the neuromotor manifestations of organic brain damage and occurs in conjunction with other manifestations of it such as seizures, mental retardation, various sensory defects and behavior or emotional disorders. It is not a specific type of brain damage, but it results from congenital defects, mechanical and chemical injury and infection. The pathologic and clinical findings are varied. It is a nonfatal (*per se*), noncurable condition that is frequently amenable to therapy and training.

Cerebral palsy is one of the leading causes of crippling in children; it is estimated that the prevalence rate is 100 to 600 cases per 100,000 population, the majority of known patients being under twenty-one years of age. The care and support of these children, who usually have multiple handicaps, represent an important economic and social as well as medical problem.

John Little's description of spastic quadriplegia in 1862 is still classic. Minear's recent classification of cerebral palsy (Table 113) is of value, since its use emphasizes that the term is not a diagnosis and that there are varied causes, manifestations and degrees of involvement. The information necessary to classify a given child plus a knowledge and understanding of his family's capabilities and limitations should lead to a rational therapeutic approach.

*Spasticity* is characterized by the pathologic stretch reflex, increased activity of deep tendon reflexes, clonus, scissoring and contractures affecting the antigravity muscles. Among early signs are fixed posturing, often opisthotonos or maintained partial tonic neck responses. Sudden lifting of the child may produce scissoring of the legs. Tonic neck

reflexes are too readily elicited or are asymmetric, and the trunk and pelvis may fail to follow the head. Stepping and placing reflexes are absent or done better with one foot than the other. Lifting the supine child with a hand under the occiput produces extension of the neck and retraction of the shoulders. In the prone position protective turning of the face does not occur, and the child remains nose down.

*Athetosis* is marked by involuntary incoordinate motion with varying degrees of muscle tension. Reflexes are usually normal. Initially the clinical manifestation may be one of hypotonia, and only during the second year may the fine wandering movements of the fingers, hands and feet become evident and develop into the typical pattern of athetosis.

*Ataxia* is manifest by lack of coordination due to disturbances of the kinesthetic and balance senses. There may be associated hypotonia.

*Tremors* may be intentional or involuntary motions with a rhythmic pattern.

*Atonia* or *hypotonia* is characterized by soft muscles and usually by increased deep tendon reflexes. It frequently is a precursor of other types of involvement. Disturbances of muscle tone are present in almost all types of involvement.

Mixed types are seen, but usually one form predominates. Spasticity is the most frequent type and together with athetosis accounts for approximately 75 per cent of all cases; seizures occur in approximately 25 per cent and are frequently of the myoclonic type in infancy.

**Diagnosis.** Early diagnosis of brain injury is important to the child and his family, since many of the physical and psychologic complications can be decreased or avoided if parents are given help and guidance during the first year or two of the child's life.

When one manifestation of brain damage is recognized, others should be suspected. Children who have a history of any of the factors outlined above should be observed carefully for abnormalities. The presence of



Table 113. Classification of Cerebral Palsy

- 
- I. Physiologic (motor)
    - A. Spastic
    - B. Athetotic
      - 1. Tension
      - 2. Nontension
      - 3. Dystonic
      - 4. Tremor
    - C. Rigidity
    - D. Ataxic
    - E. Tremor
    - F. Atonic (rare)
    - G. Mixed
    - H. Unclassified
  - II. Topographic
    - A. Monoplegia—involves one limb; condition is rare; should be checked closely to determine whether one is dealing with a paraplegia or hemiplegia
    - B. Paraplegia—involves the legs only and is practically always of the spastic or rigidity type
    - C. Hemiplegia—lateralized half of the body is affected, and it is usually spastic, although pure athetoid hemiplegias are occasionally seen, as are pure rigidity hemiplegias. There is often sensory involvement in the areas of proprioception to point discrimination and form perception. Aphasias appear more frequently in right than in left hemiplegias and are much more common in acquired than in congenital cerebral palsy
    - D. Triplegia—involves 3 extremities, usually both legs and one arm, usually spastic. This may represent hemiplegia plus paraplegia, or incomplete quadriplegia. In the latter case both arms will be equal or nearly equal in length. In the former the involved arm will be shorter
    - E. Quadriplegia (tetraplegia)—involvement of all 4 extremities. Patients with the greatest involvement of the legs are usually spastic, and patients with greatest involvement of the arms are usually the dyskinetics, including athetoids
    - F. Diplegia—this term is seldom used. "Paralysis affecting like parts on either side of the body; bilateral paralysis" (*Dorland's Illustrated Medical Dictionary*, 23rd ed.)
    - G. Double hemiplegia—this term is seldom used. "... implies those cases in which the arms are more involved than the legs. These are usually spastic in type" (Cruikshank and Raus: *Cerebral Palsy—Its Individual and Community Problems*. Syracuse University Press, 1955)
  - III. Etiologic
    - A. Prenatal
      - 1. Hereditary—genetically transmitted and may involve racial or familial predilections and often sex-linked. These are often classified as "cerebral agenesis." The symptoms are often present at birth and generally do not progress. Examples: hereditary athetosis, familial tremor, familial spastic paraplegia
      - 2. Acquired in utero
        - a. Prenatal infection (toxoplasmosis), rubella or other maternal infection
        - b. Prenatal anoxia—carbon monoxide, or strangulation of mother, maternal anemia, hypotension, e.g., following spinal anesthesia, placental infarcts or placenta abruptio, kinking, knots or prolapse of the cord
        - c. Prenatal cerebral hemorrhage—maternal toxemia, direct trauma, maternal bleeding diathesis
        - d. Rh factor, kernicterus due to Rh factor\*
        - e. Metabolic disturbances, diabetes
        - f. Gonadal irradiation, harmful exposure to x-rays
        - g. Maternal malnutrition
    - B. Natal
      - 1. Anoxia
        - a. Mechanical respiratory obstruction
        - b. Atelectasis
        - c. Narcotism (due to drugs)
        - d. Placenta praevia or placenta abruptio
        - e. Maternal anoxia or hypotension
        - f. Breech deliveries with delay of the after-coming head
        - g. Bleeding in the first trimester (see Eastman)
    - C. Postnatal
      - 1. Trauma—subdural hematoma, skull fractures, wounds and contusions of the brain (accidental)
      - 2. Infections (more common in children than adults)—meningitis, encephalitis, brain abscess
      - 3. Toxic causes—lead, arsenic, coal tar derivatives, streptomycin, etc.
      - 4. Vascular accidents (more common in adults than children)—congenital aneurysms, circle of Willis, hypertensive encephalopathies, emboli due to bacterial endocarditis or fat embolism, cerebrovascular thrombosis, in debilitated infants, sudden pressure changes
- 

\* Hyperbilirubinemia of other causes may also be responsible for kernicterus.

Table 113. Classification of Cerebral Palsy (*continued*)

5. Anoxia—carbon monoxide poisoning, strangulation, high altitudes, and deep pressure anoxia, hypoglycemia
6. Neoplastic, or late developmental defects—brain tumors, brain cysts, internal hydrocephalus, hydrocephalus
- IV. Supplemental
  - A. Psychologic evaluation
    1. Degree of mental deficiency, if any
  - B. Physical status
    1. Physical growth evaluation (Wetzel grid or other)
    2. Developmental level (Gesell)
    3. Bone age
    4. Contractures
  - C. Convulsive seizures
  - D. Posture and locomotive behavior patterns
  - E. Eye-hand behavior patterns
    1. Eye dominance
    2. Eye movements
    3. Eye postures
    4. Fixation
    5. Convergence
    6. Prehensory approach
    7. Grasp
    8. Manipulation
    9. Hand dominance
  - F. Visual status
    1. Sensory
      - a. Amblyopia
      - b. Field defects
    2. Motor
      - a. Conjugate deviations (33% of motor defects)
      - b. Fixation defects
      - c. Spasmus fixus (1%)
      - d. Strabismus fixus (1%)
      - e. Esotropia (51%)
      - f. Exotropia (9%)
      - g. Hypertropia
      - h. Hypotropia
      - i. Nystagmus
      - j. Pseudopalsy of the externi (22%)
  - G. Auditory status
    1. Pitch range loss
    2. Decibel loss
  - H. Speech disturbances
- V. Neuroanatomic (see subheadings under "Brain," topographic headings, *Standard Nomenclature of Diseases and Operations*)
- VI. Functional capacity (degree of severity)
  - Class I. Patients with cerebral palsy with no practical limitation of activity
  - Class II. Patients with cerebral palsy with slight to moderate limitation of activity
  - Class III. Patients with cerebral palsy with moderate to great limitation of activity
  - Class IV. Patients with cerebral palsy unable to carry on any useful physical activity
- VII. Therapeutic
  - Class A. Patients with cerebral palsy not requiring treatment
  - Class B. Patients with cerebral palsy who need minimal bracing and minimal therapy
  - Class C. Patients with cerebral palsy who need bracing and apparatus and the services of a cerebral palsy treatment team
  - Class D. Patients with cerebral palsy limited to such a degree that they require long-term institutionalization and treatment



any anomaly or of disturbances during the neonatal period such as feeding problems, irritability or drowsiness, cyanosis, jaundice, respiratory difficulties, abnormal muscle tone or seizures should lead to a careful observation of the central nervous system.

The cases of more severe damage or deficit are usually apparent early in life. Those of less degree should be suspected when there is a significant deviation from normal rates of growth and development or when there is persistence of infantile physiologic reflexes such as the Moro and the tonic neck ones. The typical adult neurologic patterns may not develop during the first year or two of life even though the lesion is present from birth or earlier. Definite handedness apparent before twelve to fifteen months suggests hemiparesis.

The differential diagnosis may include consideration of more acute conditions such as trauma to the brain or the peripheral nerves, poisoning, infection or tumor of the central nervous system, degenerative diseases, Sydenham's chorea, amyotonia congenita and muscular dystrophies. It must be remembered that in children with motor dysfunction associated with organic brain damage the other manifestations such as seizures, retardation, sensory and perceptual changes and abnormal behavior are also frequently present.

**Prognosis.** Prognosis is dependent on a careful appraisal of all factors related to the individual child, his family and the community. With the knowledge that the basic defect cannot be cured, that associated or complicating conditions are usually present, that social, economic and psychologic factors are usually harder to control than the medical ones, the outlook for the group as a whole is not favorable for self-sufficiency or ability to compete with peers. Only a small percentage of affected children achieve independence and a satisfying way of life. The goals should be much lower in the majority of cases, and only by observation of growth and maturation, by response to treatment and training and appreciation of the child's and the family's ability to use their own and the community's resources can a realistic goal be set. In general the child's intelligence is the best prognostic guide, so that use should be made of the best psychometric help available.

**Treatment.** The general features of management of a handicapped child are described elsewhere (p. 1145); these include a realistic short- and long-term plan, assistance to the child in making full use of his residual assets,

avoidance of secondary emotional problems, support and counseling for the family and use of available community resources. The goals must be reviewed periodically in the light of progress made, and therapy must be timed in accord with the child's developmental status. In general the aim of treatment should be to secure for the patient a happy childhood and a well adjusted adult life in which he performs well within the limits of his capabilities.

In the most seriously involved children, treatment may be largely supportive and aimed at prevention of complicating factors such as contractures, nutritional deficiencies, pressure sores, infections and emotional problems in all concerned.

If the child has intelligence enough to try to learn, efforts at developing muscle strength, balance and coordination, functional posture and skills in communication and self-help should be made. Since it is usually impossible to evaluate accurately the relative detrimental effect of several handicaps, all defects that lend themselves to correction should be treated. The total benefit of such efforts frequently is rewarding, although there are few well controlled clinical trials of any individual therapeutic regimen or combination of therapies to which such children are exposed.

The group that appears least seriously involved may not reach its full capability because of lack of attention to emotional factors that may be more handicapping than the motor defect itself.

More than anything else, the handicapped child and his parents need the continuing care of a physician whose judgment is not blurred by too close contact with individual parts of the problem. The child with cerebral palsy has an injured brain whose function is not that of the normal brain. Child and parents must not be allowed to succumb to a well meaning but tyrannical optimism aimed at improved performance of individual functions, but disregarding the limit set for the whole child by his organic handicap. The desired end result of a happy adult, well adjusted and performing at his maximal ability, is best reached by early recognition of the extent of his handicap, and kindly but realistic direction toward attainable rather than unattainable goals. Acceptance by child, parents and physician of that part which cannot be altered should be achieved at least by the time of the early school years. Planning for adult life on these terms accomplishes more for the child and his parents than all the

mechanical gadgets, therapies and surgical procedures known to medicine.

The specific treatments for various manifestations are discussed elsewhere.

The orthopedist is concerned with developing and maintaining good body mechanics. This is accomplished by bracing, by physical therapy and by surgery that is largely limited to tendon lengthening, to arthrodeses and to muscle transfers in older children.

Training resulting in functional improvement of body mechanics, muscular control, gait, use of hands, and in verbal communication can be effectively carried out by parents under the direction of physical, occupational and speech therapists. Success is proportionate to the degree of physical, mental and emotional involvement of the patient, to the therapist's understanding and use of physiologic approaches and to the integration of such therapies with other services for the child.

Physiotherapy, most of which can be carried out by the parent (after instruction), should be begun in infancy to avoid development of contractures and to stimulate control of movement. The joints involved—usually ankles, knees, hips, wrists and fingers—are manipulated against the direction of maximal contraction and are finally carried through a full range of movement. Short periods of therapy repeated at intervals during the day are more effective than fewer long sessions; the procedure benefits the child physically and the parents emotionally. Active motions should be encouraged. Later, efforts at improving coordination by use of games, peg boards, training in sitting and standing in supportive chairs or at stand-up tables, walking aids such as parallel bars, skis or crutches may be added as indicated under guidance of trained therapists.

At present few therapists are available in cerebral palsy clinics, so that the individual child often gets only scanty attention. Most of the procedures are relatively simple, and most of the equipment easily constructed by amateurs. Enthusiasm for clinic care should

not overlook the powerful and much more available resources within the home. Parents should be trained and encouraged to carry out as much of the therapy as possible.

Neurosurgery may play a part in a small number of cases. Treatment of subdural collections of fluid, hydrocephalus, craniosynostosis, intracranial vascular anomalies or hemorrhage and acute trauma may play a part in modifying or preventing some of the conditions that lead to cerebral palsy. Various procedures aimed at removing foci or at interruption of pathways in the brain to reduce uninhibited activity are under clinical investigation.

Children with visual, auditory and dental problems are handled essentially as are other children with such problems with appropriate modifications for their associated disabilities and limitations.

Many drugs having varied pharmacologic actions have been used, and others are under current evaluation. None has satisfactory clinical effect without significant disadvantages. Of the newer ones, meprobamate for athetosis and zoxazolamine for spasticity appear to be occasionally helpful in diminishing symptoms, but not in improving function. Various tranquilizers relieve secondary tension and may help at times to improve over-all function. Anticonvulsive drugs should be used as indicated (see p. 1123).

**Prevention.** A review of the many causes of brain injury listed above reveals a number which are preventable. The practicing physician can make a major contribution by applying known principles of preventive and therapeutic medicine.

JOHN B. BARTRAM

#### REFERENCES

- Cruikshank, W. M., and Raus, G. M.: *Cerebral Palsy; Its Individual and Community Problems*. Syracuse, Syracuse University Press, 1955.
- Minear, W. L.: A Classification of Cerebral Palsy. *Pediatrics*, 18:841, 1956.
- Pohl, J. F.: *Cerebral Palsy*. St. Paul, Bruce Pub. Co., 1950.
- Services for Children with Cerebral Palsy*. New York, American Public Health Association, Inc., 1955.



# Behavior Problems Associated with Organic Brain Damage

Those who participate in the care of brain-damaged children are aware that behavior problems represent a significant part of the problem.

The term "brain-injured child" unfortunately has become rather widely used for a syndrome of abnormal behavior and distorted learning patterns in children with presumptive or demonstrable brain damage. It is a misleading term and does not apply to all children with central nervous system injury or defect.

This syndrome may occur in conjunction with motor and sensory defects, with seizures and with significant delay in the rate of mental development, or may appear as the only apparent manifestation of brain damage. The characteristic symptoms are unpredictable variations of behavior, distractibility or short attention span for the age (or the converse—perseveration), hyperactivity, impulsiveness, irritability, over-reaction to environmental stimuli and eventually difficulties in abstract thinking.

None of these alone is of diagnostic significance, but when several appear together in a child, the disorganization and weakened controls suggest a basis in brain damage. The child's behavior varies from day to day without relation to other recognizable factors and is apparently as unpredictable to himself as to others. His restlessness is frequently marked by running to and fro, by constant physical activity and by a short attention span for any one activity that is not consistent with that seen in others of his age. His enthusiasms are tense but short, and his acts appear to follow no pattern of thought. He tends to react violently to frustration and to other stimuli, and he may be a constant storm center in the family, at play or in school. It is not so much that any single part of his behavior is bad, but rather that there is always too much of it. At school age, although

frequently of normal or borderline intelligence, he usually has difficulty with number concepts, with associating the particular with the general and with drawing logical conclusions from abstract material. Allied to the problem of handling abstract concepts are problems in the child's perception of the world, so that instead of attending to the whole of the environment he perceives, he may attend only to a minimally important part. The ordinary relationship between figure and background in perception is lost or confused so that the child's reaction is frequently unpredictable.

As the child grows older secondary behavior manifestations related to his frustrations, to how he feels about himself and to his contacts with people may obscure the earlier pattern. In many cases these secondary symptoms appear as emotional immaturity, anxieties and fears, school failure, and the like. In the individual child it is not easy to distinguish the basic symptoms related to brain damage from the acquired ones.

There are all degrees of the condition, and there are no clear-cut diagnostic aids. The syndrome should be suspected in any child with abnormal behavior who shows clinical evidence of brain damage or whose history includes events potentially leading to sequelae in the brain. The postencephalitic or post-traumatic behavior of some children is an example of this condition in which hyperactivity is a major symptom. Many children do not show any abnormality on careful neurologic examination. Some are clumsy and maladroit in voluntary activity as compared with their contemporaries. Handedness may develop late.

Abnormalities may or may not be detected by electroencephalography, by pneumoencephalography or by cerebral arteriography, but none is accepted as being specific for the syndrome. There is suggestive evidence that

the lesion, if localized, may be in the mid-brain.

Psychologic test performance frequently gives a clue to the presence of disorganization, weakened controls and poor power of inhibition. The "organic picture" may be suggested by an experienced clinical psychologist from interpretation of the Wechsler Intelligence Scale for Children (in particular the child's approach to the visual-motor tasks), the Bender-Gestalt Motor Test, the Werner-Strauss Marbleboard Test and the Rorschach Test. There appears to be little correlation with the intelligence quotient except as this is influenced by other complicating factors. The great variability in function displayed by these children is a clue to the problem.

The syndrome of behavior problems associated with brain damage should be distinguished from mental retardation, psychoses and severe secondary behavior problems arising on a psychodynamic basis.

**Treatment.** The management of children with behavior problems resulting from brain injury should be directed toward helping the family and others associated with the child to understand him and thus minimize secondary behavior problems. Parents frequently are put at ease if behavior is explained on the basis of a physical problem rather than as a result of parental incompetence. They can meet the prolonged dependency needs by treating such children as though they were at a younger age level. The erratic behavior and lack of self-control point to the need for definite limits and consistent controls and discipline. Firm constructive guidance is much better than permissiveness. Psychiatric treatment when available may be as helpful with the management of such problems as of those on a purely psychodynamic basis.

In addition to personal support and understanding of the child and his parents medication is sometimes a helpful crutch to modify the extremes of behavior. Success in prolonging the attention span and in leveling behavior is reported with use of the amphetamines. Dextro-amphetamine, 5 to 10 mg. in the morning, or twice that amount of amphetamine sulfate may be tried. Various tranquilizing agents may modify the irritability

or decrease the impulsiveness. Reserpine in doses of 0.1 mg. two or three times a day may be increased to tolerance (as much as 4.0 mg., three times a day). Chlorpromazine, 10 to 25 mg., two or three times daily, and captodiamine (Suvren), 50 to 100 mg., three times daily are sometimes of value. The anticonvulsive drugs are of minimal help in modifying behavior, and the use of phenobarbital may have a stimulating effect on children with such behavior problems.

The physician should guide the family to experts in the field of special education. The contributions to the educational phases of this subject by Strauss and Lehtinen and by Lewis should be of aid to families and to teachers. Modification of school curricula and techniques by placement in small classes, individual attention (concrete materials in teaching abstractions) and by elimination of distractions are said to be helpful.

**Prognosis.** The outlook for such children appears to depend principally on the attitudes and guidance of those who deal with them and on the degree of success which can be achieved in daily living and social contacts. Many are failures because of the complicating secondary behavior problems attributable to disruption of family life and to social unacceptability. Some become delinquents or are placed for care in institutions for mental defectives or psychotics. Some level off during adolescence and appear to achieve a comfortable way of life in relatively nonrestricting activities.

JOHN B. BARTRAM

#### REFERENCES

- Bradley, C.: Characteristics and Management of Children with Behavior Problems Associated with Organic Brain Damage. *Pediat. Clin. North America*, 4:1049, 1957.
- Fouracre, M. H.: Learning Characteristics of Brain-Injured Children. *Exceptional Children*, 24:210, 1958.
- Lewis, R. S.: *The Other Child*. New York, Grune & Stratton, Inc., 1951.
- Strauss, A. A., and Kephart, N. C.: *Psychopathology and Education of the Brain-Injured Child*. New York, Grune & Stratton, Inc., 1955, Vol. II.
- Strauss, A. A., and Lehtinen, L. E.: *Psychopathology and Education of the Brain-Injured Child*. New York, Grune & Stratton, Inc., 1948, Vol. I.



# The Physician and the Child with a Handicap

It has become increasingly important for the physician who cares for children to become familiar with the special problems of the child who chronically deviates from normal because of some congenital or acquired disability.

The successful management of such a child depends more often on the social adjustment that can be made than on purely technical procedures. The following general principles apply especially to children with various types of brain injury and to a less degree to all children with handicaps.

**The Physician.** Some physicians are not geared to provide adequate management for the handicapped child and his family. Care of long-term illness does not provide the reward to the ego which accrues from the management of self-limiting or readily curable disturbances. Management is time-consuming, and many of the children are "uncooperative." They disrupt a busy appointment schedule, and much time must be spent with emotionally disturbed parents. However, the physician who extends his responsibility beyond the treatment of the "chief complaint" will find rewards in helping the young handicapped patient and his family to live more comfortably with a long-term illness.

A physician may feel inadequate because the complexity of the problems makes them appear unsolvable or beyond means at his immediate command. He must be able to utilize other professional disciplines and other resources in the community while he maintains his own professional relationship with the family. Abandonment or rejection of a handicapped child by a physician by ignoring the real problem, by giving the family false hopes or by not seeking help which is available only compounds everyone's difficulties. A physician may feel threatened if a specific etiologic diagnosis cannot be made or if the evaluation cannot be completed at one visit.

Intelligent management *can* begin at the first meeting with the family and with a simple functional appraisal of the child.

The physician who cannot be a patient, noncritical listener, who cannot be satisfied with small gains, who cannot project himself into the child's and the parents' position sufficiently to offer intelligent support when a cure is not available, who clings to outmoded concepts and is not realistically aware of both the possibilities and limitations of habilitation, who cannot or will not work with others in the community, and who does not provide adequate general pediatric care at all times, should not complain if others take over where he has failed.

**Management of the Child.** By continuing contacts with the child and his family the physician can help in formulating both a short- and a long-term plan that is realistic for all concerned. He should help the child make use of his intact ability as effectively as possible and become as socially acceptable and self-sufficient as his limitations permit. The child with multiple handicaps is rarely capable of achieving a great degree of independence. The physician must, on occasion, interpret the child and his behavior to those who are in regular or occasional contact with him. A physician should make every effort to minimize the secondary handicaps in the field of personality development so that they do not become more serious than the primary defect. He should above all else try to help the child lead a happy and useful life.

**The Family's Problems.** Since the child's environment and the emotional climate of the home are of equal if not greater importance than the medical care per se for the child's eventual adjustment, every effort must be made to assist the family to understand their own reactions and to fulfill their own tasks. Parents' reactions to a defective child are varied, depending on the extent to which they

feel their competency, social standing and anticipated way of life to be threatened by the handicap. Most parents initially attempt to deny the reality of the defect, particularly if it is one that is not obvious physically. This stage is usually followed by one of frustration and disorganization in which all sorts of fears about the future become overwhelming. Simple explanation, support and guidance for the family are particularly necessary during this stage. Depending on the degree of maturity and emotional resources of the family, they can be helped to accept their problems realistically and to plan constructively for the long-term needs of the child.

The types of problems are as varied as the people involved. Most parents, regardless of their background, have feelings of guilt about the defective child which must be resolved lest attitudes of self-sacrifice, excessive overprotection or rejection of the child develop. Most families develop ambivalent feelings about the child, varying from overt hostility to gross overindulgence. The establishment of limits of acceptable behavior and the consistent teaching of discipline which are so important to a child's emotional development are thus lacking. The handicapped child frequently may be the precipitating factor of marital difficulties which are not basically related to him.

As the child grows older the parents have to accept many roles, and make psychologic adaptations which would otherwise not be necessary, because of the child's prolonged dependency upon them. The problems of social isolation, sexual development and unpleasant behavior become increasingly important to the family as the child grows older.

**Family Therapy.** Parents in retrospect often complain that the status of the child was not made clear to them, that the diagnosis was based on an incomplete examination or hasty judgment, that poor prognosis was not justified or that their part in helping the child was not explained. It must be remembered that many parents hear, retain and comprehend only in part, so that various interpretations must be given in an acceptable and understandable way to those concerned. The initial explanation of the facts about a child with a handicap should be made to the parents *together* in as simple a way as possible. Technical explanations are only confusing. Long-term prognosis and planning should be left for a later interview, and emphasis should be on management of immediate prob-

lems and symptoms. Questions should be answered simply, reassurance given to minimize guilt feelings, and the importance of time in determining the developmental ability of the child stressed. Attention cannot be given too early to the avoidance of secondary emotional problems in the child and his family. The practical problems of carrying out the home program can best be appreciated by a visit to the home.

A physician who is not aware that the parents' feeling of guilt about the child may be projected to him will be unprepared to act with the necessary understanding and patience and will emerge with a bruised ego. Guidance and support to the family is a continuing affair, and acceptance of the handicapped child is probably never fully accomplished by the parents because the problems change with advancing age.

Care should be taken to assure the siblings an equal share of the parents' time, attention and interest. With neglect their problems may become greater than those of the affected child. Their questions about the abnormal child should be answered simply and honestly. The experience of living with a seriously handicapped brother or sister may be used constructively to teach tolerance, patience and understanding of others. If parents openly accept the child as an individual, despite his limitations, a good example is set for others in the community. This is the best method of "public education." The converse is also true.

The question of the probable outcome of future pregnancies is frequently raised by parents. If the cause of the disability is clearly an accidental one, it is easy to be reassuring. If it is known to be genetically determined or to arise as a result of circumstances that might be repeated, the physician should explain the facts as simply and clearly as possible and help the parents to make their own decision based on available evidence (see p. 247). When the family have made their decision on grounds that are valid for them, the physician should support them in it.

**Institutional Care.** In the case of a seriously involved child who will always be completely or partially dependent on others for his care the question of care away from home will arise. The physician should help the family to make their own decision about this by objectively discussing with them the advantages and disadvantages of such care. The decision is the family's and not the physi-



cian's, although he may diplomatically initiate the discussion if he is convinced that such a solution is beneficial to all. Current concepts emphasize the potential value to all concerned of home care during infancy and early childhood. Even severely handicapped children can profit by tender loving care at home; mongoloid children in particular have a much greater potential if given good care in the average home than if placed in an institution at birth.

It is often said that defective children should be placed away from home at birth lest the parents become abnormally devoted to them. This may occur when feelings of guilt are not relieved, but the average family with guidance can handle such children to advantage at home for a few years. Parents in general feel more comfortable about later placement if they gradually gain acceptance of the child's limitations by normally fulfilling their role as parents. Too early placement may lead to doubts and greater feelings of guilt.

Temporary placement away from home is indicated when the child himself can profit by greater opportunities in a different environment or when inevitable family emergencies arise. If the defective child becomes a serious burden to the physical or emotional health of the parents and siblings, a change should be made. Placement is wrongly used as an escape from the physician's or the family's responsibility. It is usually not wise to encourage brothers and sisters to assume the permanent care of a dependent child.

**Use of Community Resources.** The physician should make effective use of local community resources such as public health nurses, baby sitters, "home maker" services, day care centers, social agencies, voluntary health agencies and temporary boarding homes to give the family a vacation or to tide them over emergencies. The physician often overlooks the support which the church can give to families in times of stress. A religiously oriented parent is better able to accept the burden of a handicapped child than one without such a resource. Better communication between the clergy and the medical profession can lead to more effective family counseling.

In less severely affected children the physician should assist the family to get appropriate help from public or private schools that may offer programs for "exceptional children." An increasing number of classes for orthopedically, mentally and emotionally

handicapped children, as well as for those with visual and hearing defects, is being provided by the public school system in many states.

Most communities, encouraged by voluntary health agencies and by parents, are developing services of some sort for various categories of children with handicaps. These include medical facilities for early diagnosis, evaluation and treatment, social case work, home care by nurses, psychologic evaluation and counseling, baby sitting or temporary home care, educational and recreational facilities, occupational training, sheltered workshops and residential training or supportive care. None of these threaten the physician, but add to what he himself can do for the patient. Since many of these services are necessary regardless of the cause or name of the disability, it is incumbent on the physician as a community leader to encourage their development and use for all children who need them regardless of the category of handicap.

**Parent Organizations.** Parents' lay organizations can be helpful in affording those with common problems an opportunity to share their anxieties and to gain strength and hope through identification with a group. Efforts in behalf of community education, support of research and voluntary participation in medical services can be psychologically important to parents and constructively helpful to the community.

JOHN B. BARTRAM

#### REFERENCES

- Cruikshank, W. M.: *Psychological Considerations with Crippled Children*. Psychology for Exceptional Children and Youth. Englewood Cliffs, N.J. Prentice-Hall, Inc. 1955.
- Lesser, A. J., and Hunt, C. P.: *The Nation's Handicapped Children*. Am. J. Pub. Health, 44:166, 1954.
- Michal-Smith, H.: *Management of the Handicapped Child*. New York, Grune & Stratton, Inc., 1957.
- Robinson, J. F.: *Affective Deprivation and Early Institutional Placement*. Neurology and Psychiatry in Childhood. Baltimore, Williams & Wilkins Company, 1956.
- Services for Handicapped Children*. New York, American Public Health Association, 1955.
- Wishik, S. M.: *Role of the General Practitioner and Specialist in the Care of Physically Handicapped Children*. Am. J. Dis. Child., 86:447, 1953.
- Wishik, S. M.: *Interpretations to School Teachers and Other Professional Persons on Handicapping and Clinic Conditions*. Pediatrics, 20:907, 1957.

# Psychoses

Mental illness of this type is uncommon in children. It is always difficult to diagnose, because the normal child shows many behavior traits which at another age indicate psychopathology. It is important that all psychiatrists have an adequate knowledge of the behavior of normal infants and children to help them in problems of differential diagnosis. Similarly, it would be well if the pediatrician had greater experience with emotionally disturbed children so that he could distinguish between deviant and normal behavior. He errs frequently in failing to recognize mental illness until it is well advanced.

**Etiology.** It is not clear to what extent heredity plays a part. The environmental stresses and strains are more readily understood. Some children appear to be constitutionally susceptible to unhealthy life situations, and the combination of environmental plus constitutional elements predisposes to illness.

**Clinical Manifestations.** One of the most frequent forms is an *acute delirious state*, which may even become maniacal. This condition is encountered most often with acute febrile disorders. Mania may also develop as a symptom of chorea, hysteria or epilepsy.

*Manic-depressive insanity* may occur in children, sometimes in a minor degree which resembles merely exaggeration of the ordinary moods common to most children and adults. It may take the form of depression with a feeling of despondency and physical inertia, but it may proceed to attempts at suicide.

*Schizophrenia (dementia praecox)* is the most frequent of the psychoses beginning in early life. Until recently it was believed that this psychosis developed only in certain types—the quiet, shy, “model” child who was often an exceptional student. Now we are inclined to believe that there are no sure prognostic signs before twelve years of age. Beyond this age it is well, however, to note any tendency to “brittleness,” to a certain unyielding inability to adjust to differing personalities or standards, to a sort of intolerance of any but the child’s own mode of life. With

this change there appears a growing ritualism—certain hours for doing certain things, unusual orderliness, inability to make sudden new plans or decisions. In various ways the schizoid child begins to draw a veil between himself and others. This is a deep sort of reserve which seems to have only those fleeting contacts with reality that one has when he is extremely sleepy, so that he is constantly slipping away into a dream state. There develops a splitting between the content of an act and the act itself—silly laughter with some tragic statement, or tears or rage accompanying some trivial act. Dilapidation is a pretty strong word for what begins as a sort of moth-eaten existence—carelessness, sloppiness, perennial tardiness, satisfaction with empty activities or just sitting. The ritualism earlier expressed in careful dress and behavior now is manifest in more bizarre matters—always getting out of the same side of the bed, always chewing the food for a given length of time.

The physician may know such adults who are apparently happy and successful. The schizoid type of personality is indeed common, nor do we know why in some instances it goes irrevocably on to overt disease. It requires the greatest understanding to know when to warn a family that disaster lies ahead and that therapy is indicated immediately, in contrast to a situation in which irreparable damage would follow the diagnosis of incipient insanity in a formal, brittle, conforming, non-adventuresome type of person.

Schizophrenia is a term which covers a number of distinct clinical patterns which are possibly much less disease entities than they are surface phenomena. Two definite types are discernible in adolescence. In one the child seems rapidly to lose interest in his surroundings. In this *hebephrenic reaction* the child begins to lie in bed through the morning, to lose interest in appearance, to be dull and lethargic in all his actions. He does not make any effort to explain or excuse his new attitude and gradually sinks into a vegetative existence. The second type is *simple*



*dementia praecox* in which there are less marked but similar symptoms and to which are added many bizarre delusions centering usually about the problems of sexual adjustment. Thus the boy will follow in minutest ritual certain diets or exercises to restore a fancied loss of sexual power. Proposals of marriage to complete strangers or terrific despair over the bad effects of masturbation appear. Bizarre sexual delinquencies, particularly involving younger children, occur. For both the hebephrenic and simple types there is usually about a two-year prodromal period of mild depression in which suicide is not uncommon.

*Paranoid dementia praecox* tends to develop later in life. *Catatonic dementia praecox* also is uncommon in childhood.

*Infantile autism* is manifest at an early age, and sometimes even at birth the infant seems different; he never develops much capacity to relate to other human beings. Such infants have normal physical development, but fail to develop speech and affective relations with parents at anticipated times. They differ from older schizophrenics in that there is no abrupt change in behavior. Sometimes they appear deaf, but without measurable clinical evidence to support a diagnosis of deafness. There may be smiling which seems inappropriate to the occasion. A tendency to destructiveness is often manifest. For example, when older, they may show an interest in mechanical gadgets by taking them apart, but have no interest in reassembling them. Toilet training is delayed at least several years, and

social relations with other children are never satisfactory.

The *prognosis* is poor, even after institutional care or shock therapy. Individual care provided by friendly and accepting adults who are able to give their undivided attention brings the greatest response from the child, but this is usually too time-consuming for the average parents.

**Differential Diagnosis.** This is extremely difficult, since there is no symptom of any psychosis which a perfectly normal adolescent youngster cannot clearly manifest at some time. The physician should know that, although the chances of a psychosis developing are extremely small, he must be aware of such a possibility.

**Prognosis.** The separate attacks of manic-depressive insanity have an excellent prognosis. The acute delirious states accompanying infections also have a good prognosis. Until recently it was thought that the prognosis in *dementia praecox* was always bad. New forms of treatment (shock therapy) with adults, particularly when used in the early stages, seem promising, but many psychiatrists are skeptic of the permanence of the cure.

**Treatment.** Every effort should be directed toward improving the physical condition and freeing the child from social and educational pressures and frustrations. Specific treatment should be entrusted to the psychiatrist as soon as possible.

MILTON J. E. SENN

# The Endocrine System

## DISORDERS OF THE PITUITARY GLAND

The pituitary gland consists of an anterior lobe and a posterior lobe. In man the pars intermedia, which can be recognized in the fetus, loses its distinction after birth. The anterior lobe develops from the ectoderm of the stomodeum (Rathke's pouch); fetal rests of the original connection of Rathke's pouch with the primitive oral cavity may persist in postnatal life as a craniopharyngeal duct. Sometimes tumors develop from the remnants of this duct (craniopharyngiomas) and give rise to symptoms of glandular and hypothalamic disturbances (p. 1086). The posterior lobe is derived from the infundibulum of the diencephalon and remains histologically and functionally distinct from the anterior lobe.

**Function. Anterior lobe.** Six well defined hormones are produced by the anterior pituitary, and other less well defined substances have been isolated. It is generally agreed that the chromophobe cells do not produce any hormones, that growth hormone is produced by the eosinophilic cells and the follicle-stimulating hormone (FSH) by the basophilic ones. Although not conclusively proved, it is believed that the eosinophilic cells are the source of the luteinizing or interstitial cell-stimulating hormone (LH or ICSH) and of lactogenic hormones and that the basophilic cells produce thyrotropic (TSH) and adrenocorticotrophic hormone (ACTH). This concept is probably too definitive. The pituitary hormones act either directly on the body cells or on other endocrine glands to affect almost every organ. The pituitary gland itself is under the control of the hypothalamus and is reciprocally affected by the hormones produced by other endocrine glands.

The *growth hormone* is believed to act directly upon the body cells and not through other endocrine glands. It is a protoplasmic anabolic agent which promotes growth, but not development or maturation. An excess

results in gigantism or acromegaly; deficiency, in dwarfism. The active principle is a protein substance effective only when administered parenterally. Crystalline growth hormone preparations have been isolated which cause linear growth, weight gain and nitrogen retention in rats and dogs. However, these same preparations have proved remarkably ineffective in human beings. This is due to a unique species specificity of growth hormone; whereas growth hormone prepared from the beef pituitary fails to induce growth or nitrogen retention in man and monkeys, growth hormone prepared from monkey and human pituitaries is effective in man. Only small amounts of human and monkey growth hormones are available for investigative purposes. There are at present no satisfactory methods for assaying circulating growth hormone in children.

The *gonadotropic hormone* can be divided into two fractions. The follicle-stimulating hormone (FSH) is gametokinetic and stimulates growth of the ova in the female and of the germ cells in the male. The interstitial cell-stimulating hormone (ICSH or LH) regulates formation of the corpus luteum in the female and growth of the interstitial tissue of the testes (Leydig cells) in the male. These hormones are of little significance in girls before the age of ten years or in boys before the age of twelve years. At that time gonadotropins begin to appear in the urine and stimulation of the gonads follows.

Urinary gonadotropins are tested biologically, and their values are expressed in mouse or rat units. Various methods are in use. According to one method (Klinefelter and others), the range is 0 to 5 mouse units per day in girls of premenarchal age; 10 to 50 mouse units in mature females; and 100 to 500 mouse units in women after the menopause. Tested by the method of Delfs, normal mature women excrete 10 to 20 rat units in



twenty-four hours. In castrates or in patients with primary hypogonadism the anterior lobe undergoes definite cellular changes accompanied by an overproduction of gonadotropic hormone. The urinary gonadotropins are usually increased in such patients. An excess of estrogens or androgens inhibits the secretion of pituitary gonadotropic hormones.

The *thyrotropic hormone* stimulates the thyroid; an excess may result in hypertrophy and hyperplasia, whereas a deficiency results in inactivity and atrophy of the thyroid gland. A reciprocal relationship exists between the anterior pituitary and the thyroid. Thyroid hormone inhibits production of pituitary thyrotropin, and a low level of circulating thyroid hormone results in accelerated production of thyrotropin. Pituitary thyrotropin is a valuable agent in research and is useful in clinical medicine to differentiate pituitary hypothyroidism from primary thyroid deficiency.

*Adrenocorticotrophic hormone* (ACTH, corticotropin) is the hormone which stimulates the synthesis and release of steroids from the adrenal cortex. It is postulated that the release of corticotropin by the anterior pituitary gland is subject to hypothalamic control. The major hormones liberated by the human adrenal cortex when stimulated by corticotropin are hydrocortisone and corticosterone. There is evidence that androgens, estrogens and progesterone, or precursors of these compounds, are also liberated.

All the actions of corticotropin are mediated by adrenocortical steroids. In the absence of the adrenal cortex no effects are produced by corticotropin. A reciprocal relationship exists between corticotropin and production of adrenocortical hormones. Therefore when an exogenous hormone, such as cortisone, is administered, there is a reduction in corticotropin production. If this administration is prolonged and then suddenly stopped, adrenocortical insufficiency is induced as a result of the pituitary inhibition. The increased corticoid secretion induced by exogenous corticotropin also depresses corticotropin output by the pituitary in a manner similar to that of exogenous cortisone. Therefore adrenocortical insufficiency follows sudden withdrawal of corticotropin therapy. The severity of the adrenal insufficiency depends upon the duration of therapy, the dose used and the rapidity of withdrawal. This adrenal insufficiency is temporary and can be prevented by slowly tapering the dosage and increasing the interval between doses of either corticotropin or cortisone.

**NEOPLASMS.** Tumors of the anterior pituitary may arise from hyperplasia of any of the three principal types of cells. *Chromophobe adenomas* rarely occur in children. They cause symptoms by pressure on adjacent structures, but not by overproduction of a hormone. They may cause pituitary insufficiency by compression of functioning pituitary tissue. An *eosinophilic pituitary adenoma* results in *gigantism* if it occurs before closure of the epiphyses and in *acromegaly* after epiphysial growth of the bones has ceased. These tumors, rare in children, are thought to produce abnormal growth by overproduction of growth hormone. *Basophilic adenomas* may be found in patients with or without *Cushing's syndrome* and are no longer believed to be the cause of this disorder. They do not result in enlargement of the sella, nor do they cause neurologic symptoms in children. Pituitary tumors have never been reported as a cause of precocious puberty.

**Posterior lobe.** The posterior lobe of the pituitary is part of a functional unit known as the neurohypophysis, which consists of (1) the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; (2) their axons, which form the pituitary stalk; and (3) the posterior lobe of the pituitary. Extracts of the neurohypophysis exhibit antidiuretic and oxytocic activities. These hormones, produced by a process of neurosecretion in the hypothalamic nuclei, are transported along the axons down the pituitary stalk and stored in the posterior pituitary or secreted directly into the blood.

The chemical structures of the oxytocic and antidiuretic hormones have been determined by du Vigneaud, who in 1953 synthesized oxytocin. The most clear-cut example of neurohypophysial deficiency is diabetes insipidus. The closer the lesion is to the hypothalamic nuclei, the more complete is the deficiency of antidiuretic hormone. More than 85 per cent of the hypothalamic-hypophysial tracts must be severed before clinical diabetes insipidus becomes manifest. Removal of only the posterior lobe of the pituitary rarely results in diabetes insipidus. Diabetes insipidus will not develop in the absence of the anterior pituitary.

## PITUITARY DWARFISM

**Etiology.** *Pituitary dwarfism without demonstrable lesion of the pituitary (Lévil-Lorain type).* It is presumed that this condition is caused by an absence or inadequate

secretion of growth hormone. Since many of these patients also have delayed puberty, inadequate secretion of gonadotropic hormones is also present. The evidence for growth hormone deficiency is inferential, since there is no assay method sufficiently sensitive to demonstrate variations of its serum levels. Thyrotropic and adrenocorticotrophic activity is usually normal as demonstrated by normal thyroid and adrenal function.

Hereditary pituitary dwarfism has been thoroughly studied in the dwarf silver mouse, in which the condition is recessive. The symptoms and the pathogenesis of the disorder in dwarf mice resemble pituitary dwarfism in man in many respects. The pituitary glands show absence of eosinophilic cells, indicating lack of growth hormone production. Administration of anterior pituitary suspension induces growth and gonadal maturation.

**Pituitary dwarfism resulting from organic lesions of the pituitary.** Any lesion destroying the anterior pituitary causes cessation of growth. Destructive lesions are not selective, and evidence of multiple pituitary hormonal deficiencies will be present. At puberty secondary sex characteristics do not always develop. Deficiency of thyrotropic and adrenocorticotrophic hormones may be clinically apparent or be detected only by appropriate tests of thyroid and adrenal function.

The most common lesion responsible for this type of dwarfism in childhood is the craniopharyngioma. The growth failure almost always antedates the neurologic signs and symptoms associated with this tumor. In rare instances tuberculosis, syphilis, xanthomatous lesions (Hand-Schüller-Christian disease), toxoplasmosis or various tumors are the cause of pituitary destruction. These lesions are frequently associated with detectable roentgenographic changes. Enlargement of the sella or deformation or destruction of the clinoid processes usually indicates a tumor. When intrasellar or suprasellar calcifications are seen, the lesion is almost always a craniopharyngioma.

**Clinical Manifestations.** Pituitary dwarfs are usually of normal size and weight at birth. The retardation of growth is noticed within the first few years of life. There may be a regular but slow growth in height with the increments always below those of the coevals, or periods of lack of growth may alternate with short spurts of growth. Delayed closure of the epiphyses permits growth beyond the time when normal persons cease to grow.

The head is round, and the face short and

broad. The frontal bone is prominent and the bridge of the nose depressed and saddle-shaped. The nose is small, and the nasolabial folds are well developed. The eyes are somewhat bulging. The mandible and the chin are underdeveloped and infantile, and the teeth, which erupt late, are frequently crowded. The neck is short and the larynx small. The voice is high-pitched and remains high after the age of puberty. The genitals are usually undeveloped, but dwarfs have been described whose genitals functioned normally. The extremities are well proportioned, the hands and feet being small (acromicria). Aseptic necrosis of bones (Perthes' disease, Kohler's disease, and the like) is not rare. The skin is often wrinkled and lies in folds, particularly in the face (geroderma). Facial, axillary and pubic hair is usually absent; the hair of the scalp is fine. Sexual maturation may be delayed or absent. Hypoglycemic attacks may occur, and there may be failure of the usual glycemic response following insulin-induced hypoglycemia.

The intelligence of pituitary dwarfs is usually normal. Their physical peculiarities influence their emotions and behavior as they grow older, and they may become shy and retiring.

**Roentgenographic examination.** The fontanelles remain open beyond the second year; in the occipital suture wormian bones may be found. The bones of the vault are thin, and osteoporosis may be noticed. The long bones are slender and poor in minerals. The centers of ossification appear late, and the epiphysal clefts remain open.

The sella turcica is often small, a finding to be expected in a dwarf. There is great variation in the size of the sella in normal persons, and the evaluation of a small sella is difficult. A suprasellar osseous bridge cannot be considered pathologic, since it is seen in about 10 per cent of roentgenograms of the skull.

**Primordial dwarfism.** This type of dwarf is small at birth and remains smaller than persons of the same age throughout life. Aside from retardation of growth, the development is entirely normal. Dentition, ossification and sexual maturation occur approximately at the same time as in taller persons of the same age. Such dwarfs can reproduce. It has been assumed that primordial dwarfs lack only pituitary growth hormone. Primordial dwarfism can be hereditary and be transmitted as a recessive trait. In this case the dwarf is homozygous; if two persons of this type mate, all their children will be homo-



zygous dwarfs. This dwarf mutation could thus give rise to a pigmy race.

**Differential Diagnosis.** It is almost impossible to establish the diagnosis of pituitary dwarfism without a demonstrable pituitary lesion in the prepuberal years. Only with the passing of years and the elimination of other causes for dwarfism may one feel secure with such a diagnosis. It is of great importance to rule out the presence of a destructive intracranial lesion. A history of nausea, vomiting, loss of vision, headaches and increase of the circumference of the head suggests increased intracranial pressure. The eyegrounds must be carefully examined, and roentgenograms may be helpful in localization of a tumor.

Obesity suggests involvement of the hypothalamus, but does not prove the presence of a tumor. Associated hypothyroidism and adrenal insufficiency are indicative of a pituitary lesion, but are rarely present without demonstrable lesions of the pituitary.

Both types of pituitary dwarfs show sexual underdevelopment after the time when puberty should have occurred. The gonads remain underdeveloped because there is no stimulation from the pituitary. Dwarfism resulting from the chondrodystrophies, osteogenesis imperfecta, pseudohypoparathyroidism or the various types of rickets can be recognized by features characteristic of each of them. When retardation in growth is due to cardiac, renal, hepatic or intestinal disease, the cause can be identified by the diagnosis of the underlying disorder.

In girls, gonadal dysgenesis must always be considered. When associated with the usual characteristic congenital deformities, the diagnosis is not difficult. About 80 per cent of these patients are genetically male (male sex chromatin pattern), and after puberty they show high levels of gonadotropin secretion. The osseous development of pituitary dwarfs is definitely retarded, whereas girls with gonadal dysgenesis have only a slight delay of epiphysial development.

**Prognosis.** The prognosis for life depends upon the etiologic factor. If dwarfism is caused by absence of growth hormone without a demonstrable anatomic lesion, the affected person may reach old age. A tumor in the pituitary region may endanger the patient's life. If syphilitic, tuberculous or xanthomatous changes result in pituitary dwarfism, the disease process determines the fate of the patient.

Prognosis for growth is difficult, since an increase in height is possible long after the

age of adolescence because of the persistence of open epiphysial clefts. Sexual maturation may also take place ten or twenty years later than in normal persons.

**Treatment.** Treatment of patients with demonstrable organic lesions should be directed to the underlying disease process. In instances of pituitary dwarfism due to craniopharyngioma acceleration of growth may occur after surgical treatment of the tumor.

There are many contradictory reports concerning treatment with injections of crude pituitary extracts. Since spontaneous growth is possible at any age, reports of the effects of treatment are difficult to evaluate. Difficulty in establishing the diagnosis of pituitary dwarfism increases the uncertainty in evaluating published reports.

In contrast to the ineffectiveness of growth hormone prepared from beef and porcine pituitary glands to stimulate growth in the human dwarf, growth hormone prepared from human and monkey pituitary glands is very effective. Monkey and human growth hormone preparations are available only in small quantities for investigative purposes.

The protein anabolic action of testosterone and related compounds has been used to induce growth. These substances result in a strikingly increased rate of growth of the dwarf. However, the ultimate height attained is almost always subnormal. This is ascribed to accelerated osseous maturation and early closure of epiphysial lines precluding further growth. It has been shown that with the use of methyltestosterone osseous age usually advances more rapidly than height age. Testosterone and related androgens should not be used in slowly growing children, but should be limited to selected instances of severely stunted growth.

## PROGERIA

(PREMATURE SENILITY, HUTCHINSON-GILFORD SYNDROME)

Progeria is a type of dwarfism combined with premature senility. Twenty-nine typical cases have been reported since Hutchinson first described the syndrome in 1886, although many atypical ones have been recorded.

These children appear normal at birth, and their birth weight is usually within normal limits. The weight increases adequately during the first year of life, only to remain almost stationary during the remainder of the first decade, and may eventually reach that of a two- or three-year-old child during the

second decade. The height increases slowly and may not exceed that of an average four- or five-year-old child during the first decade before growth stops completely. The appearance is characteristic and has been described as that of premature old age and of a "plucked bird." The head appears large and is prematurely bald, and the eyebrows are usually absent. The eyes appear prominent, and the nose is "beaked"; the face is small in comparison with the skull, and the chin recedes. The chest is narrow, and the abdomen protrudes. The skin is atrophic, and brown pigmentations are common. The outstanding feature is the absence of subcutaneous fat in the face, on the chest and in the extremities. The veins are prominent; the nails show trophic changes, or they may be absent.

There are no characteristic changes in the blood. Amino-aciduria has been reported in one instance. Abnormally high levels of serum lipoprotein have also been reported. Roentgenograms show thinning and some decalcification of the long bones, shortening of the clavicles, coxa valga, a poorly developed mandible with crowding of the teeth and delay in primary dentition. The intelligence is not affected. Arteriosclerosis may occur as early as five years of age. Arthritis with enlargement of the joints and limitation of motion is common in older patients and has been reported in children as young as six years of age. Anginal attacks and hemiplegia have been reported in the first decade, and the most common cause of death is coronary occlusion. The average age at death is sixteen years.

The *etiology* is obscure. Metabolic studies on one patient by Talbot showed an excessive utilization of calories for energy metabolism. This hypermetabolism was not due to hyperthyroidism.

No treatment has proved effective.

## SIMMONDS' DISEASE

### (PANHYPOPITUITARISM)

Simmonds' disease, or severe pituitary insufficiency, is extremely rare in children. Pathologically, the essential finding is a complete or almost complete destruction of the pituitary gland. The etiology of the destructive lesion may be extremely varied and include tuberculosis, nonspecific granulomas, cysts and tumors; in children, tumors, especially craniopharyngiomas, are the most common finding.

Atrophy of the adrenal cortex, thyroid and gonads and cessation of growth resulting from

the pituitary lesion account for the variety of signs and symptoms. The chief clinical features are failure of growth, loss of weight, asthenia, hypothermia, hypotension, increased sensitivity to cold, mental torpor and absence of sweating. Sexual maturation fails to take place or regresses if already present. Thus there may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia and coma. Laboratory studies show a low protein-bound iodine level and diminished radio-iodine uptake, low levels of serum and urinary corticosteroids, hypoglycemia and anemia. There is an increase in serum level of corticosteroid following administration of corticotropin, and of protein-bound iodine and of radio-iodine uptake after injection of thyrotropin.

If the lesion is an expanding tumor, symptoms such as impaired vision, ocular disturbances, pathologic sleep, mental retardation and other neurologic signs may be present. Changes in or around the sella may be present.

In the differential diagnosis cachexia resulting from tuberculosis, malignancy, hyperthyroidism, malnutrition and anorexia nervosa should be considered. *Addison's disease* may present a clinical picture resembling that of Simmonds' disease, but pigmentation is slight or absent in Simmonds' disease. In *progeria* there is no evidence of reduced pituitary function.

*Treatment* should be directed against the primary disorder. If a tumor is present, surgical treatment must be considered. The secondary deficiencies of the adrenal and thyroid glands can be relieved by substitution therapy. The adrenocortical insufficiency should be treated before thyroid therapy is started, and in all cases the initial dose of thyroid should be small to prevent changing a relative hypoadrenalism into an absolute one.

## PITUITARY GIGANTISM AND

### ACROMEGALY

Certain forms of gigantism and acromegaly are associated with hyperplasia or tumors of the eosinophilic cells of the anterior pituitary gland. It is assumed that hyperfunction of the eosinophilic cells of the adenohypophysis results in increased production of growth hormone. In young persons with open epiphyseal clefts overproduction of growth hormone results in gigantism, while in patients with closed epiphyses acromegaly develops.



**Pituitary gigantism** is rare, since eosinophilic adenomas seldom occur in childhood. In most of the cases recorded the abnormal growth started at the time of puberty, and the abnormal height was attained within the next few years. Such giants may grow to a height of 8 feet and more. After closure of the epiphyses acromegaly may be superimposed upon gigantism. The *prognosis* for life is poor, since the adenoma may cause increased intracranial pressure or may undergo cystic degeneration followed by signs of pituitary deficiency.

In the *differential diagnosis* hereditary tall stature must be considered. In this condition there is usually abnormal height in one or both parents or in close relatives. Such tall persons are well proportioned and free of signs of increased intracranial pressure. The abnormal growth seen in the period of preadolescence in obese children represents a temporary state; though such children may become tall, they do not attain the height of giants. Children with precocious puberty are often unusually tall, but do not develop into giants, since their epiphyses close early and growth ceases prematurely.

**Acromegaly** is rare in children, but transitory acromegalic features are sometimes observed in adolescents. Acromegaly consists chiefly in an enlargement of the distal parts of the body, but the manifestations of abnormal growth actually involve all parts of the body. The circumference of the skull increases, the nose becomes broad, and the tongue is often so enlarged that it protrudes between the thick lips. The mandible grows, and the teeth separate. The fingers and toes grow chiefly in thickness. There is frequently a dorsal kyphosis. The skin and the mucous membranes are thickened, and the voice becomes deep. There may be enlargement of the internal organs, but the testes or ovaries become atrophic as the disease progresses. The basal metabolic rate is high in the early stage of the disease, but decreases later. Polydipsia, polyuria and glycosuria are not rare, and the glucose tolerance curve may be of the diabetic type. Fatigue and lassitude are early symptoms; signs of increased intracranial pressure appear late. Roentgenograms reveal enlargement of the sella turcica. An elevated serum phosphorus may be present.

The course is usually protracted; in rare cases pituitary insufficiency develops early.

*Treatment* depends upon the symptoms. If signs of increased intracranial pressure are

present, surgical intervention is indicated. In some cases acromegaly and headaches are improved by roentgen treatment of the pituitary gland. Large doses of estrogen have been effective in decreasing the rate of growth, perhaps by inhibiting production of growth hormone. There is no satisfactory treatment for hereditary tall stature and gigantism.

## DIABETES INSIPIDUS

Diabetes insipidus is the result of pathologic changes involving any part of the close functional unit made up of the posterior lobe of the pituitary, the supraoptic and paraventricular nuclei of the hypothalamus and the hypothalamico-hypophysial fibers. Such changes result in deficiency of the antidiuretic hormone, which acts directly on the distal tubules and collecting ducts to facilitate reabsorption of water. This disorder is, therefore, characterized by inability of the kidney to produce a concentrated urine. When antidiuretic hormone is administered, there is a remarkable decrease in the amount of urine excreted and an increase in its specific gravity. Physiologic doses of Pitressin do not influence renal solute output either quantitatively or qualitatively.

**Etiology.** Diabetes insipidus may occur as a hereditary disorder; transmission is usually as a simple dominant character or as a dominant with incomplete penetrance in the female. The largest family studied showed thirty-five affected individuals in a family of 220 members in five generations. The histopathologic changes in the hereditary form are not known.

Any lesion damaging the neurohypophysis or hypothalamus may result in diabetes insipidus. In the case of a tumor, symptoms of increased intracranial pressure may accompany, or they may follow years later, the symptoms of diabetes insipidus. Injuries of the head, such as basal skull fractures, may lead to diabetes insipidus immediately, or symptoms may appear after several months. In xanthomatosis (Hand-Schüller-Christian syndrome) the disturbance of water metabolism may be accompanied by exophthalmos and defective areas in the skull. Encephalitis, tuberculosis, leukemia, actinomycosis and congenital syphilis may occasionally cause diabetes insipidus.

In many instances no specific etiology can be determined. The search for a lesion should be continued indefinitely, since diabetes in-

insipidus may be the first recognizable sign of an intracranial tumor and antedate neurologic signs by years.

**Clinical Manifestations.** Polydipsia and polyuria are the outstanding symptoms of diabetes insipidus. In families with the hereditary disorder the polyuria is noted in early infancy. The infant cries excessively and will be dissatisfied when additional milk is offered, but is quieted by water. Hyperthermia, rapid loss of weight and collapse are common in infancy. Vomiting, constipation and growth failure may be observed. Dehydration in early infancy may result in brain damage and mental deficiency.

In a child who has acquired bladder control, enuresis may be the first symptom. The excessive thirst is a disturbing symptom and interferes with play, learning and sleep. Children with diabetes insipidus do not perspire, and their skin is dry and pale. Anorexia is a common symptom; there is a preference for carbohydrates.

The urine is pale or colorless, and the specific gravity varies from 1.001 to 1.005 and does not exceed 1.007 except during febrile episodes; the urine is hypotonic to the blood. Four to 10 liters of urine and more may be eliminated daily. Glomerular filtration and tubular excretory rates are within normal limits.

Other signs and symptoms depend on the primary lesion; thus patients with xanthomatosis may show areas of rarefaction in roentgenograms of the skull or other bones. Lesions initially causing diabetes insipidus may progress and eventually destroy the anterior pituitary. In such instances the symptoms of diabetes insipidus tend to ameliorate or disappear completely.

**Differential Diagnosis.** Primary polydipsia, a symptom occurring in psychopathic patients, can be recognized by a concentration test, since such persons are able to produce a concentrated urine. In chronic nephritis the nonprotein nitrogenous constituents of the blood and the renal function tests are abnormal. Nephrogenic diabetes insipidus can be recognized by the failure of response to Pitressin. After the diagnosis of diabetes insipidus has been established the underlying process must be determined.

**Prognosis.** The prognosis depends upon the underlying condition. It is favorable in the hereditary type and less so in cases resulting from syphilis and encephalitis. If the disorder follows trauma, spontaneous cure may occur. The prognosis of patients with a brain tumor

or xanthomatosis depends upon the site of the lesions, and with neoplasms upon the type of cell.

**Treatment.** The etiologic factor deserves first consideration in the treatment. Tumors will require surgical intervention in the majority of instances. Specific treatment is indicated in syphilis. Roentgen ray treatment is recommended in the management of the Hand-Schüller-Christian syndrome.

If the underlying condition is unknown or not amenable to therapy, symptomatic treatment with Pitressin is useful. Aqueous Pitressin is given in doses of 1 to 3 cc. per day, usually divided into two or three injections. Polyuria and polydipsia are diminished in the majority of instances, and the patient is relieved of these disturbing symptoms. This treatment is sometimes complicated by intestinal cramps, nausea, colic or pallor, which appears within fifteen to thirty minutes after injection. Pitressin tannate in oil, 0.2 to 1 cc., administered intramuscularly every one to three days as determined for the individual patient is the treatment of choice. Pitressin may also be administered intranasally, thus avoiding repeated injections. Cotton pledgets moistened with the aqueous solution may be placed in the nostrils and allowed to remain for three to five minutes, two or three times a day; or the dry powder can be placed in the nose with the finger. This therapy may cause nasal irritation, and occasionally allergy has developed in both children and their mothers.

#### PITRESSIN-RESISTANT DIABETES INSIPIDUS

(NEPHROGENIC DIABETES INSIPIDUS, "WATER-BABIES")

This is a renal tubular disorder occurring nearly always in boys and probably transmitted as a sex-linked recessive character. These patients have a normal production of antidiuretic hormone but a failure of end-organ response in the renal tubule.

The onset is shortly after birth, the symptoms being those of diabetes insipidus. In addition to polyuria and polydipsia, unexplained fever, vomiting, constipation and failure to thrive are common. Fluid restriction or elevated environmental temperature may result in rapid loss of weight and peripheral collapse. Growth is retarded, and mental development may be impaired.

Hyperelectrolytemia and azotemia are almost constant findings in early infancy, but tend to subside later in life. The urine has a



low specific gravity, which may rise to about 1.010 during severe dehydration. Administration of hypertonic saline solution or Pitressin fails to induce antidiuresis and has no effect on the volume or specific gravity of urine.

Treatment consists in administration of water at frequent intervals in amounts sufficient to prevent dehydration and fever. Hyper-electrolytemia is thought to be an important factor in causing mental retardation. It may be almost impossible to maintain normal serum electrolyte levels without giving a low protein diet, which is justifiable in early life, even if growth is retarded. When sufficient water is taken, the protein in the diet may be increased to usual levels.

PRECOCIOUS PUBERTY

Although the average age of children at the onset of puberty in the United States is eleven to twelve years in girls and twelve to thirteen years in boys, there are wide ranges of individual variation. Puberty may be delayed to eighteen to twenty years of age or may take place much earlier than usual. The following physical changes are recognized as evidence of abnormally early sexual development: (1) breast enlargement before eight years of age; (2) menarche before ten years; (3) pubic or axillary hair before nine years, especially if dark and coarse; (4) enlargement of the clitoris or penis disproportionate to the age of the child; and (5) other associated phenomena at a disproportionate age such as facial hair, acne, change in voice, pigmented areolas of the nipples and pigmentation of the sexual organs.

The normal physiologic mechanism which initiates the onset of puberty is not known. At puberty there is a release of gonadotropic hormones from the anterior pituitary which stimulate the Leydig cells of the testes to secrete testosterone and the follicles of the ovary to secrete estradiol. At the same time androgen production by the adrenal cortex increases. This latter event has been called the 'adrenarche' by Albright. The steroid hormones released then act on the various end organs to produce the secondary sex characteristics. There is evidence that this series of events is initiated by the hypothalamus, which sends neurohumeral stimuli to the anterior pituitary.

Precocious puberal development may be divided into true precocious puberty and precocious pseudopuberty. True precocious puberty is always isosexual and indicates not

Table 114. Conditions Causing Precocious Puberty\*

True Precocious Puberty	
No anatomic lesion (constitutional)	
Cerebral.....	Brain tumor Encephalitis Hydrocephalus
Cerebral (?).....	Associated with polyostotic fibrous dysplasia (McCune-Albright's syndrome)
Precocious Pseudopuberty	
Girls	
Heterosexual (male).....	Adrenocortical hyperplasia Adrenocortical tumor Adrenal rest tumor in ovary
Isosexual (female).....	Ovarian granulosa cell tumor
Boys	
Heterosexual (female).....	Feminizing adrenocortical tumor
Isosexual (male).....	Adrenocortical hyperplasia Adrenocortical tumor Leydig cell tumor Teratoma

\* Adapted from Paschkis: M. Clin. North America, Vol. 36.

only precocity of the secondary sexual characteristics, but also an increase in the size of the gonads with production of mature sperm or ova. In precocious pseudopuberty only the secondary sex characteristics appear; the gonads do not mature, and there is no spermatogenesis or ovulation. In pseudopuberty the precociously appearing sex characteristics may be isosexual or heterosexual. This latter group will be discussed in the chapters on the Adrenogenital Syndrome (p. 1186) and on the Primary Lesions of the Ovary (p. 1201) and of the Testis (p. 1197).

TRUE PRECOCIOUS PUBERTY

PRECOCIOUS PUBERTY WITHOUT OTHER PATHOLOGIC FINDINGS (CONSTITUTIONAL)

No etiologic factor can be found and the early onset of puberty is considered a physiologic process which begins at an unusually early age. It is estimated that 90 per cent of the cases of true sexual precocity are of this type and occur much more commonly in girls than in boys.

In girls there is precocious development of the breasts and of the external and internal genitals, premature appearance of axillary and pubic hair and precocious menstruation. These changes are usually associated with a moderate advancement of physical growth,



FIG. 335. Constitutional precocious puberty. Patient at (A) 3-11/12 and (B) at 5-8/12 years of age. Breast development and vaginal bleeding began at 2½ years of age. Osseous age was 7½ years at 3-11/12 and 13 years at 6-11/12 years of age. Repeated estrogen assays have varied between 12 and 132 mouse units. Gonadotropic hormone has never been demonstrated in the urine. 17-Ketosteroids have varied between 1.6 and 2.1 mg. per 24 hours. Intelligence and dental age are normal for chronologic age.

height, weight and ossification. The increased rate of skeletal growth in both boys and girls may result in earlier than usual closure of the epiphyses, so that ultimate stature may be somewhat less than it would have been otherwise. Dental age and mental development, however, are usually compatible with chronologic age. Menarche has been observed as early as seven months of age, but usually occurs after four or five years. Corpora lutea are present. The early cycles are frequently anovulatory, and, as in normal puberty, menstruation may not have a normal rhythm in the beginning. Pregnancy has been reported in this type of precocity as early as five and one-half years of age.

In boys secondary sex characteristics as well as spermatogenesis have been observed at the age of five or six years. Testicular biopsies in such cases have shown all elements

of the testes to be stimulated. If the precocity is complete, various degrees of spermatogenesis are present, but, even if incomplete, the interstitial cells make their appearance. In pseudoprecocity the interstitial cells do not develop, and spermatogenesis does not occur. Constitutional precocious somatic and sexual development in males occasionally occurs as a familial trait transmitted by a dominant gene.

The urinary excretion of gonadotropic hormones, estrogens and 17-ketosteroids may correspond to that of normal mature women or men. Gonadotropins are frequently not demonstrable in the urine of children with true precocious puberty, although pituitary release must unquestionably occur. Cornification of the vaginal epithelium can be demonstrated on stained vaginal smears.

In the *differential diagnosis* lesions of the



central nervous system, the adrenogenital syndrome, granulosa cell tumors of the ovaries, Leydig cell tumors and medicational pseudo-precocity must be considered. A carefully obtained history and physical examination in addition to appropriate laboratory studies are indicated, and a pelvic examination under anesthesia may be necessary to determine whether there is an ovarian tumor.

*Treatment* consists essentially in psychologic management of the patient and family. A detailed explanation to the parents with reassurance of the harmlessness of the condition is imperative. They should also be told that the precocious manifestations will persist, but that by the age of ten to fourteen years the child will not be different from other children. Such children should also be guarded against abuses that could result in pregnancy. The few data available indicate that these patients have a normal reproductive span and that menopause takes place within the usual time.

#### PRECOCIOUS PUBERTY WITH POLYOSTOTIC FIBROUS DYSPLASIA AND ABNORMAL PIGMENTATION

See also page 1246.

When these bony lesions are associated with patchy cutaneous pigmentation and endocrine dysfunction, the clinical combination is frequently referred to as *McCune-Albright's syndrome*. The most common endocrine disturbance is sexual precocity, which occurs principally in the female. The pathogenesis is not known, but the disease is thought to be the result of a congenital disorder of development involving the skeleton, the skin and the hypothalamus.

Vaginal bleeding has been reported as early as four months of age and secondary sex characteristics at six months, but the average age at menarche is three years. Advanced ossification is a frequent finding and is common to both sexes. Thyroid enlargement with or without hyperthyroidism, gynecomastia and acromegalic features have occasionally been observed.

The symptoms of precocity, the demonstrable hormonal deviations and the treatment are the same as those described for constitutional precocious puberty. Serum calcium and phosphorus levels are normal. Alkaline phosphatase is normal or increased. Prognosis is favorable for longevity, but deformities may result from the bony lesions and repeated pathologic fractures. The disease becomes stationary in adult life.

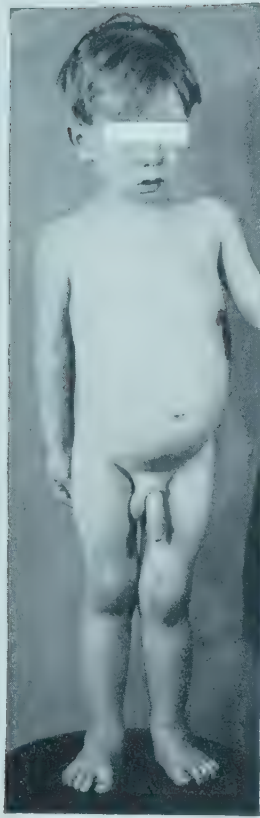


FIG. 336. Precocious puberty associated with polyostotic fibrous dysplasia (McCune-Albright syndrome) in a girl 6 years of age; at this time she weighed 46 pounds and was 43 inches in height. Note the areas of dermal pigmentation. Roentgenograms revealed osseous lesions in the femurs and pelvic bones and questionable ones in the vertebrae. Menarche was at 3½ years of age. (Courtesy of Dr. Ralph V. Platou.)

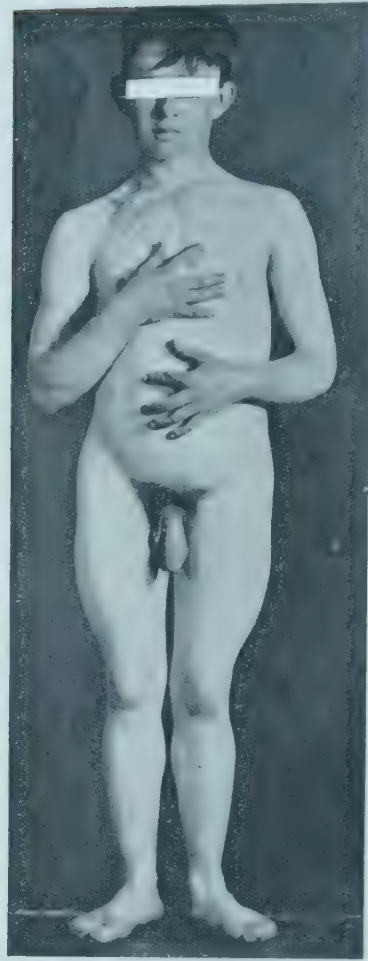
#### PRECOCIOUS PUBERTY RESULTING FROM ORGANIC BRAIN LESIONS

A wide variety of lesions of the central nervous system may be associated with precocious puberty. These lesions have in common involvement of the hypothalamus by invasion, direct contiguity or pressure mediated by occlusion of the ventricular system with dilatation of the third ventricle. Thus tumors, hamartomas, postencephalitic scars, tuberculous meningoencephalitis and hydrocephalus have been associated with precocity.

Tumors of the pineal body are a rare cause of precocious puberty. These lesions, as in all instances of sexual precocity secondary to lesions of the central nervous system, are more frequent in boys than in girls. The reason for this is unknown. It is generally agreed that precocity associated with a pineal tumor is due either to involvement of the posterior hypothalamus or to pressure exerted on the aqueduct of Sylvius and posterior hypothalamus. The pineal body has no known endocrine function. Because some of the non-endocrine symptoms associated with pineal tumors are rather characteristic, they have



A



B

FIG. 337. Precocious puberty in a boy which was induced by a lesion of the floor of the third ventricle involving the suprasellar region. Age at the time of picture A was  $2\frac{1}{2}$  years. Weight and measurements were those of a child 4 years of age. Anterior fontanel did not close until 27 months of age. Began to have polyuria and polydipsia at one year of age. Penis began to enlarge at the age of about 2 years. Had a deep voice. Eyegrounds were normal. Roentgenogram of the skull showed intracranial calcifications. At 9 years of age had no failure of vision; was mentally backward; was overweight and overheight for age; had pubic and axillary hair. At 11 years of age (B) growth had ceased for about 2 years; secondary sexual characteristics were overdeveloped, but apparently there was no libido. Epiphysial closure was advanced, the calcified masses were still visible on the roentgenogram, eyegrounds were normal, polyuria and polydipsia were present, but not marked, and there was mental retardation. (Courtesy of Dr. Stewart Matthews, Wyoming, Ohio.)

been referred to as the pineal syndrome (*Pellizzi's syndrome*).

Central nervous system lesions always cause isosexual true precocity. It is believed that these lesions produce their effect through the intact anterior pituitary gland. The lesions either stimulate the anterior lobe or interfere with a mechanism which normally inhibits gonadotropic release in children before puberty. Pituitary tumors have never been shown to cause precocious sexual development.

The endocrine pattern of hypothalamic lesions is identical with that observed in true precocious puberty without demonstrable organic lesions. Precocious puberty of this type

may precede by several years the onset of signs of increased intracranial pressure. Thus a child who is considered initially to have precocious puberty without a lesion may eventually be found to have a hypothalamic tumor. Some of these lesions, such as the hamartomas, may grow slowly and cause few signs of increased intracranial pressure. Other hypothalamic signs or symptoms such as diabetes insipidus, hyperthermia, obesity, unnatural crying or laughing may suggest the diagnosis. A history of convulsions, retarded mental development or other neurologic signs should also make one suspect a lesion of the central nervous system.

Roentgenographic examination of the skull



and electroencephalographic studies, although rarely of value, are essential parts of the examination, and on occasion pneumoencephalography or ventriculography is indicated.

*Treatment* depends on the lesion. Surgical decompression followed by roentgen therapy is usually indicated when removal of a tumor is not possible.

#### INCOMPLETE (PARTIAL) PRECOCIOUS DEVELOPMENT

Individual manifestations of puberty without the complete picture of precocious development are occasionally encountered; development of the breasts and growth of sexual hair are the two most common ones.

#### SIMPLE HYPERTROPHY OF THE BREASTS

Precocious enlargement of the breasts may occur without any other secondary sex change. Enlargement of the breasts may represent the first sign of true or pseudoprecocious puberty or may merely represent a harmless abnormality. Thorough diagnostic study and a prolonged period of observation are indicated in all instances. Occasionally the hypertrophy of the breasts disappears spontaneously. It has been suggested that the mammary gland may be unusually sensitive to small amounts of estrogens secreted by the ovaries, whereas



FIG. 338. Simple hypertrophy of the breasts in 3-month-old girl. No demonstrable urinary estrogens or gonadotropin. Normal growth and genitals. Note the disparity in size of the two breasts. This is common finding in this condition as well as in normal puberty.

other structures, being normally responsive, do not react until greater amounts are produced at puberty. The usual tests for urinary estrogens are not sensitive enough to detect their presence. There is no cornification of the vaginal epithelium, and gonadotropins and 17-ketosteroids are normally present in the urine only in small amounts.

#### PREMATURE DEVELOPMENT OF SEXUAL HAIR

The appearance of sexual hair at an early age without any other evidence of maturation has been termed "premature pubarche" and is considered a harmless variation of precocious adolescence. It is much more frequent in girls than in boys. Hair appears first on the labia majora, later in the pubic region and finally in the axilla. Most of these children are taller than average, and the bone age is generally one to four years in advance of the chronological age. There is no evidence of true virilization. In our experience this disorder has been most common in mentally defective girls. Wilkins suggests that this variation in pattern of sexual development may be due either to an increased sensitivity of sexual hair follicles to normal levels of androgens present during the preadolescent period or to premature increase in secretion of adrenal androgens before the pituitary gonadotropic mechanism becomes activated. The 17-ketosteroids are not increased beyond values normal for the age. This condition must be differentiated from early true precocious puberty, adrenal cortical tumors and adrenal hyperplasia. Parents need to be assured that this condition is a harmless variation of development.

#### MEDICATIONAL PRECOCITY

Although this is a type of pseudopuberty, it is included here to emphasize the fact that a variety of medicaments can induce the appearance of secondary sexual characteristics which may be confused with true precocious puberty. A careful history to exclude accidental exposure to or ingestion of sex hormones is of paramount importance. Precocious pseudopuberty in girls accidentally ingesting stilbestrol has been reported. Exogenous estrogens may induce an intense, dark brown color to the areola of the breasts which is not usually seen in endogenous types of precocity. The precocious changes disappear after cessation of administration of the exogenous hormones.

**Table 115. Comparison of Fröhlich's Syndrome, Obesity of Adolescence and Laurence-Moon-Biedl Syndrome**

	<i>Fröhlich's Syndrome</i>	<i>Obesity of Adolescence</i>	<i>Laurence-Moon-Biedl Syndrome</i>
Onset of symptoms.....	Any age	About 8 years	Birth
Obesity.....	Moderate	Moderate to excessive	Marked
Genital development.....	Delayed	Boys: slow Girls: normal	Delayed
Development of secondary sex characters.....	Delayed	Boys: slow Girls: normal	Delayed
Skin.....	Dry, scaly	Moist; perspiration increased	Moist
Skeleton.....	Slender	Heavy	Heavy; polydactylism
Headaches; vomiting.....	Present	Absent	Absent
Eye grounds.....	Choked disk or optic atrophy often present	Normal	Retinitis pigmentosa; optic atrophy
Mentality.....	Usually normal	Usually normal	Retarded
Family history.....	Usually negative	Often familial	Often familial

### ADIPOSOGENITAL DYSTROPHY INDUCED BY LESIONS OF THE HYPOTHALAMUS AND OF THE PITUITARY GLAND

#### FRÖHLICH'S SYNDROME

Lesions of the hypothalamus caused by craniopharyngiomas, tumors of the pituitary or other structures adjacent to the hypothalamus, trauma or encephalitis can cause a syndrome of obesity and sexual infantilism. Some of the patients also have diabetes insipidus and retardation of growth. Since obesity may occur in pituitary dwarfs, transitional forms are encountered in which the differential diagnosis between Fröhlich's syndrome and pituitary dwarfism becomes uncertain. It is assumed at present that lesions of this type cause obesity by infringing upon hypothalamic areas, while retardation of sexual development is explained by interference with function of the anterior pituitary. The patient originally described by Fröhlich had a cyst in the region of the pituitary gland which caused headaches, vomiting, loss of vision, destruction of the dorsum sellae, obesity of the trunk, abdomen and genital region, and retardation of sexual development. It is useful to limit the term "Fröhlich's syndrome" to cases which show this group of symptoms.

**Clinical Manifestations.** The obesity is usually moderate in children and affects chiefly the regions of the breast, lower abdomen and genitals. In males the penis may be imbedded in adipose tissue and the testes undescended and small. The face remains beardless and the voice high-pitched after the age of adolescence. These symptoms as well as the fat distribution give such boys a femi-

nine appearance. In females there is accumulation of fat in the mammary region, but the glandular tissue is undeveloped. The external and internal genitals remain undeveloped, and menstruation is delayed or absent. Ossification is delayed in both sexes, and pubic and axillary hair is sparse or absent. The skin is dry and scaly.

It is important to diagnose the presence of a brain tumor (see p. 1084) as early as possible. In differential diagnosis the benign adiposity of adolescence and the Laurence-Moon-Biedl syndrome must be considered. Klinefelter's syndrome (p. 1197), associated with a female sex chromosomal pattern, must also be considered.

**Prognosis and Treatment.** The prognosis is usually unfavorable. Surgical intervention is often indicated if a brain tumor is demonstrated.

ANGELO M. DiGEORGE  
JOSEF WARKANY

#### REFERENCES

##### General

- Paschkis, K. E., Rakoff, A. E., and Cantarow, A.: *Clinical Endocrinology*. 2nd ed. New York, Paul B. Hoeber, Inc., 1958.
- Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D.: *Functional Endocrinology from Birth through Adolescence*. Cambridge, Harvard University Press, 1952.
- Wilkins, L.: *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. 2nd ed. Springfield, Ill., Charles C Thomas, 1957.

##### Pituitary Dwarfism

- Bayley, N., Gordan, G. S., and Lisser, H.: Long Term Experiences with Methyltestosterone as Growth Stimulant in Short Immature Boys. *Pediat. Clin. North America*, 4:819, 1957.



- DiGeorge, A. M., and Paschkis, K. E.: Dwarfism. *Pediat. Clin. North America*, 4:925, 1957.
- Li, C. H., and Papkoff, H.: Preparations and Properties of Growth Hormone from Human and Monkey Pituitary Glands. *Science*, 124:1293, 1956.
- Martin, M. M., and Wilkins, L.: Pituitary Dwarfism: Diagnosis and Treatment. *J. Clin. Endocrinol. & Metab.*, 18:679, 1958.
- Progeria*
- Cooke, J. V.: The Rate of Growth in Progeria, with a Report of Two Cases. *J. Pediat.*, 42:26, 1953.
- Thomson, J., and Forfar, J. O.: Progeria (Hutchinson-Gilford Syndrome). Report of a Case and Review of the Literature. *Arch. Dis. Childhood*, 25:224, 1950.
- Simmonds' Disease*
- Farquharson, R. F.: Simmonds' Disease. Extreme Insufficiency of the Adenohypophysis. Springfield, Ill., Charles C Thomas, 1950.
- Pituitary Gigantism and Acromegaly*
- Behrens, L. H., and Barr, D. D.: Hyperpituitarism Beginning in Infancy. *Endocrinology*, 16:120, 1932.
- Davidoff, L. M.: Studies in Acromegaly. *Endocrinology*, 10:453, 1926.
- Humbert, C. D.: Gigantism. *J.A.M.A.*, 108:544, 1937.
- Talbot, N. B., and Sobel, E. H.: Endocrine and Other Factors Determining the Growth of Children; in *Advances in Pediatrics*. New York, Interscience Publishers, 1947, Vol. 2.
- Todd, R. Mcl.: Acromegaly in a Girl of 3 Years. *Arch. Dis. Childhood*, 33:49, 1958.
- Diabetes Insipidus*
- Gautier, E., and Simpkins, M.: The Management of Nephrogenic Diabetes Insipidus in Early Life. *Acta Paediat.*, 46:354, 1957.
- Pender, C. B., and Fraser, F. C.: Dominant Inheritance of Diabetes Insipidus: A Family Study. *Pediatrics*, 11:246, 1953.
- Thomas, W. C.: Diabetes Insipidus. *J. Clin. Endocrinol. & Metab.*, 17:565, 1957.
- Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children; A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases. *Am. J. Dis. Child.*, 57:603, 1939.
- Precocious Puberty*
- Bauer, H. G.: Endocrine and Other Clinical Manifestations of Hypothalamic Disease; A Survey of 60 Cases with Autopsies. *J. Clin. Endocrinol. & Metab.*, 14:13, 1954.
- Cook, C. D., McArthur, J. W., and Berenberg, W.: Pseudoprecocious Puberty in Girls as a Result of Estrogen Ingestion. *New England J. Med.*, 248:671, 1953.
- Jacobsen, A. W., and Macklin, M. T.: Hereditary Sexual Precocity. Report of a Family with 27 Affected Members. *Pediatrics*, 9:682, 1952.
- Jolly, H.: Sexual Precocity. Springfield, Ill., Charles C Thomas, 1955.
- Jungck, E. C., Brown, N. H., and Carmona, N.: Constitutional Precocious Puberty in the Male. *Am. J. Dis. Child.*, 91:138, 1956.
- List, C. F., Dowman, C. E., Bagchi, B. K., and Bebin, J.: Posterior Hypothalamic Hamartomas and Gangliogliomas Causing Precocious Puberty. *Neurology*, 8:164, 1958.
- Paschkis, K. E.: Precocious Puberty and Pseudopuberty. *M. Clin. North America*, 36:1711, 1952.
- Russell, W. O., and Sachs, E.: Pinealoma. A Clinicopathologic Study of Seven Cases, with a Review of the Literature. *Arch. Path.*, 35:869, 1943.
- Silverman, S. H., Migeon, C., Rosemberg, E., and Wilkins, L.: Precocious Growth of Sexual Hair without Other Secondary Sexual Development; "Premature Pubarche," a Constitutional Variation of Adolescence. *Pediatrics*, 10:426, 1952.
- Sobel, E. H., Sniffen, R. C., and Talbot, N. B.: The Testis. V. Use of Testicular Biopsies in the Differential Diagnosis of Precocious Puberty. *Pediatrics*, 8:701, 1951.
- Vines, R. H.: Polyostotic Fibrous Dysplasia. *Arch. Dis. Childhood*, 27:351, 1952.
- Fröhlich's Syndrome*
- Bruch, H.: The Frölich Syndrome; Report of the Original Case. *Am. J. Dis. Child.*, 58:1282, 1939.
- Fröhlich, A.: Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie. *Wien. klin. Rundschau*, 15:883, 1901.

## DISORDERS OF THE THYROID GLAND

### GENERAL CONSIDERATIONS

The main function of the thyroid gland is to synthesize thyroxin. Iodine is essential for the production of thyroxin, and it has been estimated that the daily requirement of this element is about 40 to 100 micrograms. Regardless of the chemical form upon ingestion, iodine eventually reaches the thyroid gland as iodide. Thyroid tissue has a special avidity for this element and is able to collect, concentrate and store it for subsequent use.

Before the trapped iodide can be utilized it must be oxidized to its elemental form. This reaction probably occurs within the thyroid cells and is catalyzed by an enzyme which is believed by some to be a peroxidase. The thyroid cells also elaborate the thyroid protein, which is a globulin with tyrosine units. The amino acid tyrosine is iodinated to form diiodotyrosine; two molecules of diiodotyrosine unite to form one molecule of thyroxin. The hormone is then stored in the lumen of the follicle in the colloid until ready

to be delivered to the body cells. The thyroglobulin has a molecular weight of about 675,000 and cannot diffuse through the cell wall of the follicle, but must be split into smaller molecules by proteolytic enzymes before it can diffuse into the capillaries.

Triiodothyronine occurs in appreciable quantities in the normal thyroid. It has also been demonstrated in the serum and in other tissues, but its role is not clear. Triiodothyronine is similar in structure to thyroxine, except that it has three rather than four atoms of iodine. This substance is four to five times as active physiologically as thyroxine and has a much shorter latent period. It provides complete replacement in human hypothyroidism. It is not clear whether triiodothyronine is secreted by the thyroid or is formed in peripheral cells by deiodination of thyroxine.

The thyroid gland is under control of the anterior pituitary, which is, at least in part, under the control of the hypothalamus. In the anterior pituitary the basophilic cells produce the thyroid-stimulating hormone, also known as thyrotropin, or TSH. This hormone stimulates the proteolytic enzymes in the thyroid gland and effects release of the thyroid hormone. An excess of TSH results in hypertrophy and hyperplasia of the thyroid cells, increased collection of iodine and increased synthesis of thyroid hormone. Anterior pituitary production of thyrotropin is inhibited by the thyroid hormone secreted, and thyrotropin production is activated in states of decreased thyroid hormone production. Exogenous thyroid likewise inhibits TSH production, resulting in decreased synthesis of endogenous thyroid hormone.

In the circulation thyroxine becomes bound to a specific fraction of the serum protein. This iodine is known as the protein-bound iodine (PBI); it furnishes an accurate index of the circulating thyroid hormone. The serum level of PBI for euthyroid children or adults is 4 to 8 gammas (micrograms) per 100 ml. At birth the PBI in the infant approximates that of the mother's, with a mean value of 8.3 gammas per 100 ml. This value increases further during the first week of life to reach a mean value of 12 gammas. Then it gradually decreases, but does not reach a mean value as low as that of older children until about one year of age. In hypothyroidism the value is usually considerably below 3 gammas per 100 ml., and in hyperthyroidism it is above 8 gammas. Administration of iodides in large doses to euthyroid persons or the use of radiographic contrast media con-

taining iodine, prior to the determination of the PBI, will result in misleading, elevated values.

The iodine-trapping or concentrating mechanism of the thyroid can be used as a test of thyroid function. Radioactive iodine ( $I^{131}$ ), with a half-life of eight days, is given to the patient orally (usually by gavage to infants). The quantity used is based on the patient's weight; doses as small as 5 microcuries have been adequate in small infants. The radioiodine concentrated in the thyroid gland emits gamma rays, which can be measured by placing a "counter" over the patient's thyroid. The estimate of the uptake is usually made twenty-four hours after the radioiodine has been administered. Normal values vary, depending upon the equipment and technique used, but an uptake of less than 10 per cent usually indicates hypothyroidism. Falsely low values may be due to vomiting of the radioiodine, ingestion of large amounts of iodine either as food or medicine, or administration of exogenous thyroid. Some cases of hypothyroidism are associated with normal or elevated uptakes of radioiodine (p. 1167).

The thyroid hormone increases the metabolic processes of the body by direct action on the cells. It increases basal consumption of oxygen and elimination of carbon dioxide and influences water metabolism. The glucose tolerance is decreased and calcium and phosphorus excretion increased by it. It stimulates the circulation and increases the cardiac rate. Large doses of thyroid lead to myasthenia and increased creatinuria.

There is some evidence that in hypothyroidism the conversion of carotene to vitamin A is disturbed. Patients with hypothyroidism tend to have low vitamin A values and high carotene values in the blood plasma.

Congenital athyreosis in the human subject results in stunting of mental, physical and sexual development. The thyroid, however, is not capable of stimulating growth in the absence of growth hormone, although large doses of growth hormone are capable of stimulating some growth in completely thyroidectomized animals.

The synthesis of hormone by the thyroid is disturbed by certain "antithyroid drugs." The thiocyanate ion prevents concentration of iodide in the gland and causes a discharge of stored iodide. Propylthiouracil and related compounds do not interfere with collection of iodide by the gland, but in some way prevent its fixation in organic combination. These substances interfere with formation of thyroid



hormone, which in turn results in increased production of thyrotropic hormone and enlargement of the thyroid. Thus these compounds are termed goitrogens.

### CONGENITAL HYPOTHYROIDISM

(CONGENITAL APLASIA [HYPOPLASIA] OF THE THYROID GLAND, SPORADIC CRE TINISM)

**Etiology.** In the majority of instances sporadic cretins have either complete absence of the thyroid gland or rudiments which are hypoactive and may be found in the tongue or neck. The factors which interfere with normal embryologic development of the thyroid are not known. In rare instances several members of a family may be born without thyroid glands (*familial cretinism*); such instances must not be mistaken for endemic cretinism. Sporadic cretinism has occurred in one of monozygotic twins at least six times. It therefore appears that unknown intrauterine factors may play a role in its etiology.

Occasionally children living in regions where iodine is abundant and hence in which endemic cretinism is not present, have evidences of hypothyroidism with normally sized or enlarged thyroid glands. They have been found capable of accumulating iodine normally, but are unable to secrete adequate

amounts of hormone. The gland may eventually become goitrous as a result of stimulation with excessive thyrotropin secreted in response to the low level of circulating thyroid hormone. This type of hypothyroidism may occur in more than one sibling, and can be subdivided, depending upon the kind of defect in the synthesis of the hormone. Four different defects have been demonstrated, including those in which some of the glands appear unable to combine iodine with tyrosine and those in which the gland primarily produces iodinated amino acids other than thyroxine which are relatively inactive physiologically.

A selective deficiency of thyrotropin, as a cause of hypothyroidism, has been observed in children with acquired hypothyroidism, but not in congenital hypothyroidism.

**Clinical Manifestations.** Sporadic cretinism is seldom recognized at birth, since the congenital symptoms, such as pallor, constipation, and dryness of the skin, are not sufficiently characteristic to permit the diagnosis. Retardation of osseous development can be shown roentgenographically at birth. Cretins may be significantly heavier at birth than normal newborn infants. Unusual prolongation of physiologic icterus may be the earliest sign, and difficulty in feeding is a common early manifestation. These infants cry little,



FIG. 339. Congenitally hypothyroid infant at 6 months of age. Infant fed poorly in neonatal period and was constipated. Had persistent nasal discharge and large tongue. Very lethargic, no social smile and no head control. A, Note puffy face, dull expression, hirsute forehead. Serum cholesterol 172 mg. per 100 ml., alkaline phosphatase 4.8 Bodansky units, negligible uptake of radio-iodine. Osseous development that of newborn. B, Four months after treatment with U.S.P. thyroid. Note decreased puffiness of face, decreased hirsutism of forehead and alert appearance.



FIG. 340. Epiphyseal dysgenesis in 2 patients. A, Dysgenesis of the epiphyses of the knee in a 7-months-old infant with untreated cretinism indicating prenatal hypothyroidism. B, Dysgenesis of the head of the humerus in an 8½ year old child who had been inadequately treated with thyroid.

sleep much, and have poor appetites. The abdomen is large, and an umbilical hernia is usually present. The temperature is subnormal. The retardation of physical and mental development becomes greater during the following months, and by the end of the first year the clinical picture is fully developed. However, the signs and symptoms may be sufficiently characteristic to permit the diagnosis within the first few weeks of life.

The child is stunted in growth, the extremities being short and the head large. The anterior fontanel is widely open, the eyes are far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen. The mouth is kept open, and the thick and broad tongue protrudes from it. Dentition is delayed, and the erupted teeth have a tendency to decay rapidly. The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders. The hands are broad and the fingers short. The skin is dry and scaly, and there is little perspiration. Myxedema manifests itself particularly in the skin of the eyelids, of the back of the hands and of the external genitals. Carotenemia may cause a yellow discoloration of the skin, but the scleras remain white. The scalp is thickened, and the hair is coarse, brittle and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled. The skin is cold to the touch. The pulse is slow.

The increasing discrepancy between the chronologic and bone ages can be demonstrated roentgenographically in untreated cases. The epiphyses often show multiple foci of ossification (epiphyseal dysgenesis). Deformity ("beaking") of the twelfth thoracic or first or second lumbar vertebra is also common. The muscles are usually hypotonic. In rare cases a generalized muscular hypertonia has been observed. Such children may have an athletic appearance due to a pseudohypertrophy of the muscles. There is obstinate constipation which usually does not respond to laxatives. Anemia is often present and is refractory to treatment with hematinics.

The mental development of cretins is usually retarded. They appear lethargic and are late in sitting and standing. The voice is coarse, and they do not learn to talk. The degree of physical and mental retardation increases as they become older. Sexual maturation is delayed or does not take place at all.

The basal metabolic rate is decreased. The cholesterol level of the serum is often, but not always, increased; fluctuations are marked. Values of 250 to 600 mg. per 100 ml. of serum are found in children with hypothyroidism, as compared to a range of 100 to 300 mg. in normal children. There is an increase in the cholesterol level of treated children with hypothyroidism six to eight weeks after treatment has been discontinued. In young infants with hypothyroidism the cholesterol level is frequently not elevated,



so that determinations may be of little help in the early recognition of cretinism.

The serum phosphatase is decreased and the carotene level often increased.

The protein-bound iodine (or butanol-extractable iodine) level of the serum is a reliable measurement of thyroid function (p. 1164). In cretins values under 2 gammas per 100 ml. are usually obtained. Uptake of radioactive iodine by the thyroid gland is also a fairly reliable test of thyroid function (p. 1164).

In *goitrous cretinism* (see Etiology) there are all the manifestations of cretinism with supportive laboratory evidence, except a normal or elevated uptake of radioactive iodine. These patients are not iodine-deficient, nor have they been exposed to known goitrogens. Apparently the thyroid gland is capable of accumulating iodine normally, but is unable to convert it into thyroxine. Most of the patients reported to date have shown intense compensatory hypertrophy of the gland with large goiters. Cretinous infants who show a normal or elevated radioactive iodine uptake and thyroids of normal size presumably are too young to show the goitrous enlargements seen in some of the older children because they have not been stimulated long enough with endogenous TSH. The serum protein-bound iodine level may be low, normal or elevated.

When there is only a partial deficiency of the thyroid hormone, the symptoms may be milder, the syndrome incomplete and the onset delayed.

Other malformations are occasionally found in children with congenital absence of the thyroid. These may be skeletal or may affect other organic systems. Those associated with abnormalities of the brain are of practical importance, since they may cause spastic paraplegia, athetosis, ataxia and convulsions. Whether these symptoms are due to the cretinism is a question, but at any rate they do not respond to its specific treatment.

**Differential Diagnosis.** Since the symptoms appear gradually, the early diagnosis of hypothyroidism may be difficult, but one should think of it in any case of retarded growth or mental development. If diagnosis and treatment are delayed, the infant may suffer much harm. In mild cases roentgenographic evidence of retardation of ossification is an important diagnostic aid. Elevation of the cholesterol and carotene levels of the blood and reduction of the serum phosphatase

support the clinical diagnosis. A low protein-bound iodine and a low radio-iodine uptake are diagnostic.

Since *mongolism* is apparent at birth, it can usually be readily differentiated from sporadic cretinism, whose manifestations develop during the first few months of postnatal life (see Table 112, p. 1134).

*Gargoylism* can be mistaken for cretinism, since the stunted growth, the retarded mental development, the thickness of the skin, the shortness of the extremities and the appearance of the hand form a syndrome which resembles cretinism on superficial examination. Roentgenograms of the bones, enlargement of the spleen or liver, cloudiness of the cornea and an adequate PBI level make the diagnosis of gargoylism.

In *chondrodystrophy* there is shortness of the extremities combined with enlargement of the head and flattening of the bridge of the nose as in cretinism, but there is no other resemblance. *Pituitary dwarfs* show retarded growth, and often the closure of the fontanel and ossification are delayed, but other signs of hypothyroidism are absent.

**Prognosis.** Without treatment cretins frequently die of intercurrent infections in childhood. Those who live become mentally deficient dwarfs. Normal physical, sexual and osseous development is attained with thyroid treatment and may proceed satisfactorily even after a delay in starting treatment. The mental development, however, is often not so satisfactory. Although it is generally stated that the results are better the earlier in life treatment is started, the correlation between mental development and adequacy of therapy is not too good. It has been estimated that about half of infants with hypothyroidism who are treated adequately before six months of age will achieve an intelligence quotient of 90 or more. Some infants with mild hypothyroidism will achieve an equal mental status, even if treatment is delayed a year or two. Children who acquire hypothyroidism after two years of age have a good prognosis for mental development, if treatment is adequate. There is suggestive evidence that impairment of cerebral development in the cretin may begin in some instances in utero.

**Treatment.** Desiccated thyroid in tablet form is given orally to cretins and children with hypothyroidism as substitution therapy. It must be given continuously, but the dose may need to be altered; increased doses may be required for the periods of growth, puberty

and reproduction. It requires some time to saturate the tissues of the body with the hormone, which then has a cumulative effect. Thus an immediate effect of therapy cannot be expected, and the dose should not be judged by the results after a few days of administration. The total daily requirement is given as a single dose. As soon as the diagnosis of cretinism is made an initial dose of 0.015 gm. ( $\frac{1}{4}$  grain) of desiccated thyroid (U.S.P.) should be given daily. If this dose is well tolerated, 0.03 gm. per day may be prescribed one week later. Further increases of the drug should be made at intervals of one or two weeks, and the increment should not exceed 0.015 to 0.03 gm. In the first year of life the dose should be 0.045 to 0.090 gm. ( $\frac{3}{4}$  to 1.5 grains) daily, and in older children daily doses of 0.12 to 0.2 gm. (2 to 3 grains) will usually prove satisfactory. The dose must be adjusted to the demands of the individual child. Determination of the protein-bound iodine (or butanol-extractable iodine) level is the best laboratory procedure to evaluate the adequacy of therapy. One should attempt to maintain levels between 6.0 and 8.0 micrograms per 100 ml.

Sodium-l-thyroxine given orally is also effec-

tive, but has no advantages over desiccated thyroid. Each 0.1 mg. is equivalent to approximately 0.09 gm. ( $1\frac{1}{2}$  grains) of U.S.P. thyroid. Triiodothyronine also appears to afford adequate replacement therapy, but seems to have no advantages over U.S.P. thyroid. Protein-bound iodine levels are of no value in determining adequacy of therapy when this compound is used.

### ACQUIRED HYPOTHYROIDISM

Symptoms of hypothyroidism, which can become manifest at any age, may be due to primary disturbances of the thyroid by infections, particularly the contagious ones, by operative removal of a lingual or a normally situated thyroid or by unknown causes. Thyroid deficiency may also be secondary to deficiency of thyrotropin in generalized or selective pituitary disturbances. A congenitally hypoplastic thyroid gland may furnish amounts of hormone sufficient for the early periods of life, but a deficiency may develop when the demands on the gland are increased by changes within the organism such as rapid growth and/or increased size. This congenital form, which becomes manifest in later life,



FIG. 341. Acquired hypothyroidism in a girl 6 years of age. Treated with a wide variety of hematinics for refractory anemia for 3 years. Almost complete cessation of growth, constipation and sluggishness of years' duration. Height age, 3 years; bone age, 4 years; sallow complexion, and immature facies with poorly developed nasal bridge. A, Serum cholesterol 501 mg. per 100 ml., alkaline phosphatase 1.8 Bodansky units, radio-iodine uptake 7 per cent at 24 hours, PBI 2.8 micrograms per 100 ml. B, After therapy for 18 months. Note nasal development, increased luster and decreased pigmentation of hair and maturation of face. Height age,  $5\frac{1}{2}$  years; bone age, 7 years. Marked improvement in general condition.



may be misinterpreted as acquired hypothyroidism.

The symptoms depend upon the age of the child and the severity of the destruction. The later in life hypothyroidism is acquired, the less will be the impairment of growth and development. However, myxedematous changes of the skin, constipation, sleepiness and a mental decline may develop. Cessation or retardation of growth in a child whose growth has previously been normal should always alert one to the possibility of hypothyroidism. Obese children are frequently, but erroneously, considered to have hypothyroidism. Most obese children are taller than average, have warm moist skin, ruddy complexion, and normal thyroid function (see Fig. 341).

Deficiency of pituitary thyrotropic factor may be suspected when there are signs of deficiency of other anterior pituitary hormones, such as gonadotropins and corticotropin. It is possible to differentiate primary and secondary hypothyroidism by studying the response of the thyroid to parenterally administered thyrotropin. After an initial study to determine the radio-iodine uptake, TSH is administered intramuscularly for several days, and the radio-iodine tracer study is repeated and compared with the original one. In primary thyroid failure there is little or no change, whereas in hypothyroidism associated with panhypopituitarism or due to selective deficiency of thyrotropin there is a significant increase in thyroid uptake of radio-iodine. Although the optimal dose of TSH to be used for this diagnostic test has not been definitely determined, it appears that 5 to 15 mg. given intramuscularly twice daily for three days is effective.

*Treatment* consists in administration of desiccated thyroid. The dose must be adjusted to the demands of the individual child (see p. 1167). The prognosis with adequate replacement therapy is good.

## GOITER

A goiter is an enlargement of the thyroid gland. Persons with enlarged thyroids may have normal function of the gland (*euthyroidism*), thyroid deficiency (*hypothyroidism*) or overproduction of the hormone (*hyperthyroidism*). Goiter may be congenital or acquired, endemic or sporadic.

### ENDEMIC GOITER

#### (IODINE-DEFICIENCY GOITER)

It is generally assumed that simple goiter is essentially a manifestation of iodine defi-

ciency, but other "goitrogenic" factors may also play a role in its etiology. As a rule the function of the thyroid is not disturbed. The thyroid hormone circulating in the blood is adequate, and the serum iodine values are within the normal range.

The hormone used in the metabolism of the tissues is decomposed and the liberated iodine returned to the thyroid; only small amounts of iodine are lost in the secretions and excretions of the body. These small amounts (estimated to be 50 micrograms daily) are ordinarily replaced by the iodine contained in food and water. However, water and food are deficient in iodine in certain areas, such as the northwestern states and the states surrounding the Great Lakes in the United States. The dietary iodine deficiency is even greater in certain mountainous districts in Switzerland, Austria and France, in the Carpathian, Himalayan and Andean mountains, and in many other regions. If food and water are derived entirely from an area in which the soil is poor in iodine, as in isolated communities in the mountains, the entire population may be affected by iodine deficiency, and goiter becomes endemic. Seawater is rich in iodine, and the iodine content of fish and shellfish is also high. Endemic goiter is therefore rare in populations living along the sea. Food derived from the sea is now shipped to distant places inland, and the iodine content of the diet in deficient areas may thereby be improved. In persons who have only a mild deficiency of iodine the enlargement of the thyroid does not become noticeable except when there is an increased demand for the hormone. This is true during the periods of growth and adolescence and in pregnancy. In regions of moderate iodine deficiency, goiter may be observed in school children. It may disappear when maturity is reached and reappear in pregnancy and during the period of lactation. In areas of iodine deficiency many more girls have goiters than do boys.

**Pathogenesis.** The thyroid stores and produces the thyroid hormone. If there is a shortage of one of the essential materials (iodine), the demand can be satisfied by increased efficiency in production and prevention of waste. Iodine liberated in the tissues is returned quickly to the gland, which resynthesizes the hormone at a higher rate than normal. This increased activity is achieved by a compensatory hypertrophy and hyperplasia. The cells become enlarged and change from a flat-cuboidal to a columnar shape. As soon as the

hormone is formed it must be transported to the tissues, and storage of colloid does not occur. The radio-iodine uptake is frequently elevated and may be 70 per cent or more of the administered dose. Usually during childhood the thyroid continues to function even when there is a scarcity of iodine; thus the demand of the tissues for thyroid hormone is satisfied. Decompensation and hypothyroidism as a result of iodine deficiency in children are rare in this country.

**Clinical Manifestations.** In simple goiter the thyroid gland becomes palpable and visible; its surface is smooth and its consistency soft. The enlargement is usually moderate, and pressure symptoms are rare. Bruits may often be heard on auscultation of the gland. Signs of endocrine disturbance usually do not develop, and the basal metabolic rate remains within normal limits.

**Differential Diagnosis.** Simple goiter must be distinguished from toxic goiter. In toxic goiter the increased basal metabolic rate and the symptoms of toxicity establish the diagnosis. In endemic cretinism the goitrous person is mentally retarded, and signs of hypothyroidism are present. Carcinoma and chronic lymphocytic thyroiditis must also be considered in the differential diagnosis.

**Prevention.** Simple goiter is prevented by regular ingestion of small amounts of iodine. In regions where a shortage exists the diet should be supplemented. Iodized salt, which in this country contains 0.01 per cent of potassium iodide, provides one of the best forms of prophylaxis.

**Treatment.** Tablets containing 10 mg. of iodine are given once a week until the enlargement of the thyroid disappears.

#### ENDEMIC CRETINISM

**Etiology.** Endemic cretinism is rare or nonexistent in the United States. Wherever endemic goiter occurs in mountainous regions, endemic cretinism is frequently found. Although a definite correlation exists between the iodine deficiency in the soil, food and water of these regions and endemic goiter and cretinism, it does not entirely explain the etiology of cretinism. Iodine deficiency is believed to lead to goiter in the mother and, if the deficiency persists during pregnancy, to cretinism in some of her children. It is possible, however, that in addition to iodine deficiency other unknown factors contribute to the causation of cretinism.

The endemic cretin, in contrast to the athyroid sporadic cretin, is usually born with

an enlarged thyroid gland. Such a congenital goiter is poor in colloid; the cells appear large and crowded, and the blood vessels distended and filled with blood. Compression of the trachea may interfere with respiration in early infancy and be a lethal factor. In those children who survive, degenerative processes in the thyroid result in atrophy of the glandular tissue and in hypothyroidism. At such times goiter may be absent.

**Clinical Manifestations.** The symptoms of endemic cretinism are dwarfism, retarded ossification, epiphysal dysgenesis, myxedema, deafness, dental caries, constipation, delay in sexual maturation and mental deficiency.

**Prevention.** Endemic goiter and congenital goiter, as well as endemic cretinism, are disappearing in goitrous areas where iodized salt is used by most of the population.

**Treatment.** Iodine has no effect, since synthesis of thyroid hormone is not possible in the absence of functioning glandular tissue. Substitution therapy is required, and if desiccated thyroid is administered soon after birth, some symptoms of hypothyroidism can be avoided, but mental retardation cannot be prevented by treatment after birth.

#### SPORADIC GOITER

This type of goiter is seen most frequently in puberal girls. It occurs sporadically in areas where the food and water are not deficient in iodine and where goiters are uncommon. One can rarely elicit a history of reduced iodine intake or of ingestion of excessive amounts of known goitrogenic foods such as turnips, rutabagas or cabbage. The etiology is not understood, but it has been suggested that the goiter may be a manifestation of increased demand for thyroid hormone during adolescence, which the glands overcome by hyperplasia in response to increased secretion of thyrotropin.

Recent studies indicate that some instances of sporadic goiter are the result of an intrinsic biochemical defect in the synthesis of the thyroid hormone. When this derangement is slight, compensatory hypertrophy of the thyroid gland is sufficient to maintain the patient in a euthyroid state. Severe defects of thyroid synthesis result in goitrous cretinism (see p. 1167).

Sporadic goiter may also be iatrogenic. Prolonged administration of para-aminosalicylic acid or cobalt and externally applied resorcinol have been reported to cause goiter. In allergic children treated for a long time with Lugol's solution, potassium iodide or syrup of hydriodic acid goiter has occasion-



ally developed. In such instances hypothyroidism eventually develops if the goitrogen is not discontinued.

The goitrous thyroid is diffusely enlarged and soft. The enlargement is usually slight or moderate, but occasionally is marked. No constitutional symptoms are present, and only rarely are there local pressure symptoms. Many patients show an elevated twenty-four-hour radio-iodine accumulation. Other studies of thyroid function are usually within normal limits.

Small goiters require no treatment; the larger ones are treated primarily for cosmetic reasons. The treatment of choice is desiccated thyroid, 60 to 120 mg. a day, which may be continued for a year or longer as needed.

If remission does not occur within three to six months, it is unlikely that continued treatment will be effective. In most instances a permanent remission is obtained.

#### CONGENITAL GOITER

Sporadic congenital goiter is being reported with increasing frequency; at least half the cases are accounted for by the administration of propylthiouracil and/or iodine during pregnancy for the treatment of thyrotoxicosis. Administration of iodides for asthma during pregnancy has also occasionally resulted in

thyroid enlargement of the newborn infant. Although some congenital goiters appear to be the result of a defect in synthesis of thyroid hormone, no etiologic factor has been established in a number of them.

The enlargement of the thyroid at birth may be sufficient to cause severe respiratory distress and interfere with nursing. The head may be maintained in extreme hypertension. Death has been attributed to respiratory embarrassment. When respiratory obstruction is severe, partial thyroidectomy may be helpful; tracheotomy has not been. Administration of thyroid hormone generally hastens the disappearance of goiter.

#### THYROIDITIS

Thyroiditis in children is rare. Specific etiologic agents such as cat-scratch disease, tuberculosis and mumps virus have been reported to cause thyroiditis. In most instances the etiology is not known.

*Suppurative thyroiditis* is usually preceded by a respiratory tract infection or is secondary to trauma. When suppuration occurs, incision and drainage and administration of antibiotics are indicated.

*Chronic lymphocytic thyroiditis (struma lymphomatosa, Hashimoto's struma)* occurs occasionally in childhood. The onset is usually between the sixth and tenth years of life. It occurs almost exclusively in females, usually being manifest as a painless, slowly growing mass in the neck. Physical examination reveals a firm gland, which is lobular and may give the impression of being nodular.

Most patients are euthyroid, but some show clinical and laboratory signs of hypothyroidism. Pathologically, the outstanding feature is diffuse lymphocytic infiltration throughout the thyroid gland with lymph follicle formation and only a slight increase in fibrous tissue.

Recent studies have shown that this type of goiter is associated with elevation of serum gamma globulins, with positive thymol and zinc sulfate turbidity tests and with colloidal gold flocculation. Auto-antibodies against thyroglobulin have been demonstrated in the serum of such patients, and the serum protein changes are thought to result from the auto-immunization. It has been suggested that destruction of the gland results from progressive interaction of the auto-antibody with thyroglobulin in the gland. These aberrations may be of diagnostic value and obviate the need for surgery. In the absence of these diagnostic aids a biopsy is indicated to elim-



FIG. 342. Congenital goiter in 6-weeks-old infant with increasing respiratory distress and cervical mass since birth. Operation revealed large goiter which almost completely encircled the trachea. Note anterior deviation and posterior compression of the trachea. Partial thyroidectomy completely relieved symptoms. No etiology for goiter found. It is apparent why a tracheotomy is not adequate treatment for these infants.

inate the possibility of a malignant neoplasm.

Replacement therapy with thyroid is indicated.

### EXOPHTHALMIC GOITER; HYPERTHYROIDISM

(THYROTOXICOSIS, TOXIC GOITER,  
GRAVES' DISEASE, BASEDOW'S DISEASE)

**Etiology.** Hyperthyroidism and thyrotoxicosis are terms for an anomaly of the thyroid gland which is characterized by excessive liberation of thyroid hormone. As a rule such patients have a goiter, which is usually diffuse, but may be nodular. Exophthalmos may or may not be present.

The etiology is not known. The uptake of iodide by the hyperactive gland is excessively rapid, as is the production of hormone, which is released rapidly into the blood. The iodine and the thyroxin content of the hyperthyroid gland is low.

Hyperthyroidism is uncommon in children. Approximately one per cent of all cases occur under the age of fifteen years, and, of these, 80 per cent occur between the ages of ten and fifteen years. The disease has been observed, however, in infants as young as one year. The incidence is about seven times higher in girls than in boys. Exophthalmic goiter may be found in several members of a family. Infectious diseases or psychic trauma may precipitate the disease. Hyperthyroidism occurs occasionally with polyostotic fibrous dysplasia and sexual precocity (p. 1246).

**Pathologically,** there is hypertrophy, hyperplasia and striking vascularity. The epithelial cells are high and columnar, and the colloid is reduced. In some instances there are also areas of adenomatous tissue which may contain colloid.

**Clinical Manifestations.** The earliest signs in children may be emotional disturbances accompanied by motor hyperactivity. The children become irritable and excitable and cry easily. Their schoolwork suffers, and their restlessness, which resembles that of chorea, causes conflicts. Tremor of the fingers can be noticed if the upper extremity is extended. There may be a voracious appetite combined with loss or no increase in weight. The thyroid is enlarged, visible and palpable, and bruits are usually audible over it. Exophthalmos is noticeable in the majority of cases. *Graefe's sign* (lagging of the upper eyelid as the eye looks downward), *Moebius' sign* (inability of convergence) and *Stellwag's sign* (retraction of the upper eyelid and infrequent blinking) may be present. The skin is smooth

and flushed, and excessive sweating is noticed. Muscular weakness progresses as the disease continues. Tachycardia, palpitation, dyspnea and cardiac enlargement and insufficiency cause discomfort and may endanger the patient's life. The systolic blood pressure and the pulse pressure are increased. Children with hyperthyroidism are usually tall, their osseous development is advanced for their age, but sexual maturation is delayed.

The basal metabolic rate is increased from +20 to +60 per cent. The glucose tolerance is decreased, and there may be glycosuria. Lymphocytosis is found in the blood. The cholesterol tends to be low. The urinary output of creatine is increased and that of creatinine diminished. The protein-bound iodine in the serum is high, most levels being in the range of 10 to 20 gammas per 100 ml. Uptake of radioactive iodine is rapid, the majority of patients having an uptake of over 40 per cent. Diagnostic doses of radio-iodine should be kept as small as possible.

**Differential Diagnosis.** Simple goiter may be as large as or larger than the goiter of hyperthyroidism, and a bruit may be heard on auscultation of the gland, but the absence of toxic symptoms determines the differentiation. The cardiac symptoms may simulate organic heart disease, but the presence of goiter and exophthalmos favor hyperthyroidism. The restlessness and agitation may suggest chorea. The clinical pattern of pheochromocytoma may resemble that of hyperthyroidism in many respects, but the elevation of blood pressure is greater, may be paroxysmal and responds to adrenolytic drugs.

**Prognosis.** Recovery is often possible with medical treatment. Untreated severe cases may develop psychotic patterns; toxic crises in which vomiting, diarrhea, fever and prostration dominate the clinical picture may terminate in death. When operation is required, preparatory treatment with iodine renders the prognosis favorable in most instances.

**Treatment.** There is general agreement that most children with thyrotoxicosis should be given a trial of medical therapy before surgery is considered. During adolescence in particular an attempt should be made to tide the child over this period of rapid growth with antithyroid drugs in the hope of inducing a permanent remission.

Excitement must be avoided, and an adequate and liberal diet should be prescribed. Supplementary vitamins are indicated, and phenobarbital may be needed until the dis-



ease is under control. A sympathetic understanding by the family of the physical and emotional problems is essential.

Of the antithyroid drugs, propylthiouracil, an effective and relatively safe agent, is the one most widely used. Methimazole (1-methyl-2-mercaptoimidazole) is also effective and approximately twenty times as potent as propylthiouracil. These compounds inhibit incorporation of trapped inorganic iodide into organic compounds and thus produce a progressive lowering of circulating thyroid hormone. Toxic reactions occur with about equal frequency with the two drugs. Because of variations in the responses of different patients, the initial dose of these drugs should be small; for example, 50 mg. of propylthiouracil three times daily. Subsequently the dose is increased as indicated; as much as 500 mg. or more a day may be necessary. Smaller initial doses should be used in early childhood. Because of the rapid excretion of propylthiouracil, an attempt should be made to space doses at intervals of eight hours (e.g., on arising, midafternoon and bedtime). Overdosage can lead to a hypothyroid state and should be avoided. Clinical response becomes apparent in two to three weeks, and adequate control in two to three months.

The thyroid frequently becomes larger after initiation of treatment, but eventually it usually decreases in size. The drug should be continued for at least a year after complete control of the disease has been obtained, and then should be discontinued slowly. Approximately 75 per cent of children will have a permanent remission; if a relapse occurs, it will usually appear within three months and almost always within six months after therapy has been discontinued. Therapy may be resumed in case of a relapse. In puberal children it may be advisable to continue treatment throughout early adolescence.

Less than 2 per cent of patients treated in this manner have minor toxic reactions such as fever, skin rash, nausea, diarrhea, abdominal cramps and headache. More serious reactions such as agranulocytosis are rare.

Operation is indicated when adequate co-operation for medical management is not possible or when medical management has failed. Subtotal thyroidectomy, a rather safe procedure, is performed after the patient has been brought to a euthyroid state. This may be accomplished with propylthiouracil or methimazole over a two- to three-month period. After a euthyroid state has been attained 5 drops of a saturated solution of potassium

iodide per day are given in addition for two weeks prior to operation. The iodide decreases the vascularity of the gland. Complications of surgical treatment include recurrence of thyrotoxicosis, hypothyroidism, hypoparathyroidism and paralysis of the vocal cords.

Radioactive iodine should not be used for treatment in children because, theoretically, permanent harmful irradiation effects might occur either on the thyroid or on other tissues. To date there have been no reports of carcinomas occurring in any thyroid treated with radio-iodine. However, a period of observation of many years will be needed to exclude this possibility. In a patient in whom medical treatment is not feasible and operation is contraindicated or refused, radio-iodine may have to be resorted to. It has been used with success in cases complicated by other disorders such as rheumatic heart disease or when cooperation for long-term medical management was not possible.

### CARCINOMA OF THE THYROID

Carcinoma of the thyroid in children is not rare. Winship has collected 334 cases from published and unpublished sources. The etiology is unknown. Contrary to popular belief, the incidence in goitrous areas is no higher than in nongoitrous areas. It has been suggested that there may be some relation between cancer of the thyroid and irradiation to the neck or thymus. A history of irradiation of the thymus was obtained in approximately 20 per cent of the cases of carcinoma of the thyroid in children in the United States.

Girls are affected more often than boys. Although the onset is usually after the age of nine years, it may be as early as the first year of life. The first evidence is usually a painless nodule in the thyroid. However, metastases in cervical lymph nodes are the initial sign sufficiently often to warrant including cancer of the thyroid in the differential diagnosis of all masses in the neck. The most common site of distant metastases is in the lung, where they may be present without any clinical manifestations. On the roentgenogram the pulmonary lesions appear as diffuse miliary or nodular infiltrations located principally in the basal portions. They may be mistaken for tuberculosis or histoplasmosis. Carcinoma of the thyroid frequently grows slowly and may even remain dormant for years. Small cell carcinomas of the thyroid, however, frequently have a rapidly fatal course.

There is some disagreement about the indications for diagnostic resection of nodules in the thyroid. Some, including the authors, believe that every identified nodule should be removed and examined, since the incidence of carcinoma in nodules of the thyroid in children is estimated to be as high as 70 per cent. However, Astwood suggests treatment with 120 to 250 mg. of thyroid daily on detection of a nodule to determine whether its growth can be suppressed. Only if the thyroid continues to grow during such therapy does he believe that resection is indicated.

The treatment of proved carcinoma of the thyroid is also controversial. One group recommends thyroidectomy (hemithyroidectomy with removal of the isthmus if the disease is unilateral), dissection of enlarged cervical nodes and postoperative roentgen therapy. Another group recommends total thyroidectomy and regional dissection of lymph nodes even though there is no evidence of involvement of them. Even inoperable tumors should be removed as completely as possible together with any existing normal thyroid tissue in preparation for the possible use of radioiodine. Radioiodine should be used only when the lesion cannot be removed surgically and when the cancerous tissue is capable of concentrating cancerocidal doses of the drug. Regression of extensive pulmonary metastases has been observed following the use of radioiodine.

Although it has not been established with certainty that irradiation of the thyroid area (thymus) constitutes the carcinogenic agent, it seems clear that the indiscriminate use of irradiation such as with roentgen rays or radioiodine should be scrupulously avoided.

ANGELO M. DiGEORGE  
JOSEF WARKANY

## REFERENCES

### General

- Means, J. H.: *The Function of the Thyroid Gland*. Springfield, Ill., Charles C Thomas, 1949.  
Salter, W. T.: *Chemical Developments in Thyroidology*. Springfield, Ill., Charles C Thomas, 1950.  
Werner, S. C.: *The Thyroid*. New York, Paul B. Hoeber, Inc., 1955.

### Hypothyroidism

- Cooke, R. E., and Man, F. B.: Management of Hypothyroidism in Infancy and Childhood. *Pediatrics*, 17:617, 1956.  
Lowrey, G. H., and others: Early Diagnostic Criteria

of Congenital Hypothyroidism. A Comprehensive Study of Forty-Nine Cretins. *A.M.A. Am. J. Dis. Child.*, 96:131, 1958.

- Oliner, L., Kohlenbrener, R. M., Fields, T., and Kunstadter, H.: Thyroid Function Studies in Children: Normal Values for Thyroidal  $I^{131}$  Uptake and  $PBI^{131}$  Levels up to the Age of 18. *J. Clin. Endocrinol. & Metab.*, 17:61, 1957.  
Smith, D. W., Blizzard, R. M., and Wilkins, L.: The Mental Prognosis in Hypothyroidism of Infancy and Childhood. A Review of 128 Cases. *Pediatrics*, 19:1011, 1957.  
Stanbury, J. B., and McGirr, E. M.: Sporadic or Non-endemic Familial Cretinism with Goiter. *Am. J. Med.*, 22:712, 1957.  
Wilkins, L.: *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*. 2nd ed. Springfield, Ill., Charles C Thomas, 1957.

### Goiter

- Brush, B. E., and Altland, J. K.: Goiter Prevention with Iodized Salt: Results of a Thirty Year Study. *J. Clin. Endocrinol.*, 12:1380, 1952.  
Greer, M. A., and Astwood, E. B.: Treatment of Simple Goiter with Thyroid. *J. Clin. Endocrinol.*, 13:1312, 1953.  
Herlitz, G.: Iodine and Sporadic Goiter in Childhood. *Acta paediat.*, 41:556, 1952.  
Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter. *American Medical Association, Council on Pharmacy and Chemistry: Glandular Physiology and Therapy*, Chap. 22, 1935.  
Statland, H., Wasserman, M. M., and Vickery, A. L.: Struma Lymphomatosa (Hashimoto's Struma). *Arch. Int. Med.*, 88:659, 1951.

### Endemic Cretinism

- Stanbury, J. B., and others: *Endemic Goiter: The Adaptation of Man to Iodine Deficiency*. Cambridge, Harvard University Press, 1954.

### Thyrotoxicosis

- Arnold, M. B., Talbot, N. B., and Cope, O.: Concerning the Choice of Therapy for Childhood Hyperthyroidism. *Pediatrics*, 21:47, 1958.  
McClintock, J. C., Frawley, T. F., and Holden, J. H. P.: Hyperthyroidism in Children: Observations in 50 Treated Cases, Including an Evaluation of Endocrine Factors. *J. Clin. Endocrinol. & Metab.*, 6:62, 1956.  
Van Wyk, J. J., Grumbach, M. M., Shepard, T. H., II, and Wilkins, L.: The Treatment of Hyperthyroidism in Childhood with Thiouracil Drugs. *Pediatrics*, 17:221, 1956.

### Carcinoma of the Thyroid

- Astwood, E. B.: The Problem of Nodules in the Thyroid Gland. *Pediatrics*, 18:501, 1956.  
Duffy, B. J., Jr.: Can Radiation Cause Thyroid Cancer? *J. Clin. Endocrinol. & Metab.*, 17:1383, 1957.  
Winship, T.: Carcinoma of the Thyroid in Childhood. *Pediatrics*, 18:459, 1956.



# DISORDERS OF THE PARATHYROID GLANDS

Disturbances of the parathyroid glands with gross morphologic changes are not frequent in infants and children. In some clinical syndromes the parathyroids are the site of primary disturbance; in others they are only secondarily affected.

Though complete absence of the parathyroid glands has been reported, there may be some doubt of the authenticity of the observations, since the small glands may have been overlooked. Variations in number are not uncommon; more than four glands are frequent, but rarely are there less than four.

**Function.** The parathyroid hormone is an integral factor in the maintenance of calcium and phosphorus balance. This is its principal known function, although indirectly through its effect on calcium metabolism it is a controlling factor in the structure of bone, in the regulation of neuromuscular activity, in the conduction of cardiac impulses, in the coagulation of blood, in the permeability of cellular membranes, and perhaps in the regulation of other functions of the body. There is no known tropic hormone from the anterior pituitary gland which stimulates the parathyroid glands. As far as is known the parathyroid glands respond directly to tissue calcium and phosphorus requirements.

If administration of parathyroid extract is discontinued in a parathyroidectomized person, there is a decrease in the urinary excretion of phosphorus and a rise in serum phosphorus which is quickly followed by a fall in serum calcium and a decrease in urinary excretion of calcium. When parathormone therapy is resumed, these metabolic alterations are reversed. It is generally agreed that a fall below the usual serum calcium level of 10.5 plus or minus 1 mg. per 100 ml. provides the stimulus to the gland to free stored calcium. The calcium in the blood is principally in two forms, calcium ions and calcium proteinate. Since the total serum calcium concentration may be reduced by a decrease in the serum protein level, the ionized or active serum calcium cannot be evaluated adequately without knowledge of the concentration of serum protein (see Nomogram, p. 1407).

It is generally accepted that there are two distinct actions of parathormone. It has a direct action on the renal tubular mechanism, causing a phosphate diuresis by the kidney.

It also causes direct resorption of bone, possibly through direct action on the matrix. Because commercially available parathyroid hormone shows two components on electrophoresis, it has been suggested that there may be two parathyroid hormones.

## HYPOPARATHYROIDISM

Hypofunction of the parathyroid glands is manifest clinically as tetany (p. 1110). It may be primary or secondary. Temporary dysfunction is observed in so-called tetany of the newborn (p. 342). Secondary hypoparathyroidism is observed at times in association with deficiency of vitamin D (p. 378) and with celiac disease (p. 723). Primary and permanent lack of function occurs after surgical removal, traumatic destruction or atrophy of the glands.

**Surgical Tetany.** Removal or damage of the parathyroid glands may occur as a complication of thyroidectomy. This is seen in a small percentage of thyrotoxic patients treated by partial thyroidectomy, and in a much larger percentage of patients with carcinoma of the thyroid subjected to total thyroidectomy. Hypoparathyroidism has developed even in patients in whom the parathyroid glands had been identified and left undisturbed at the time of operation. This, presumably, is the result of interference with the blood supply and/or of postoperative edema and fibrosis. Symptoms of tetany may occur abruptly postoperatively and be permanent or temporary. In some instances symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally the first evidence of secondary hypoparathyroidism may be the development of cataracts.

All patients subjected to thyroidectomy should be carefully studied to determine the status of parathyroid function. Treatment is the same as that for primary hypoparathyroidism.

**Chronic Idiopathic Hypoparathyroidism.** The etiology of this condition is obscure; it may be related to idiopathic adrenal insufficiency, since the two conditions may occur in the same patient or may alternate in members of the same family. In at least one example of familial hypoparathyroidism and hypoadrenalism the parents were first cousins.

The majority of reported cases began during childhood and remained unrecognized for many years. In at least one instance the onset was in the neonatal period. Early diagnosis and institution of treatment may forestall permanent physical and mental deterioration.

Convulsions usually dominate the clinical picture. A typical convulsion may begin with abdominal pain followed by general tonic rigidity of the body and of the extremities with retraction of the head, and cyanosis. There is loss of consciousness, and the attacks may occur at intervals of weeks or months. Numbness and tingling of the hands and feet may precede the attacks. Carpopedal spasms and other manifest signs of tetany may be absent for many years. These facts explain why this form of hypoparathyroidism is frequently mistaken for epilepsy. The differentiation from a brain tumor may also be difficult, since the intracranial pressure is frequently increased. Headaches, vomiting and papilledema may be found in patients with convulsions. Roentgenograms may reveal calcifications of the brain which are particularly marked in the basal ganglia. Keratoconjunctivitis, lacrimation, photophobia, corneal ulceration and scar formation occur. Cataract may develop. The skin is dry and scaly, the hair thin and patchy, and complete alopecia may develop. The nails of the fingers appear short, thick and overgrown by skin. The teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. Monilia infection of the fingernails, tongue and angles of the mouth is common. In cases of long standing, mental deterioration occurs.

The serum calcium is low (5 to 7 mg. per 100 ml.) and the phosphorus elevated (7 to 12 mg. per 100 ml.). The serum phosphatase is normal or low. The Sulkowitch test (p. 1221) of the urine is negative for calcium. Even moderate amounts of calcium in the urine are strong evidence against hypocalcemia. Roentgenograms of the bones may reveal a generalized increased density limited to the metaphyses suggestive of heavy metal poisoning, or an increased density of the lamina dura. The electrocardiogram typically shows a prolongation of the Q-T interval, which returns to normal when the hypocalcemia is corrected. Electroencephalographic tracings usually show widespread slow activity; the tracings return to normal after the serum calcium has been within the normal range for a few weeks unless irre-

versible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. At autopsy the parathyroids may be absent or replaced by fatty tissue.

**Treatment.** In case of tetany, emergency treatment consists in intravenous injections of 5 to 10 ml. of a 10 per cent solution of calcium gluconate at the rate of 0.5 to 1 cc. per minute. Initially either vitamin D or dihydrotachysterol (A.T.-10) should also be used. Since A.T.-10 acts more rapidly, it is perhaps preferable in the early stages of treatment. Calcium chloride orally in a dilute solution is also useful because it induces a mild acidosis which in itself tends to combat the tetany. It should not be administered parenterally because it results in thrombosis when given intravenously and in sloughing when given subcutaneously. Foods with a high phosphorus content, such as milk, eggs and cheese, should be eliminated from the diet.

Dihydrotachysterol may be given initially in doses of 1 to 4 cc. daily. Maintenance therapy consists in oral administration of vitamin D in daily doses of 50,000 to 250,000 U.S.P. units. After the initial period of standardization, calcium should be given orally in the form of calcium gluconate or calcium lactate.

Clinical evaluation of the patient and frequent determinations of the serum calcium are indicated in the early stages of treatment in order to determine the dosage requirements of vitamin D and of calcium. Maintenance treatment can be continued for many years, and the patient can estimate the urinary excretion of calcium by the Sulkowitch test (p. 1221). A moderate amount of calcium should be excreted in the urine. Most of the symptoms of hypoparathyroidism disappear under the treatment outlined. If hypercalcemia occurs, vitamin D should be discontinued and resumed at a lower dose when the serum calcium level has returned to normal. In cases of long standing, repair of cerebral or dental changes may be impossible. Development of pigmentation or lowering of the blood pressure indicates beginning adrenal insufficiency and requires specific treatment (p. 1182).

**Pseudohypoparathyroidism.** This syndrome, first described by Albright in 1942, is a familial disorder of unknown etiology. To date over forty cases have been reported. In contrast to the situation in idiopathic hypoparathyroidism, there is an adequate production of parathyroid hormone, and histo-



logically the parathyroid glands are normal or hyperplastic. It is believed that the chemical disturbance is due to a failure of the end organs, particularly of the kidney, to respond to parathyroid hormone (phosphate diuresis does not occur after its administration, as is normally the case [Ellsworth-Howard test]). Albright has termed this type of end organ resistance "Seabright-bantam syndrome" because in this breed of fowl the rooster fails to develop male characteristics, owing to failure of the end organs to respond to male sex hormones.

In addition to clinical and chemical findings similar to those of idiopathic hypoparathyroidism, these patients are characterized by a short, stocky build and a round face. Growth failure may be striking, and there is a tendency to brachydactylia. The metacarpals are more often involved than the metatarsals but the second metacarpal is often not affected, and, as a result, the index finger may be longer than the middle finger. There may be other skeletal abnormalities, such as short and wide phalanges, bowing and gnarling of the radius and ulna, and general demineralization of the bones. In addition to calcifications in the basal ganglia, these patients almost characteristically have calcium deposits and metaplastic bone formation subcutaneously. Mental retardation is common and may be due to brain damage resulting from repeated seizures.

The chemical disturbance characteristically does not respond to parathyroid extract, but does to vitamin D. Therefore *treatment* is the same as described for idiopathic hypoparathyroidism.

"Pseudo-pseudohypoparathyroidism." In this disorder the usual anatomic stigmata seen in pseudohypoparathyroidism occur, but the serum calcium and phosphorus levels are normal. The diagnosis is established by roentgenographic demonstration of typical ossification and by demonstration of a phosphate diuresis following administration of parathyroid hormone (Ellsworth-Howard test).

## HYPERPARATHYROIDISM

Adenomas, hypertrophy or hyperplasia of the parathyroids may produce increased amounts of parathormone, which result in a tendency to raise the serum calcium level and to lower the serum phosphorus. If such overproduction of parathormone occurs in a basically normal organism, then more hormone is re-

leased than is needed and a state of "primary hyperparathyroidism" results. If, however, more hormone is released into an organism which is metabolically disturbed and requires more hormone for compensatory purposes, then one speaks of a state of "secondary hyperparathyroidism." In primary hyperparathyroidism the surplus of hormone is harmful, and treatment is aimed at reduction of the hormone to normal levels. In secondary hyperparathyroidism the surplus of hormone is beneficial or at least necessary, and reduction would be harmful. Treatment of secondary hyperparathyroidism must aim at removal of the basic disturbance. Chronic renal disease, rickets and celiac disease are disorders which require compensatory secondary hyperparathyroidism.

### PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is rare in children. In older children the manifestations resemble more or less those in adults, but the symptoms in infants may differ greatly.

Hyperparathyroidism may be due to a single or to multiple adenomas or to idiopathic hypertrophy and hyperplasia of all four parathyroid glands. Hyperplastic glands may be enlarged to about 100 times the normal, and the cells may also be enlarged in volume.

In hyperparathyroidism the serum calcium is elevated, at times to 16 to 20 mg. per 100 ml. The serum phosphorus is reduced to 3 mg. per 100 ml. or below; in cases with skeletal involvement the serum phosphatase is increased. A normal total serum calcium value does not exclude primary hyperparathyroidism, since an increase of the ionized calcium fraction may be masked when the serum protein and the calcium proteinate are reduced. The urinary excretion of both calcium and phosphorus may be increased. Low levels of serum magnesium have been reported in association with primary hyperparathyroidism.

The osseous changes are characterized by increased absorption or osteoclastic activity. There are also signs of repair or osteoblastic activity, but the former process predominates. Tumors consisting of osteoclasts and osteoblasts are termed benign giant cell tumors or osteoclastomas. Secondary changes may lead to degeneration and softening of abnormal bone tissue, and cysts of various sizes may be formed. Fractures may occur in areas of abnormal bone structure. The cellular bone marrow is replaced by fibrous tissue, a change

once considered characteristic of generalized osteitis fibrosa cystica. It is now interpreted as a nonspecific reaction to rapid absorption of the osseous structure, which is also found in polyostotic fibrous dysplasia, Paget's disease and other osseous disorders.

The renal changes are due to the increased demand for excretion of calcium and phosphorus. Renal stones are frequently formed, and calcium deposits in the pyramids may interfere with renal function. Anuria and renal insufficiency may result from the nephrolithiasis and nephrocalcinosis.

**Clinical Manifestations.** Generalized osteitis fibrosa cystica was the first recognized manifestation of primary hyperparathyroidism. Later it was recognized that renal changes may occur with or without skeletal involvement. Gastrointestinal symptoms may also be the only expression of hyperparathyroidism.

Osseous changes may be responsible for pain in the back or extremities, disturbance of gait, deformities, fractures and tumors. There may be decrease in height resulting from compression of vertebrae, and the patient may be bedridden. In infants enlargement and tenderness of the epiphysal regions have been observed; the anterior fontanel may be large and bulging. These clinical findings suggest rickets. Muscular weakness, anorexia, nausea, vomiting, loss of weight, emaciation and fever are general symptoms. Mental retardation or deterioration, generalized seizures, headache and blindness may also occur. Renal, ureteral or vesical calculi develop and are responsible for renal colic and hematuria. Calcium may also be deposited in the renal parenchyma, resulting in so-called nephrocalcinosis, which can be recognized on the roentgenogram. The clinical manifestations are those of the nephrosclerotic type of renal disease and consist in polyuria, polydipsia, and a urine with a low fixed specific gravity. These symptoms may be present before renal calcification is radiologically demonstrable. Renal function is progressively diminished. A high incidence of duodenal ulcers in adults with primary hyperparathyroidism and at least one case in a child have been reported.

Roentgenograms reveal generalized rarefaction of the bones, thinning and scalloping of the cortex, cysts, tumors, fractures and deformities. Calcification of soft tissues has been observed. In infants cupping and fraying are seen at the ends of the shafts, and the

distance between the calcified diaphysis and the epiphysis is increased. These findings, as well as flaring of the ends of the ribs, and scoliosis are suggestive of rickets. In the adult type the skull may show gross trabeculation or a granular appearance resulting from focal rarefaction. In infants there may be increased digitations, and vascular and intracranial calcifications have been observed. Subperiosteal resorption of bone is a common finding and is seen most frequently along the margins of the phalanges of the hands. Disappearance of the lamina dura is another common finding.

**Diagnosis.** Idiopathic hypercalcemia of infancy may be easily confused with hyperparathyroidism. The signs and symptoms are the same in both disorders, and both are characterized by hypercalcemia. The serum phosphorus level is normal or slightly elevated in *idiopathic hypercalcemia* and depressed in ordinary hyperparathyroidism. Roentgenographically, the increased bone density of idiopathic hypercalcemia contrasts strikingly with the rarefaction of primary hyperparathyroidism.

*Hypercalcemia*, of any etiology, results in a similar clinical pattern. In most of these disorders, as in vitamin D intoxication, the roentgenograms show increased density of bone.

*Hypophosphatasia*, especially when severe, is frequently associated with mild to moderate hypercalcemia. The serum phosphorus is normal, and the serum alkaline phosphatase activity is depressed. Roentgenograms of the bones may show complete disappearance of the zone of provisional calcification and lack of calcification of the metaphysal bone. In *rickets* the serum calcium is normal or low, which helps in differentiating it from primary hyperparathyroidism of infants.

Polyostotic fibrous dysplasia, osteogenesis imperfecta, xanthomatosis, Gaucher's disease and metastases of malignant neoplasms have normal calcium and phosphorus levels of the serum and sufficiently characteristic roentgenographic findings to cause little difficulty in diagnosis. The differentiation from secondary hyperparathyroidism is discussed below.

**Prognosis.** The prognosis is good if the disease is recognized early, and a parathyroid adenoma or adenomas can be demonstrated and removed. When extensive osseous lesions are present, permanent deformities may persist; when renal damage has occurred, the prognosis is less hopeful.



**Treatment.** Surgical exploration is indicated in all but completely hopeless cases. All glands should be carefully inspected, and any existing adenoma should be removed or, if there is only generalized hyperplasia, a subtotal parathyroidectomy should be performed. If the serum calcium level is exceedingly high, calcium should not be injected postoperatively until the concentration is lowered, or fatal poisoning may result. In the presence of extensive osseous disease and a high serum phosphatase, removal of the entire tumor may result in hypocalcemia and tetany, due to cessation of bone destruction and continuation of bone formation at excessive rates. Owing to this danger, Albright recommends partial removal of the tumor when bone involvement is marked. If, however, the entire tumor should be removed, continuous intravenous administration of calcium gluconate may be required immediately after the operation (see above). Likewise, when there is extensive renal damage, only partial removal of the tumor is recommended. It is thought that a certain amount of hyperparathyroid activity is required in such instances to maintain a normal calcium level.

Under ordinary circumstances average amounts of vitamin D and diets high in calcium and phosphorus should be maintained for several months after the operation.

#### SECONDARY HYPERPARATHYROIDISM

Secondary hyperactivity of the parathyroid glands is commonly observed in chronic renal insufficiency, in vitamin D-deficient rickets and in celiac disease with or without rickets. In each of the latter two intestinal absorption of calcium and phosphorus is deficient, and hypocalcemia and tetany are averted by the increased activity of the parathyroid glands. When the parathyroids fail to respond to the stimulus of the low serum calcium and do not increase their activity to a sufficient extent to maintain a normocalcemia or when they "play out," hypocalcemic tetany results (p. 1110).

#### RENAL DISEASE WITH HYPERPARATHYROIDISM

In many instances of experimental and clinical chronic renal disease an associated hyperparathyroidism has been observed. In renal insufficiency there is usually retention of serum phosphate, and Albright postulates that the hypocalcemia which is secondary to the hyperphosphatemia is the stimulus to increased parathyroid activity. In many, but not in all,

instances there is an associated involvement of the osseous structures.

#### RENAL HYPERPARATHYROIDISM AND BONE DISEASE

(RENAL HYPERPARATHYROIDISM WITH OSTEOPOROSIS [OSTEITIS] FIBROSA CYSTICA [Park and Eliot], RENAL OSTEITIS FIBROSA CYSTICA [Albright], RENAL RICKETS, RENAL DWARFISM, RENAL INFANTILISM)

The multiplicity of terms used for this syndrome is indicative of the lack of complete understanding of its pathogenesis. It is generally agreed that the primary lesion is a renal one. This is in contrast to the renal lesion of nephrocalcinosis which may result from primary hyperparathyroidism.

**Etiology.** Though the renal insufficiency may result from a variety of factors, in children most cases appear to be caused by congenital obstructive lesions of the lower urinary tract. Such lesions include urethrovesical and ureterovesical obstructions and bilateral anomalies of the ureters. In sequence there is dilatation of the structures above the obstruction, hydronephrosis, and finally pressure atrophy of the renal parenchyma. Chronic glomerulonephritis and chronic pyelonephritis are other causes of renal insufficiency leading to secondary hyperparathyroidism.

**Pathology.** It is assumed that hyperphosphatemia is the primary stimulus to increased activity of the parathyroid glands. Whether the increased amount of circulating parathyroid hormone acts directly or indirectly on bone is a moot point. Whatever the mechanism of action, the resulting osseous lesions are histologically similar to those occurring in primary hyperparathyroidism. There is an increased number of osteoclasts, resorption of bone, cystlike spaces and a widespread distribution of fibrous connective tissue in place of marrow. If the onset occurs after endochondral growth is complete or essentially so, the changes are limited chiefly to the shaft. Prior to this time, the younger the child the greater the changes in the epiphyseal areas. In the very young, and especially when the process is rapid, there is an accumulation of proliferative cartilage which is due, not to overproduction, but to continued endochondral growth without conversion of the cartilaginous matrix into bone. The result is a soft epiphyseal plate which is easily distorted, resulting in a rachitic-like appearance. These osseous changes are responsible for the deformities and partly for dwarfing.

**Clinical Manifestations.** The younger the child at the time of development of the osseous lesions, the greater the degree of dwarfing; and the longer the process continues, the greater are the deformities. The clinical and roentgenographic skeletal manifestations are similar to those observed in untreated severe infantile rickets or in vitamin D-refractory rickets. Either the skeletal deformities or the renal symptoms may be the manifestations first observed.

The clinical manifestations of the renal disturbance are essentially those of the nephrosclerotic kidney with progressive loss of ability to concentrate urine, retention of nitrogen and hypertension. In some instances the latter two seem to be less marked than in other comparable chronic disturbances of the kidney.

The results of laboratory examinations vary, but in general there is some degree of nitrogen as well as phosphorus retention. Serum calcium is usually normal or below normal in spite of the increased activity of the parathyroid glands. Renal function tests reveal progressive loss of excretory capacity, and though the blood pressure may not be so high as in other types of chronic renal involvement, there is, as a rule, progressive hypertension. Roentgenograms of the skeleton reveal increased radiolucency of the shaft and rachitic-like deformities at the ends of the long bones. Urographic studies are indicated in all instances.

**Prognosis.** The prognosis is unfavorable, since extensive renal lesions are usually present by the time the diagnosis is suspected. The only hope lies in removal of a urinary

tract obstruction before irreversible renal damage has occurred.

**Treatment.** Obstructive lesions of the urinary tract should be removed as early as possible. A diet high in calcium and low in phosphorus has been recommended. There is apparently no benefit in excessively high doses of vitamin D, and there is danger of overdosage.

ANGELO M. DiGEORGE  
JOSEF WARKANY

## REFERENCES

- Albright, F., and Reifenstein, E. G., Jr.: *Parathyroid Glands and Metabolic Bone Disease*. Baltimore, Williams & Wilkins Company, 1948.
- Ellsworth, R., and Howard, J. E.: *Studies on the Physiology of the Parathyroid Glands*. VII. Some Responses of Normal Human Kidneys and Blood to Intravenous Parathyroid Extract. *Bull. Johns Hopkins Hosp.*, 55:296, 1934.
- Grant, D. K.: Papilloedema and Fits in Hypoparathyroidism. *Quart. J. Med.*, 22:243, 1953.
- Harmon, M.: Parathyroid Adenoma in a Child: Report of a Case Presenting a Central Nervous System Disease and Complicated by Magnesium Deficiency. *Am. J. Dis. Child.*, 91:313, 1956.
- Harrison, H. E.: Idiopathic Hypoparathyroidism. *Pediatrics*, 17:442, 1956.
- Kaplan, E.: Parathyroid Gland in Infancy. *Arch. Path.*, 34:1042, 1942.
- Macgregor, M. E., and Whitehead, T. P.: Pseudohypoparathyroidism. *Arch. Dis. Childhood*, 29:398, 1954.
- Soper, R. T., Mason, E. E., and Buckwalter, J. A.: Hypoparathyroidism in Children and Adolescents. *Pediatrics*, 20:1097, 1957.
- Whitaker, J., Landing, B. H., Esselborn, V. M., and Williams, R. R.: The Syndrome of Familial Juvenile Hypo-adrenocorticism, Hypoparathyroidism and Superficial Moniliasis. *J. Clin. Endocrinol. & Metab.*, 16:1374, 1956.

## DISORDERS OF THE ADRENAL GLANDS

### GENERAL CONSIDERATIONS

The adrenal gland is composed of two endocrine systems, the chromaffin system contained in the medulla, and the interrenal system of the cortex.

The medulla is of ectodermal origin, and its cells are derived from sympathetic ganglia. The cortex is formed in the embryo by about six weeks' gestation from peritoneal mesothelium and is, therefore, of mesodermal origin.

In a fetus of two months the adrenals are much larger than the kidneys; but from the fourth month the kidneys grow rapidly, and

become about twice as large as the adrenals by the end of the sixth month. At birth the adrenal gland is one third the size of the kidney, and the average combined weight of both glands is 7 to 9 gm. in the full term infant.

The adrenal cortex in the fetus and newborn infant is composed of two histologically distinct components. The outer portion of the gland consists of the true cortex, and the more central portion is known as the "fetal adrenal cortex." At birth the fetal cortex makes up about 80 per cent of the gland. Within a few days after birth it undergoes extensive degeneration which results in a 50



per cent reduction in the total mass by two weeks of age. This fetal cortex completely disappears by one year of age; its physiology is unknown, and its involution is not associated with any recognized deficiency or change in function of the newborn infant.

The true cortex consists of three zones. In the zona glomerulosa, which is situated beneath the capsule, there is an alveolar arrangement of the cells; in the broader zona fasciculata the columns of cells are radially arranged; in the zona reticularis the cells form a network next to the medulla.

**Function.** Removal of both adrenal glands results in death. Vomiting, loss of appetite, thirst, anuria, muscular weakness, tachycardia and fall in blood pressure are followed by coma and death.

The *adrenal cortex* secretes various steroid compounds into the blood stream which are responsible for functions essential to life. The known compounds show different activities when tested in biologic assays. They can be divided into several general groups:

1. *Glucocorticoids.* These steroids have a 21-carbon structure and are also referred to as 17-hydroxycorticoids or 17-hydroxycorticosteroids or simply as corticosteroids. The principal hormone of this group is hydrocortisone, which is also known as cortisol or compound F. Cortisone (compound E) is another steroid in this group.

These substances have carbohydrate-regulating and antiphlogistic properties. The fall of the blood sugar in fasting, adrenalectomized animals is attributed to a lack of these hormones; in their absence, formation of new sugar, gluconeogenesis, from endogenous protein is impaired. The influence of these adrenocortical hormones on fat metabolism is manifest by obesity in children with Cushing's syndrome. There is also experimental evidence indicating that corticosteroids play a role in fat metabolism. Excessive amounts of these substances lead to protein catabolism, osteoporosis and growth failure. They also result in sodium and water retention and loss of potassium.

The corticosteroids and their metabolites are excreted in urine. They can be measured chemically and are interpreted as an index of the production of carbohydrate-regulating hormones by the adrenal gland. Methods are also available for measurement of their blood levels; "normal values" differ somewhat according to the method used. In patients with Addison's disease or pituitary insufficiency the levels of corticosteroids are reduced, and in

those with Cushing's disease they are increased.

The rate of corticosteroid production is under pituitary adrenocorticotropin control. One of the most frequently used tests to assess adrenocortical reserve is the measurement of blood or urinary levels of the corticosteroids before and after the administration of corticotropin.

Many synthetic analogues of cortisone and hydrocortisone are available. Derivatives with an additional double bond in ring A are known as prednisone and prednisolone. They are three to four times as potent in anti-inflammatory and carbohydrate activity as the parent steroids, but have less effect on salt and water retention. Halogenated derivatives are also available. Thus 9- $\alpha$ -fluoro-hydrocortisone is approximately twenty times as active as hydrocortisone in carbohydrate activity, but is more than twenty times as active in salt and water retention. Triamcinolone ( $\Delta$ -1, 9- $\alpha$  fluoro, 16  $\alpha$ -hydroxy-hydrocortisone) is approximately seven times as potent as hydrocortisone and is said to have no effect on retention of water and electrolytes. These analogues are usually used in pharmacologic doses for their antiphlogistic properties.

2. *Mineralo-corticoids.* It has been known for years that the adrenal cortex elaborates a specific hormone capable of prolonging the life of adrenalectomized animals by regulating electrolyte and water metabolism. It was termed the "sodium-retaining" hormone by Albright and "mineralo-corticoid" by Selye. This substance was finally isolated and crystallized in 1953. The following year its chemical structure was found to be the 18-aldehyde of corticosterone, and it was named aldosterone. This substance is now known to be the principal naturally occurring mineralo-corticoid in man.

Since only small amounts of aldosterone occur in natural form and since its large-scale chemical synthesis is not yet economic, the substance is not commercially available. Desoxycorticosterone, however, can be synthesized; it is effective in restoring electrolyte metabolism in adrenal insufficiency, and is used therapeutically for this purpose. Aldosterone is approximately thirty times as active as desoxycorticosterone in its mineralo-corticoid effects. Large amounts of cortisone and hydrocortisone also cause retention of sodium and chloride, but are less than one twentieth as active as desoxycorticosterone.

Aldosterone, unlike the glucocorticoids, is

not under control of corticotropin. Restriction of sodium intake results in increased secretion of aldosterone. There is evidence that secretion of aldosterone is effected mainly by changes in body fluid volume.

3. *Androgens.* Dehydroepiandrosterone is representative of this group. These hormones are capable of increasing retention of nitrogen, potassium, phosphorus and sulfate. They promote growth and have an androgenic effect, properties which are most conspicuous under pathologic conditions when adrenal hyperplasia or adrenal tumors induce precocious growth and development of secondary male sex characteristics. There is evidence that the adrenal androgens are partly responsible for the development of axillary and pubic hair in the female.

Metabolized adrenal androgens are excreted in the urine as 17-ketosteroids. They can be measured and accepted as an index of the production of adrenal androgens in the female. In the male approximately one third of the urinary 17-ketosteroids can be attributed to testicular and two thirds to adrenal androgens. In children under nine years of age the urinary excretion of these substances is small (p. 1195), but there is a constant increase throughout adolescence until adult levels are reached. Under pathologic conditions increased production of adrenal androgens is reflected in increased secretion of urinary 17-ketosteroids.

4. *Estrogens.* Adrenal cortical production of estrogens is most strikingly illustrated in patients with feminizing adrenal cortical tumors (p. 1191).

The *adrenal medulla* consists of irregularly shaped cells and of blood sinuses located between the strands of cells. The secretion of the hormone of the medulla is regulated by the splanchnic nerves. Two hormones are elaborated by the adrenal medulla; epinephrine (Adrenalin) and norepinephrine (noradrenalin; arterenol). Norepinephrine is a primary amine differing from epinephrine only by the absence of an N-methyl group. The proportions of epinephrine and norepinephrine in the adrenal vary at different ages. In early fetal stages there is practically no epinephrine, and even at birth norepinephrine is predominant. In adults norepinephrine makes up only 10 to 30 per cent of the total pressor amines in the medulla. Both epinephrine and norepinephrine increase the mean arterial blood pressure. Norepinephrine accomplishes this without changing the cardiac output. By increasing peripheral vascular

resistance, it increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorogenic effects of norepinephrine are much less pronounced than those of epinephrine. Both hormones are believed to be secreted into the blood stream in approximately the same proportion as elaborated in the adrenal. The variations of the clinical pattern of patients with pheochromocytomas may be explained by the different proportions of the two hormones elaborated. In the majority of these tumors 50 to 90 per cent of the hormonal material recovered is norepinephrine.

### HYPOADRENOCORTICISM

Adrenal insufficiency may result from a wide variety of pathologic lesions of the adrenal glands and is not a rare disorder. The symptoms may be severe or mild, and the deficiency may be temporary or permanent.

**Etiology.** *Adrenal insufficiency associated with congenital adrenal hyperplasia* and characterized by an inability to regulate electrolyte metabolism is probably the most common form. The mechanism for this aberration is still unknown (p. 1188).

*Congenital adrenal hypoplasia* is a much less frequent cause of adrenal insufficiency. Anencephalic monsters consistently have adrenal hypoplasia; it is a rare occurrence in infants with an intact cranium who have pituitary hypoplasia and insufficient secretion of corticotropin. Occasionally it occurs as an isolated congenital anomaly.

*Adrenal hemorrhage* may occur in the neonatal period as a consequence of difficult labor or of asphyxia and occasionally may be sufficiently extensive to result in acute adrenal insufficiency. In some instances the hemorrhage is asymptomatic initially, but progressive fibrosis, calcification or cystic changes may develop. Gradual impairment of function may then culminate in adrenocortical insufficiency in infancy or childhood.

*Bilateral adrenalectomy* or the removal of an adrenal in the absence of the contralateral adrenal will result in adrenal insufficiency. Such a situation may arise after removal of a functioning adrenal tumor, especially one resulting in Cushing's syndrome, when the contralateral adrenal is atrophied (p. 1189).

A recent cause of adrenal insufficiency which may increase in frequency is the *abrupt*



cessation of administration of corticotropin or a corticosteroid. Symptoms are most likely to occur when these substances have been given in large doses for a long time to patients subjected to stressful situations such as severe infections or surgical procedures. Administration of these substances results in impaired pituitary or adrenal cortical function, and their effects may sometimes outlast treatment for a long time.

The term *Waterhouse-Friderichsen syndrome* has been applied to the characteristic state of shock accompanying hemorrhage into the adrenal glands during the course of meningococcemia. Since a similar clinical picture may accompany hemorrhage or necrosis of the adrenals as a result of trauma or fulminating septicemia caused by other organisms, it would appear preferable to include all these conditions under the term *acute adrenal insufficiency*. Occasionally in the course of an acute infection a patient may have all the signs and symptoms of the Waterhouse-Friderichsen syndrome, and yet at autopsy no adrenal hemorrhage is found. A number of investigators have reported cases which at autopsy showed extensive necrosis of the adrenal cortical cells. Measurements of blood corticosteroids in patients with typical symptoms of the Waterhouse-Friderichsen syndrome have usually demonstrated elevated levels indicating normal adrenal function. The circulatory collapse in such instances is probably the result of the severe toxemia and not of impaired adrenal function.

*Chronic adrenal insufficiency*, which develops in infants or children with previously normal adrenal function, is referred to as *Addison's disease*. Tuberculosis, once the most frequent cause of Addison's disease, is no longer a major etiologic factor. At present a "cytotoxic" degeneration or idiopathic atrophy, the cause of which is not known, is noted in most cases. In these cases the glands may be so small that they are not visible at autopsy, and only a few remnants of tissue are found in microscopic sections. The medulla, however, is usually not destroyed, and there is lymphocytic infiltration in the area of the former cortex and in the medulla. Histoplasmosis, coccidioidomycosis, torulosis, amyloidosis, metastatic malignancies and mycosis fungoides have been identified as etiologic agents in adults, but not in children.

Addison's disease resulting from "cytotoxic" degeneration of the adrenal gland has been reported in siblings. In such instances it is not uncommon to find an associated

atrophy of the parathyroid glands. Addison's disease may develop in patients with hypoparathyroidism, and, conversely, hypoparathyroidism in patients with Addison's disease. Siblings are known in which one member had adrenal insufficiency and another hypoparathyroidism. This association of Addison's disease and hypoparathyroidism, and at times of moniliasis, represents a definite genetically determined disorder of variable expressivity.

**Clinical Manifestations.** In older children the onset in the chronic form is gradual with weakness, lassitude, anorexia, loss of weight, vomiting and diarrhea. There may be an intensive craving for salt. Abdominal pain may simulate an acute abdominal process. If water and salt are withheld, dehydration rapidly ensues and circulatory collapse develops, soon to be followed by death. Convulsions, which occur occasionally, have been attributed to hypoglycemia. The pigmentation seen in adults with Addison's disease and consisting of brownish discoloration about the genitals, umbilicus, axillas, nipples and joints may be less striking in children. It may be first apparent on the face and hands or, rarely, be generalized rather than confined to the areas mentioned above. At times vitiligo-like pale spots may be interspersed with the dark areas. In the buccal mucosa the pigmentation is usually bluish-brown. Other physical findings are muscular weakness, general wasting, low blood pressure and microcardia (Fig. 343). In adolescent girls breast development and menstruation begin normally, but axillary and pubic hair are characteristically absent.

Acute adrenal insufficiency, which may be due to adrenal hemorrhage or fulminating infections, may also occur in patients with chronic adrenal insufficiency, when it is known as an *adrenal crisis*. The patient suddenly becomes cyanotic, his skin is cold and clammy and his pulse rapid and thready. The blood pressure falls, respirations are rapid and labored, and the patient sinks into a deep coma. In patients with infections such as meningococcemia, petechial and purpuric rashes appear suddenly over the body, often coalescing into large ecchymotic areas (see Fig. 118, p. 427). In instances of massive hemorrhage the adrenal glands may become palpable. The course of an adrenal crisis is rapid and, if untreated, fatal. In patients with Addison's disease a crisis can be precipitated by infection, trauma, excessive fatigue or drugs such as morphine, barbiturates, laxatives, thyroid hormone or insulin.

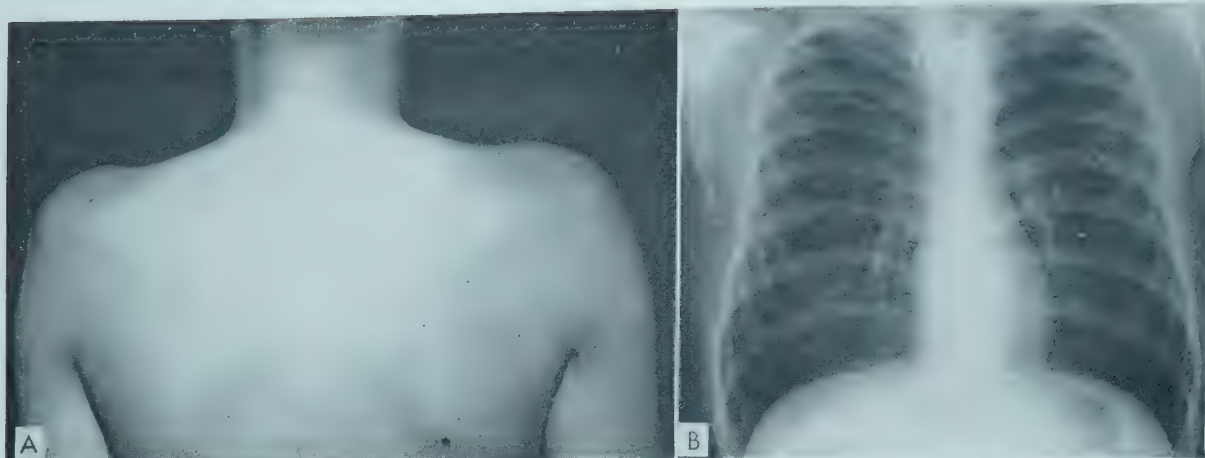


FIG. 343. Addison's disease in a 10-year-old boy. On admission he was dehydrated; there was bronzing of the skin and hypotension. Note the deeply pigmented freckles (black freckles) in A, and the microcardia in B; both are characteristic of untreated Addison's disease. Serial measurements of cardiac size are an excellent criterion of adequacy of treatment.

**Laboratory Data.** In Addison's disease the sodium and chloride concentrations in the serum are low and that of potassium is elevated, and there is hypoglycemia. The non-protein nitrogen is usually within the normal range unless the patient is dehydrated. There is an increase in the urinary excretion of sodium and chloride and a decrease of that of potassium. The protein concentration of the plasma is increased. These changes are accentuated during acute crises. Oral administration of glucose may paradoxically result in a fall rather than a rise of the blood sugar level, which may be prolonged and lead to manifestations of hypoglycemia. The urine may contain small amounts of albumin and a few casts; the specific gravity tends to be low.

Roentgenograms of the abdomen occasionally reveal calcified areas in the region of the adrenals, especially when tuberculosis or hemorrhage has been the etiologic factor. A small and narrow shadow of the heart is characteristic of Addison's disease. Abnormalities in the electroencephalogram include absence or a greatly decreased number of low voltage, fast frequency waves. Hypoglycemia may be found after a twenty-four-hour fast. The circulating eosinophils are usually increased in number, but may be normal and even absent during crises. Since pronounced eosinopenia is usually present during acute infections when the function of the adrenal glands is adequate, a normal eosinophil count in the presence of severe infection is suggestive of impaired adrenal function.

Tests of adrenal function have been devised which permit confirmation of the diagnosis. The four-hour corticotropin test is a

useful screening procedure; the number of eosinophils in the blood is counted immediately before and four hours after the intramuscular administration of 25 units of corticotropin. A decrease of less than 50 per cent in the number of eosinophils is suggestive of adrenal insufficiency. One of the most definitive tests of adrenal function is the measurement of urinary and/or plasma levels of corticosteroids before and after the administration of corticotropin in patients with primary adrenal insufficiency. Resting levels of corticosteroids are low in the urine and plasma, and there is no increase after administration of corticotropin. In occasional instances the resting levels of corticosteroids are normal, but there is no increase following administration of corticotropin, indicating the absence of any adrenocortical reserve. A low initial level followed by a significant increase in urinary or blood levels of corticosteroids indicates adrenal insufficiency secondary to pituitary corticotropin insufficiency. The urinary 17-ketosteroids are decreased in men and absent in women, but in children, who normally do not excrete these substances before the age of nine years, no characteristic changes can be expected in Addison's disease.

**Prognosis.** The prognosis in Addison's disease must be guarded despite great advances in therapy. Patients with this disease are similar to those with diabetes in their need for constant supervision; acute crises may develop suddenly and on slight provocation. The patient may become dehydrated quickly during minor infections or during periods of salt restriction, and death may ensue if therapy is not prompt or adequate. The mortality



rate is high in infants and children with acute adrenal insufficiency due to adrenal hemorrhage or infection, but they have an excellent prognosis if they survive the acute episode.

**Treatment.** *Patients with Addison's disease* require replacement therapy for their deficiency of electrolyte-controlling hormones; desoxycorticosterone acetate (DOCA) in sesame oil is administered intramuscularly in single daily injections; maintenance doses usually range from 0.5 to 3 mg. The dose depends upon the intake of sodium chloride, which must be kept constant while the maintenance dose is determined. The daily requirements of sodium chloride are usually 3 to 6 gm. in addition to that contained in the food; sodium chloride can be administered in 1-gm. enteric-coated tablets. During the first few months of treatment there is a gradual decrease in requirements for DOCA. After the maintenance dose has been determined and continued for several months, daily intramuscular administration can be replaced by use of the long-acting preparation, desoxycorticosterone trimethylacetate, a single intramuscular injection of which can provide a constant supply of the hormone for about a month. In lieu of the intramuscular administration, subcutaneous implantation of pellets may be used. A pellet containing 125 mg. of DOCA is equivalent to daily injections of about 0.5 mg. of this drug for about twelve months.

Overdosage with DOCA or salt results in retention of sodium chloride and water and in excretion of excessive amounts of potassium; edema, hypertension, cardiac enlargement and muscular weakness or paralysis are clinical manifestations.

Hydrocortisone should also be administered to all patients with adrenocortical insufficiency in order to maintain normal carbohydrate metabolism and normal vigor. It may be given orally in doses of 5 to 10 mg. twice daily. During situations of stress, such as periods of infection or operative procedures, the dose of hydrocortisone should be increased. Antibiotic therapy is indicated for all infections, even minor ones, since they are poorly tolerated.

*Treatment for acute adrenal insufficiency* or for crises must be instituted immediately and must be vigorous. Five per cent glucose in saline solution is given intravenously at a rate permitting the administration of about 75 ml. per kilogram of body weight per day.

This may be modified, depending on the deficits of the individual. Administration of plasma or, in case of a low hemoglobin level or of adrenal hemorrhage, of whole blood is indicated. Concomitantly a water-soluble form of hydrocortisone, such as the sodium salt of the hemisuccinate, should be given intravenously. High levels may be achieved instantaneously in this manner. No definite dosage schedule has evolved, but large doses can be used safely. As much as 25 mg. for infants and 50 mg. for young children may be given immediately and then continued by intravenous drip on the basis of the foregoing doses for each six-hour period. Intramuscular administration of the steroid should be instituted when intravenous therapy is discontinued. Desoxycorticosterone in oil may be added in doses of 1 to 5 mg., if necessary, to maintain electrolyte balance.

Norepinephrine can be given intravenously in instances of shock and circulatory collapse. Four milligrams per liter may be added to the intravenous solution; the blood pressure should be measured at frequent intervals. Oxygen administration is indicated. In newborn infants with adrenal hemorrhage, vitamins K and C should also be given. In acute adrenal insufficiency associated with infection appropriate antibiotic therapy is essential.

## HYPERADRENOCORTICISM

Three distinct syndromes are attributable to hyperadrenocorticism: the *adrenogenital syndrome*, *Cushing's syndrome* and *primary aldosteronism*. The adrenogenital syndrome is caused primarily by hypersecretion of androgenic hormones and may be congenital or acquired. It may be caused by a defect of steroidogenesis, in which case there is bilateral cortical hyperplasia, or it may be caused by a tumor of the adrenal cortex. Congenital adrenal hyperplasia results in pseudohermaphroditism in the female and in macrogenitosomia praecox in the male. When the disorder develops postnatally, as the result of a tumor or hyperplasia, virilization develops in the female and macrogenitosomia in the male. Cushing's syndrome is the result of hypersecretion of hydrocortisone, which may also be caused by adrenal hyperplasia or a tumor of the adrenal cortex. Primary aldosteronism is caused by excessive secretion of aldosterone, which too may be due to adrenal hyperplasia or a tumor.



FIG. 344. External genitals of a 6-year-old boy with congenital adrenal hyperplasia whose height and weight were those of an average  $8\frac{1}{2}$ -year-old boy. Skeletal maturation was at a level of  $10\frac{1}{2}$  years. The appearance of a few pubic hairs was the reason for seeking medical advice. The testes were relatively small for the size of the penis. Prompt suppression of the elevated urinary levels of 17-ketosteroids and pregnanetriol with cortisone established the diagnosis.

### CONGENITAL ADRENAL HYPERPLASIA

#### (VIRILIZING ADRENAL HYPERPLASIA)

**Pathogenesis.** This disorder is caused by an inborn defect of biosynthesis of certain steroids of the adrenal cortex; the primary disturbance is an inability to synthesize hydrocortisone from its precursor, 17-hydroxyprogesterone, owing to a deficiency of the enzyme "21-hydroxylase." This substance accumulates, is metabolized and excreted in the urine as pregnanetriol. The deficiency of hydrocortisone, a potent inhibitor of pituitary activity, results in increased secretion of corticotropin, which in turn leads to adrenocortical hyperplasia and overproduction of adrenal androgens and other intermediary metabolites.

Another form of this disease is associated with hypertension. The defect appears to be a deficiency of a second adrenal cortical enzyme, "11-hydroxylase." In this disorder there is, in addition to the deficiency of hydrocortisone, an overproduction of desoxycorti-

costerone, to which the hypertension has been attributed.

A third form of this disorder is associated with a defect in electrolyte regulation, and patients are referred to as "salt-losers." The cause for this form of the disease is not definitely established (see p. 1188).

Administration of hydrocortisone or one of its analogues inhibits the production of corticotropin, which in turn results in reduced production of androgens and other abnormal intermediary compounds of the adrenal cortex. The salt-losing form of this disorder is alleviated by administration of sodium chloride, desoxycorticosterone and hydrocortisone (p. 1189).

Congenital adrenal hyperplasia (p. 238) is inherited as a recessive trait. Parents who have one affected child have one out of four chances of having another affected child with each subsequent pregnancy. It seems that the three forms of the disorder mentioned above are genetically specific. If one form occurs in a family, subsequently affected infants will have the same disorder. The defect in steroidogenesis varies in degree and is often not complete, a fact which accounts for the spectrum of clinical manifestations described in subsequent sections.

**Clinical Manifestations.** In the *male* the main clinical manifestations are those of premature isosexual development, namely, early signs of masculinization such as enlargement of the penis, scrotum and prostate, appearance of pubic hair and development of acne and of a deep voice (Fig. 344). There is accelerated linear growth, the muscles are well developed, and the bone age is advanced for the chronologic age (infant Hercules; macrogenitosomia praecox).

The infant usually appears normal at birth, but signs of sexual and somatic precocity may appear within the first half-year of life or more gradually with sexual precocity not developing until four or five years of age or later (Fig. 344). Owing to premature closure of the epiphyses, growth stops relatively early, and the result is stunted stature.

In congenital adrenal hyperplasia the penis is large and the testes normal, so that they appear relatively small in size. In contrast, both the penis and the testes are enlarged in sexual precocity of hypothalamic origin. Since ectopic adrenocortical cells are occasionally present in the testes, they may, in adrenal hyperplasia, become hyperplastic just as the adrenal glands do and produce enlargement of the testes. In such instances the



patient may be suspected of having true precocious puberty, which, however, does not develop, since spermatogenesis does not take place. The mental development of affected children is usually normal, but the abnormal physical development may result in behavior problems.

The small percentage of patients who have the second type of defective steroidogenesis have severe hypertension in addition to the clinical features described above. A larger number of patients are "salt-losers" (the third type); symptoms of adrenal insufficiency develop early in life (see p. 1188). Hypoglycemic manifestations, secondary to the deficiency of hydrocortisone, are rare.

In the *female*, congenital adrenal hyper-

plasia results in symptoms of heterosexual pseudoprecocity. Since the disorder of steroidogenesis begins early in fetal life, there are almost always evidences of some degree of masculinization of the female fetus manifest at birth by enlargement of the clitoris and variable degrees of labial fusion. These patients are known as female pseudohermaphrodites (Fig. 345).

The clitoris may be so enlarged that it resembles a penis, and, since the urethra opens below this organ, a mistaken diagnosis of hypospadias and cryptorchidism is often made. The vagina has a common opening with the urethra (urogenital sinus). The internal genital organs are those of a normal female.

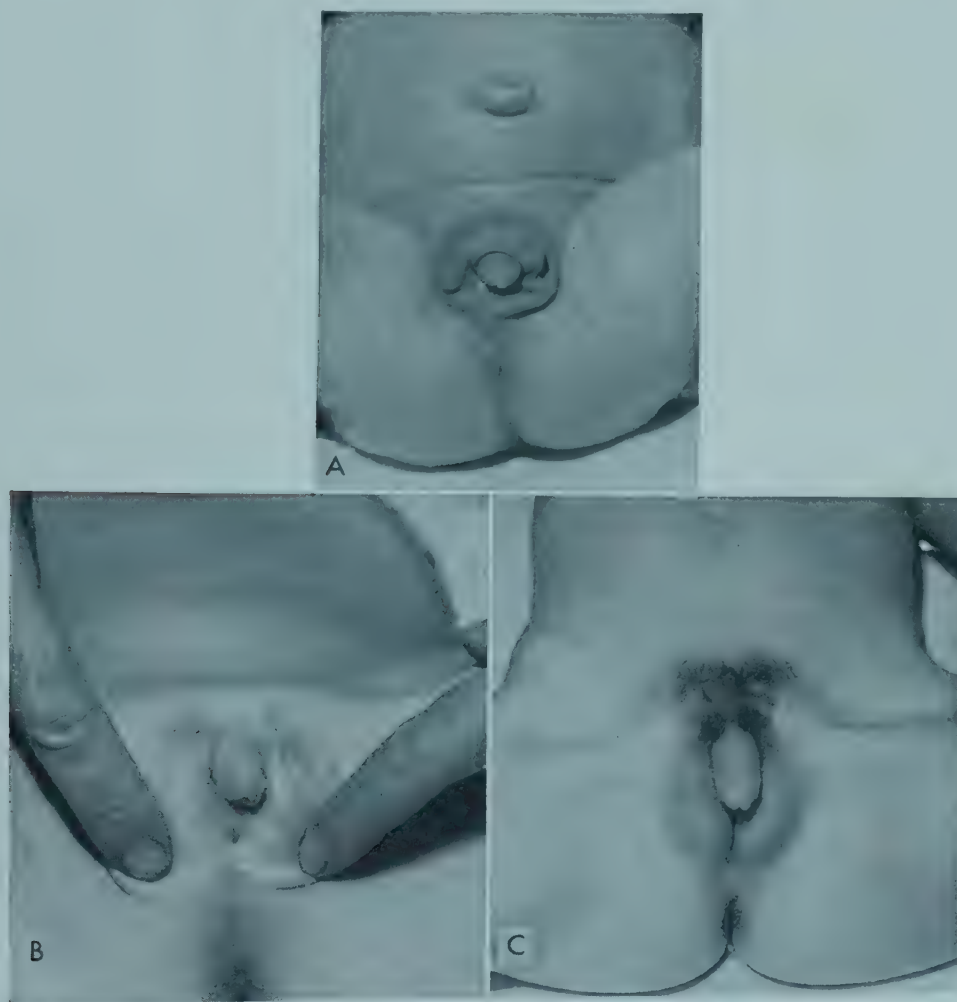


FIG. 345. Three female pseudohermaphrodites with untreated congenital adrenal hyperplasia. Note the clitoral enlargement and labioscrotal fusion with formation of a urogenital sinus. A, External genitalia of an infant 10 days of age, who was erroneously diagnosed as a cryptorchid, hypospadiac male. Although she was asymptomatic, she weighed 1 pound less than birth weight and was found to be a "salt-loser." B, External genitalia of a 6-year-old girl who was considered normal until 2 years of age, when clitoral enlargement was first noted. Increasing growth of the clitoris and appearance of pubic hair at 5 years of age led to the proper diagnosis. C, External genitalia of a 4-year-old girl with clitoral enlargement from birth and growth of pubic hair beginning at 3 years. All 3 patients showed elevated urinary 17-ketosteroids and pregnanetriol, a female chromosomal sex pattern, a normal vagina on vaginogram and prompt suppression of cortical adrenal activity with cortisone.

After birth the masculinization progresses. Pubic and axillary hair develops prematurely, and acne appears on the face, neck and chest. The voice assumes a masculine quality. These girls are tall for their age, show good muscular development and, in general, have the body build of a boy. Ossification is advanced for their age. Although the internal genitals are female, breast development and menstruation never occur unless the excessive production of androgens is suppressed by adequate treatment.

Hypertension, salt-losing symptoms and hypoglycemia may occur as in the male.

#### CONGENITAL ADRENAL HYPERPLASIA WITH DISTURBED ELECTROLYTE REGULATION

(MIXED ADRENAL CORTICAL DISEASE,  
"SALT-LOSERS")

Addisonian-like symptoms are seen in approximately one third of all infants with congenital adrenal hyperplasia. The diagnosis is being established more frequently in females than in males. This sex predilection may be only apparent and the result of easier diagnosis of the female pseudohermaphrodite early in life. Because of the absence of external genital changes in the male, the symptoms of adrenal insufficiency are often not recognized, particularly when an adrenal crisis simulates a gastrointestinal disorder.

Anorexia, vomiting, diarrhea, loss of weight and extreme dehydration are the outstanding manifestations. Anuria, tachycardia and cyanosis may develop. Restriction of fluid and salt intake results in sudden collapse and death, often preceded by convulsions. Without specific treatment death occurs within a few days or weeks after the onset of symptoms, which begin during the first month of life in more than 90 per cent of affected infants.

The clinical manifestations have frequently led to the diagnosis of intestinal obstruction, pyloric stenosis or a diarrheal disturbance. Instances have been reported in which the presenting problem was a disturbance in cardiac rate and rhythm, suggesting congenital heart disease.

The reason for salt-losing symptoms in some of these patients is not known. Both normal and low levels of the salt-retaining hormone, aldosterone, have been reported. It has also been suggested that these patients secrete a "salt-losing" hormone, but no such substance has thus far been isolated. The

difference between the "salt-loser" and the patient without an electrolyte disturbance may be due to quantitative differences of the underlying enzymatic defect of hydrocortisone synthesis.

**Laboratory Data.** All patients with virilizing adrenal hyperplasia have increased values of urinary 17-ketosteroids for their age. Young infants may excrete as much as 10 mg. in a twenty-four-hour period, and older patients as much as 80 mg. or more. Pregnanetriol, the metabolite of 17-hydroxyprogesterone, is also present in large amounts in the urine of these patients. Blood and urine levels of hydrocortisone are usually low and fail to increase after administration of corticotropin. The circulating eosinophils are, as a rule, increased, and eosinopenia does not follow administration of corticotropin.

Female pseudohermaphrodites with this disorder always have a female sex chromatin pattern. Roentgenographs taken after injection of contrast medium into the urogenital sinus may demonstrate the vagina and uterus. Osseous maturation is advanced, the degree depending on the severity of the disorder and the age of the patient before treatment.

"Salt-losers" have low concentrations of serum sodium and chloride and elevated levels of serum potassium and nonprotein nitrogen. Elevation of the serum potassium may be responsible for abnormal electrocardiographic tracings.

**Differential Diagnosis.** It is important to differentiate congenital adrenal hyperplasia from a virilizing adrenocortical tumor, since treatment of the former is medical and that of the latter is surgical. Females with congenital adrenal hyperplasia offer little difficulty in differential diagnosis because of the presence of a urogenital sinus and enlarged clitoris at birth. In males with congenital adrenal hyperplasia, virilization may not become apparent for several years after birth, thus making differentiation from an adrenal tumor more difficult. A history of congenital adrenal hyperplasia in siblings or the development of Addisonian-like symptoms favors the diagnosis of adrenal hyperplasia. Whenever postnatal virilization occurs under the age of ten years, the presence of a tumor should be strongly suspected; it may be palpable or suggested by displacement of the adjacent kidney as demonstrated by pyelography.

Although the urinary 17-ketosteroid excretion is elevated in both conditions, high values favor the diagnosis of a neoplasm. Large amounts of urinary pregnanetriol are highly



suggestive of adrenal hyperplasia. A therapeutic test with a corticosteroid is one of the most valuable differential procedures, since cortisone quickly suppresses excretion of urinary 17-ketosteroids in patients with congenital adrenal hyperplasia, but not in those with a virilizing tumor. Cortisone, by inhibiting secretion of corticotropin, reduces the abnormal stimulation of the adrenals in patients with hyperplasia, whereas adrenal cortical tumors are not subject to pituitary regulation.

In males an interstitial cell tumor of the testis and true precocious puberty must also be considered. In true precocious puberty gonadotropins may be present in the urine, the urinary 17-ketosteroid level is never above normal adult values, pregnanetriol is not found in the urine, the testes are usually well developed, and interstitial cells may be seen in biopsy specimens. In virilizing adrenal hyperplasia urinary assays are negative for gonadotropins, and abnormal levels of pregnanetriol are found. Urinary levels of 17-ketosteroids are often higher than in normal adults. Biopsy of the testis shows a failure of the interstitial cells to develop. Urinary estrogens are increased in both males and females with virilizing adrenal hyperplasia.

**Treatment.** Cortisone and hydrocortisone are equally effective in inhibiting excessive production of adrenal androgens in patients with adrenal hyperplasia. Intramuscular administration is preferable initially because the results are more predictable. During the first week of treatment 100 mg. of cortisone per day are given intramuscularly to children over six years of age, 50 mg. daily to children between two and six years of age, and 25 mg. daily to children under two years of age.

The urinary excretion of 17-ketosteroids should be used as a guide for determination of the dose. Careful measurements of growth are important in determining the adequacy of dosage, since restoration of normal physical and skeletal growth is a prime objective of treatment. The maintenance dose of cortisone may be administered orally. Fifty to 75 mg. daily for children and 20 mg. daily for infants, given in two or three divided doses, are usually adequate. Such doses suppress excessive androgen secretion without producing undesirable effects. The analogues of cortisone, such as prednisone, are effective in suppressing adrenal androgens, but seem to have no advantage over the parent compounds.

Patients who have disturbance of electro-

lyte regulation ("salt-losers") must be treated with a high salt intake and desoxycorticosterone acetate in addition to cortisone. For adequate replacement therapy of dehydrated infants as much as 4 to 8 gm. of sodium chloride may be required for the first twenty-four hours. For maintenance 2 to 6 gm. of salt per day should be added to the diet and intramuscular injection of 2 to 5 mg. of DOCA should be given daily. Pellets of DOCA may be implanted after the maintenance dose has been determined, or a long-acting form of DOCA may be injected monthly (p. 1185).

#### VIRILIZING ADRENOCORTICAL TUMOR

Tumors of the adrenal cortex result in masculinization in girls and pseudoprecocity in boys. In males the symptoms are usually the same as those occurring with congenital adrenal hyperplasia. It is virtually impossible to differentiate the two conditions on clinical grounds. In females virilizing tumors of the adrenal cause masculinization of a previously normal female, whereas congenital adrenal hyperplasia is almost always associated with genital abnormalities at birth (p. 1187). However, there have been a few instances of adrenal hyperplasia in which virilization had its onset postnatally. The differential diagnosis of virilizing adrenal hyperplasia and adrenal cortical tumor is discussed on page 1188.

The *treatment* is surgical; a transperitoneal approach is usually recommended. Some of these neoplasms are highly malignant and metastasize widely, but cure with regression of the masculinizing features may follow removal of less malignant encapsulated tumors.

A neoplasm of one adrenal may be responsible for atrophy of the contralateral one, owing to excessive production of cortical hormones by the tumor and suppression of the normal gland. Consequently adrenal insufficiency may follow surgical removal of the tumor. This situation can be avoided by giving 100 mg. of cortisone daily, starting on the day of operation and continuing for three or four days postoperatively. It may also be necessary to give corticotropin concurrently with cortisone to reactivate the atrophied gland. Adequate quantities of water, sodium chloride and glucose must also be provided.

#### CUSHING'S SYNDROME

The clinical pattern of Cushing's syndrome is the result of hyperfunction of the adrenal

cortex. When Harvey Cushing described the entity in 1932, he thought it was caused by a basophilic adenoma of the pituitary. In many instances such an adenoma cannot be found at necropsy, and there is evidence that the changes in the pituitary may be secondary to prolonged elevation of corticosteroid levels. Prolonged administration of corticotropin or hydrocortisone or its analogues results in a clinical pattern similar to the spontaneous disorder. Whether Cushing's syndrome is primarily a pituitary, adrenal or hypothalamic disturbance is uncertain.

Cushing's syndrome is most common in young adults and is rare in children; adrenal cortical carcinoma is the main cause in infants and children under ten years of age. Bilateral adrenal hyperplasia is an especially rare cause in children, as is benign adrenal cortical adenoma. An excess of hydrocortisone is essential for the development of this syndrome, although there is usually a mixed form of hypercorticism. Thus, in addition to overproduction of the carbohydrate-regulating hormone, there may be increased amounts of androgens and estrogens. According to the prevalence of a particular hormone, the clinical pattern may vary, and intermediate forms between the adrenogenital and Cushing's syndromes may be manifest.

**Clinical Manifestations.** Symptoms may begin in the neonatal period or any time thereafter. In this form of adrenocortical hyperfunction, obesity of the "buffalo type" and hypertension are outstanding symptoms. The characteristic appearance of these patients is determined by the accumulation of fat on the cheeks, chin and upper parts of the trunk, but sometimes there is a relative lack of fat on the extremities. In spite of their monstrous appearance, such patients are not much above average weight, and they are frequently stunted in growth. There is hypertrichosis on the face, trunk and in the pubic region. The skin appears plethoric, and the cheeks, in particular, are intensely red. Acne is a frequent manifestation even in very young children, but purplish striae on the hips, abdomen and thighs are seen mainly in older children. The voice becomes deep and coarse. In girls the clitoris is generally, but not invariably, enlarged. Sometimes the breasts develop precociously and menstruation begins at an early age. Thus signs of abnormal masculinization and feminization may be seen simultaneously in such girls. In boys the external genitals appear

normal. The blood pressure is elevated, the heart often enlarged, and cerebral hemorrhage may occur. The mentality is initially normal, but as the disease progresses the children frequently become listless, apathetic and dull.

**Laboratory Data.** The red blood cell count and the hemoglobin level are usually in the range of high normal values and there is usually an eosinopenia. The blood sugar level may be normal or high, and there may be glycosuria. The plasma electrolyte pattern is sometimes disturbed, and high concentrations of sodium and bicarbonate and a decrease in potassium may be present. Patients with Cushing's syndrome excrete increased amounts of 17-hydroxycorticosteroids in the urine. These levels may fluctuate from day to day, and repeated determinations may be required to establish the diagnosis. The urinary output of 17-ketosteroids may also be increased. Ossification may be normal or advanced for the patient's age, and there may be osteoporosis with spontaneous fractures.

**Treatment.** All children with Cushing's syndrome should be surgically explored to rule out a tumor. If an adrenal tumor is present, excellent therapeutic results can be achieved by its removal. Adrenal cortical carcinomas frequently metastasize, especially to the liver and the lungs, and the prognosis may be unfavorable in spite of their removal. In instances of a hormone-producing tumor the contralateral adrenal is atrophic, and replacement therapy with cortisone and adrenal stimulation with corticotropin are important adjuvants in the preoperative and postoperative management of the patient. Benign cortical adenomas causing Cushing's syndrome are occasionally bilateral. In such cases the treatment of choice is subtotal adrenalectomy. It is usually necessary to remove 90 per cent of the adrenal cortex to obtain a permanent remission.

#### PRIMARY ALDOSTERONISM

Excessive secretion of aldosterone as a primary disorder of the adrenal cortex due to hyperplasia or a tumor is known as primary aldosteronism. This condition is to be distinguished from that of increased levels of aldosterone seen in many common disorders such as nephrosis, congestive cardiac failure and cirrhosis of the liver and during dietary restriction of sodium leading to secondary aldosteronism. Conn (1955) was the first to recognize the syndrome of excessive aldoster-



onism in a patient, who was subsequently found to have elevated levels of urinary aldosterone. Removal of an adrenal cortical adenoma resulted in spectacular clinical improvement.

**Clinical Manifestations.** The patient has episodes of muscular weakness simulating periodic paralysis. Polyuria, polydipsia, inability to concentrate urine and hypertension are common, and intermittent paresthesias and tetany may be present. The majority of patients do not have edema. There is no evidence of Cushing's syndrome.

The urine is persistently alkaline, and there is mild proteinuria, and a low specific gravity unresponsive to Pitressin. The serum pH and carbon dioxide content and sodium concentration are elevated, and potassium level is decreased. Serum calcium levels, urinary 17-ketosteroids and 17-hydroxycorticoids are normal, but urinary aldosterone levels are elevated. The severe muscular weakness is the result of the low serum levels of potassium. The urinary findings are attributed to "clear-cell nephrosis," a lesion characteristic of chronic hypokalemia.

In the majority of reported instances a benign adrenal cortical adenoma has been found, but a few instances of adrenocortical carcinoma and of bilateral adrenal hyperplasia have also been reported. Removal of the tumor or subtotal adrenalectomy in instances of hyperplasia results in disappearance of the clinical and biochemical abnormalities.

Thus far there have been only three or four instances of this disorder reported in children or adolescents, all of which have had bilateral adrenal hyperplasia. One child with polydipsia and polyuria since early childhood also had moderate growth failure.

#### FEMINIZING ADRENAL TUMORS

Adrenal carcinoma as a cause of gynecomastia has been reported in thirty-five males, but only one of these was a child. Gynecomastia developed during infancy, and the breasts were well developed at two years of age. Growth and development were otherwise normal. At five years of age, after removal of an encapsulated adenoma of the adrenal cortex, there was a gradual decrease in the size of the breasts.

There has been a report of a 5½-year-old girl with isosexual precocity caused by an adrenocortical neoplasm. There was no clinical evidence of Cushing's syndrome or of virilism. An abnormally elevated level of urinary 17-ketosteroids led to the diagnosis.

#### PHEOCHROMOCYTOMA

Several types of tumors are derived from the cells of the adrenal medulla, but only one of them consists of tissue with an internal secretion. These tumors, termed "pheochromocytomas," consist of chromaffin cells which produce large amounts of epinephrine and norepinephrine. Their size varies from a centimeter to about 10 cm. in diameter; they are found more often on the right side than on the left. Less than 5 per cent of the reported cases have been in children. In about 25 per cent of affected children there are bilateral tumors, and in about 15 per cent active tumors have been found outside the adrenal gland. In some instances these tumors occur both in the adrenal and in an extra-adrenal site in the same patient. Pheochromocytomas may occur in more than one member of a family, and in such instances the tumors are usually bilateral. Other neural disorders such as neurofibroma and aganglionic megacolon have been reported in association with these tumors.

**Clinical Manifestations.** These are due to the excess of circulating epinephrine and norepinephrine. The variability of the clinical picture in different patients is explained on the basis of the varying proportions of these two substances excreted. All patients have hypertension at some time. The hypertension may be paroxysmal, a feature which has been thought to be pathognomonic. However, most often the hypertension is sustained, and this is especially so in children. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually may be replaced by a continuous hypertensive state. Between attacks of hypertension the patient may be free of symptoms. During attacks the patient complains of headache and palpitation, and pallor, vomiting and sweating are noticed. In severe cases precordial pains radiate into the arms, and pulmonary edema and cardiac and hepatic enlargement may develop. The child has a good appetite, but does not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The systolic blood pressure may range from 180 to 260 systolic and 120 to 210 diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate and arterial constriction.

**Laboratory Data.** The urine contains al-

bumin, a few casts and occasionally glucose. In many instances the basal metabolic rate may be as high as plus 50 or 60.

A variety of drugs may be used diagnostically, but the two most useful ones are histamine and phentolamine (Regitine). If the hypertension is paroxysmal, histamine administered intravenously stimulates release of epinephrine and norepinephrine, thus provoking an attack similar to those occurring spontaneously. When the hypertension is continuous, Regitine may be used as an adrenergic agent. Three to 5 mg. of this substance administered fairly rapidly by the intravenous route will result in a prompt fall of more than 35 mm. of systolic pressure and of 25 mm. of diastolic pressure if a pheochromocytoma is present. Falsely positive results may be obtained if the patient is taking sedatives or narcotic drugs, and falsely negative ones in patients taking antihypertensive drugs.

The most direct and specific test for the detection of pheochromocytomas is the measurement of urinary excretion or blood levels of catechol amines. Norepinephrine is increased in the urine in all patients; epinephrine is not invariably increased. There is a direct relation between the proportion of these substances in the tumor and in the urine.

**Differential Diagnosis.** The usual causes of hypertension in children must be considered, such as renal disease, coarctation of the aorta, acrodynia, hyperthyroidism, Cushing's syndrome, congenital adrenal hyperplasia and essential hypertension. If the hypertension is paroxysmal, the diagnosis of familial autonomic dysfunction must be ruled out; a number of children with this entity have been explored for pheochromocytoma. Neuroblastomas occasionally produce hypertension and increased excretion of catechol amines.

**Treatment.** Localization of the tumor is often difficult; occasionally it can be discovered by palpation, and in some instances massage of one side produces paroxysms of hypertension. Pyelography, presacral injection of oxygen or, preferably, of pure carbon dioxide, or aortography may reveal the location of the tumor, but often it is demonstrated only by surgical exploration. Removal of the tumor has resulted in cures. The operation is not without danger, because an extreme rise of blood pressure may result from massive discharge of hormone during operative manipulation. Another danger is that of shock from a precipitous drop of blood pressure during operation or within the first forty-eight postoperative hours. These dangers can now

be coped with by the use of Regitine before and during operation to prevent hypertensive crises and of norepinephrine to prevent shock. Utmost vigilance is required postoperatively. The urinary excretion of catechol amines should be determined after operation as a measure of the completeness of the surgical procedure.

ANGELO M. DiGEORGE

JOSEF WARKANY

## REFERENCES

### General

- Gaunt, R., Renzi, A. A., and Chart, J. J.: Aldosterone—A Review. *J. Clin. Endocrinol. & Metab.*, 15:621, 1955.
- Lanman, J. T.: The Fetal Zone of the Adrenal Gland; Its Developmental Course, Comparative Anatomy and Possible Physiologic Functions. *Medicine*, 32: 389, 1953.
- Von Euler, U. S.: Nor-adrenaline, Chemistry, Physiology, Pharmacology and Clinical Aspects. Springfield, Ill., Charles C Thomas, 1956.
- Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. 2nd ed. Springfield, Ill., Charles C Thomas, 1957.
- Hypoadrenocorticism**
- Harlem, O. K., and Myhre, E.: Congenital Adrenal Hypoplasia. *A.M.A. Am. J. Dis. Child.*, 94:696, 1957.
- Haydar, N. A., St. Marc, J. R., Reddy, W. I., Laidlaw, J. C., and Thorn, G. W.: Adrenocortical Insufficiency with Normal Basal Levels of Urinary 17-Hydroxycorticosteroids, Diagnostic Implications. *J. Clin. Endocrinol. & Metab.*, 18:121, 1958.
- Lanman, J. T.: Adrenal Steroids in Meningococcemia. *J. Pediat.*, 46:724, 1955.
- Malloy, B. M., and Woodruff, C. W.: Addison's Disease in Three Six-year-old Boys. *A.M.A. Am. J. Dis. Child.*, 95:364, 1958.
- Salassa, R. M., Bennett, W. A., Keating, F. R., and Sprague, R. G.: Postoperative Adrenal Cortical Insufficiency. Occurrence in Patients Previously Treated with Cortisone. *J.A.M.A.*, 152:1509, 1953.
- Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency. 2nd ed. Springfield, Ill., Charles C Thomas, 1951.
- Whitaker, J., Landing, B. H., Esselborn, V. M., and Williams, R. R.: The Syndrome of Familial Juvenile Hypo-adreno-corticism, Hypoparathyroidism and Superficial Moniliasis. *J. Clin. Endocrinol. & Metab.*, 16:1374, 1956.
- Williams, A., and Robinson, M. J.: Addison's Disease in Infancy. *Arch. Dis. Childhood*, 31:265, 1956.
- Hyperadrenocorticism, Adrenogenital Syndrome, Cushing's Syndrome, Primary Aldosteronism**
- Blizzard, R. M., and Wilkins, L.: Present Concepts of Steroid Therapy in Virilizing Adrenal Hyperplasia. *Arch. Int. Med.*, 100:729, 1957.
- Bongiovanni, A. M., and Eberlein, W. R.: Defective Steroidal Biogenesis in Congenital Adrenal Hyperplasia. *Pediatrics*, 21:661, 1958.



- Bongiovanni, A. M., and Eberlein, W. R.: Clinical and Metabolic Variations in the Adrenogenital Syndrome. *Pediatrics*, 16:628, 1955.
- Childs, B., Grumbach, M. M., and Van Wyk, J. J.: Virilizing Adrenal Hyperplasia: A Genetic and Hormone Study. *J. Clin. Invest.*, 35:213, 1956.
- Conn, J. W.: Primary Aldosteronism, a New Clinical Syndrome. *J. Lab. & Clin. Med.*, 45:3, 1955.
- Guin, G. H., and Gilbert, E. F.: Cushing's Syndrome in Children Associated with Adrenal Cortical Carcinoma. A Case Report with Review of the Literature. *A.M.A. Am. J. Dis. Child.*, 92:297, 1956.
- Hewlett, J. S., and others: Aldosterone-Producing Tumors of the Adrenal Gland. *J.A.M.A.*, 164:719, 1957.
- Iversen, T.: Congenital Adrenocortical Hyperplasia with Disturbed Electrolyte Regulation. *Pediatrics*, 16:875, 1955.
- Jailer, D. W., Longson, D., and Christy, N. P.: Cushing's Syndrome—An Adrenal or Pituitary Disease. *J. Clin. Endocrinol. & Metab.*, 16:1276, 1956.
- Snaith, A. H.: A Case of Feminizing Adrenal Tumor in a Girl. *J. Clin. Endocrinol. & Metab.*, 18:318, 1958.
- Sobel, E. H., Lee, C. M., Jr., Esselborn, V. M., and Clark, L. C., Jr.: Functioning Adrenal Tumors in Childhood. Consideration of Diagnosis, Surgical Approach and Postoperative Management. *Am. J. Dis. Child.*, 86:733, 1953.
- Van Buchem, F. S. P., Doorenbos, H., and Elings, H. S.: Conn's Syndrome, Caused by Adrenocortical Hyperplasia. I and II. *Koninkl. Nederl. Akademia Van Wetenschappen*, 59:578, 705, 1956.
- Wilkins, L.: A Feminizing Adrenal Tumor Causing Gynecomastia in a Boy of Five Years Contrasted with a Virilizing Tumor in a Five Year Old Girl. *J. Clin. Endocrinol.*, 8:111, 1948.

#### *Pheochromocytoma*

- Cone, T. E., Jr., Allen, M. S., and Pearson, H. A.: Pheochromocytoma in Children, Report of Three Familial Cases in Two Unreported Families. *Pediatrics*, 19:44, 1957.
- Tevetoğlu, F., and Lee, C.: Adrenal Pheochromocytoma Simulating Diabetes Insipidus. Report of a Case and Review of the Other Pediatric Cases. *Am. J. Dis. Child.*, 91:365, 1956.
- Von Euler, U. S., and Ström, G.: Present Status of Diagnosis and Treatment of Pheochromocytoma. *Circulation*, 15:5, 1957.

## DISORDERS OF THE GONADS

The endocrine function of the testes is attributed to the male sex hormone, testosterone, a product of the interstitial cells of Leydig. This hormone has been extracted and isolated from the testes and can be obtained in crystalline form. Little is known about the endocrine role of the testes during childhood; though such a function cannot be denied *a priori*, there is little proof to substantiate its existence. Signs of castration and testicular failure do not become manifest before puberty. Testicular androgens begin to appear about twelve years of age and act by inducing growth of the penis and development of male secondary sex characters. Spermatogenesis begins about two or three years later. The Leydig cells and the production of their hormone are stimulated by the pituitary interstitial cell-stimulating hormone; spermatogenesis is influenced by the pituitary follicle-stimulating hormone.

The mature ovaries produce two types of hormones, the estrogens and progesterone. Several natural estrogens have been isolated: estrone, estriol and alpha estradiol. The last is the most potent of the natural estrogens and may be the true follicular hormone. Stilbestrol, which is active when administered

orally, is a synthetic compound with estrogenic effects. Estrogens stimulate growth of the uterus, vagina, mammary glands and other female secondary sex characters. Progesterone is a product of the corpus luteum. The female hormones are secreted in periodic cycles, which last in the human being about twenty-eight days. During the first half of the cycle the follicle matures until ovulation occurs in the middle of the intermenstrual period. During this phase of the cycle the estrogens induce proliferation of the uterine mucosa and of the mammary duct system. The secretion of estrogens reaches a peak at the time of ovulation and continues at a lower level during the second (luteal) phase of the cycle. After ovulation a corpus luteum is formed, which produces progesterone. Progesterone inhibits further proliferation of the endometrium, induces secretory activity of its cells, and prepares it for nidation of the ovum. It also develops the alveolar system of the mammary gland. In the absence of a fertilized ovum the progestational uterine endometrium degenerates. The products of degeneration are expelled, with blood and uterine secretions, in the process of menstruation.

The onset of menstruation, the menarche,

is observed most frequently between the ages of twelve and thirteen years. There is, however, a wide range of physiologic variation between eleven and sixteen years. Menarche beyond this range is not necessarily abnormal, but a thorough examination should be made to rule out pathologic processes. Irregularities of cycles are frequent during the first year or two after the menarche, and during this time ovulation does not usually occur. Cramps are associated with ovulatory cycles only.

The normal and pathologic activities of the sex glands are reflected to a certain extent by hormonal substances excreted in the urine. The excreted sex hormones also permit certain conclusions about the functions of the pituitary and adrenal glands. The gonadotropic follicle-stimulating hormone (FSH) and the estrogens are estimated by biologic methods, the androgens (17-ketosteroids) by colorimetric methods.

The gonads are stimulated in both boys and girls by the anterior pituitary. This stimulation becomes manifest at puberty. Only minute amounts of FSH are secreted in both sexes before puberty. In girls FSH can be detected in the urine frequently in the eleventh year of life and usually at least one year before the first menses. In boys this hormone does not appear in measur-

able amounts before the age of thirteen years. These findings are in agreement with the fact that, in general, somatic signs of maturation are seen earlier in females than in males.

Boys as well as girls secrete small but fairly constant amounts of estrogens until the age of seven years (Fig. 346); about that time the excretion of these substances begins to increase in both sexes, but there is little difference in their respective values until the age of eleven years. Then girls show an augmented rate of excretion of estrogens, while that of boys undergoes little change. At the same time cyclic changes of excretion appear in girls. The values charted in Figure 346 represent average monthly excretion rates which deviate from the various daily excretion levels. A single determination of urinary estrogens does not represent a measure of a girl's average excretion, since the values vary a great deal during every cycle. These cyclic variations precede the appearance of secondary sex characters and the menarche. Progesterone is converted into pregnanediol and excreted in the urine.

The excretion levels of 17-ketosteroids in both sexes during childhood and adolescence are indicated in Figure 347. The amounts excreted are less than 1 mg. daily before the

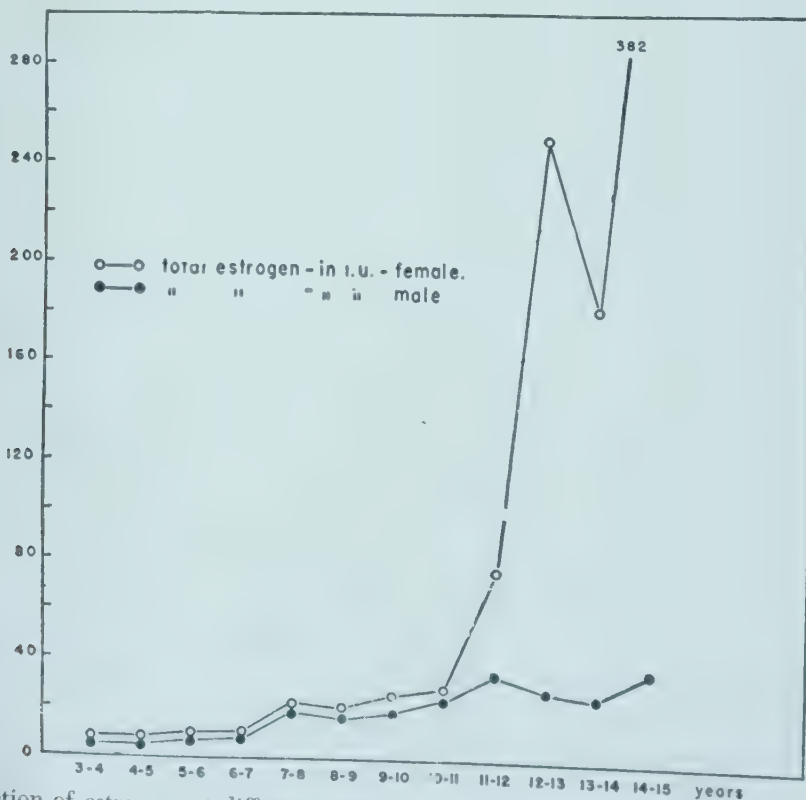


FIG. 346. Excretion of estrogens at different ages. (Adapted from Nathanson, Towne and Aub. *Endocrinology*, Vol. 28.)



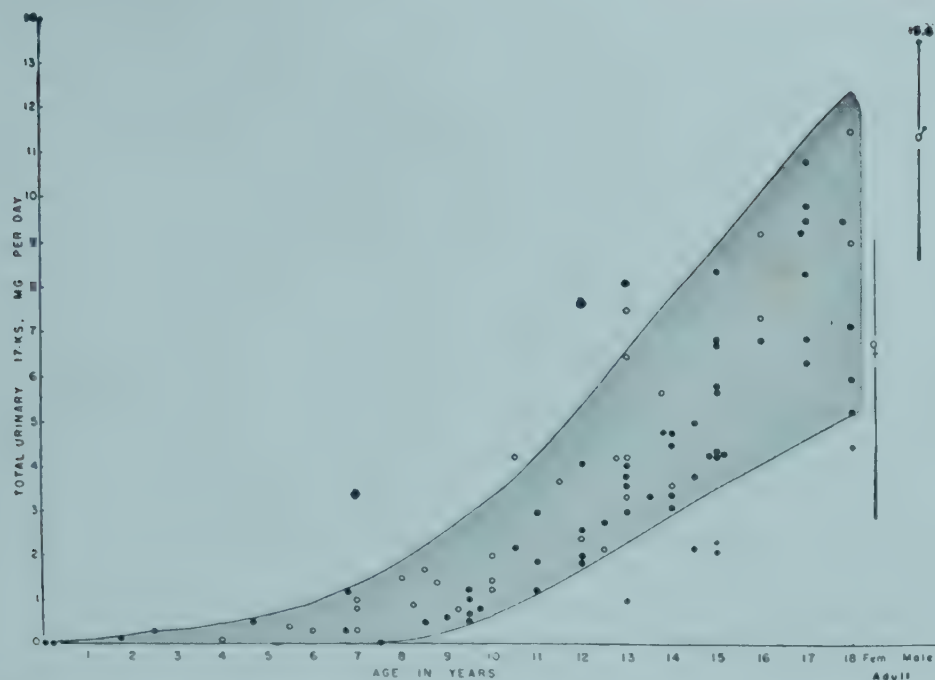


FIG. 347. Excretion of 17-ketosteroids in normal persons. The black dots indicate values for boys; the circles, for girls. (Talbot and others: *Am. J. Dis. Child.*, Vol. 65.)

age of eight years, but there is a decided rise between the ages of eight and eighteen years. There is no striking difference in the androgen excretion of boys and girls during childhood, but men show a higher excretion rate than women. The urinary 17-ketosteroids of the female are chiefly of adrenal origin; those of the male are of adrenal and testicular derivation. There are no great daily variations in rates of excretion.

The fact that boys and girls secrete about equal amounts of androgens and estrogens suggests that these hormones are not derived

from the gonads in early childhood. It seems more likely that they are derived, at least in part, from the adrenal cortex. The greater output of sex hormones at puberty parallels the development of the gonads and secondary sex characters so closely that it seems justified to attribute this increase to gonadal function. In various forms of hypogonadism urinary excretion of the sex hormones remains low. Under pathologic conditions high values of androgens and estrogens in the urine may be due to hyperfunction of the gonads or of the adrenal cortex.

## HYPOFUNCTION OF THE TESTES

Testicular hypofunction may be due to primary hypogonadism, to dysfunction of other glands of internal secretion (secondary hypogonadism) or to debilitating disease. After puberty, spermatozoa are formed in the seminiferous tubules of the testes. These organs may also be considered endocrine glands, since the interstitial cells of Leydig produce the male sex hormone, testosterone. These cells are also thought to be the source of estrogen elaborated by the human testis. The spermatogenic and endocrine functions of the testes are to some extent independent of each other. In the absence of spermatogenesis the interstitial cells may continue to function, and

the secondary sex organs and sex characters may remain intact.

### THE EUNUCHOID SYNDROMES

In the absence of the endocrine functions of the testes during puberty and subsequent years, the secondary sex characters fail to develop, resulting in the syndrome of eunuchism. Facial, pubic and axillary hair is scant or absent, and the voice remains high-pitched. The skin of the face becomes wrinkled and assumes a yellowish tinge. The face has a characteristic young-old appearance. There is neither acne nor recession of scalp hair. Fat accumulates in the region of the hips and

buttocks and sometimes also in the breasts and on the abdomen. The epiphysal spaces close late in life. The extremities become long. The span is several inches longer than the height, and the measurement from the symphysis pubis to the soles of the feet is much greater than that from the symphysis pubis to the vertex. These are "eunuchoid proportions." The penis remains small and may be almost obscured by pubic fat.

#### ABSENCE OR ATROPHY OF THE TESTES

The eunuchoid syndrome may be due to congenital absence of the testes (*anorchia*), traumatic or surgical castration, prenatal developmental errors or postnatal infections. In some of these cases the clinical picture may be complicated by associated malformations or defects which are not the result of gonadal hypofunction. This factor explains the great variety of syndromes in which retarded sexual development is a part of the clinical picture. Thus patients with multiple congenital anomalies, including webbed neck and cubitus valgus in association with hypoplasia of the testes, have been described. These patients generally are short in stature and do not have eunuchoid proportions, and the disorder is referred to as *Turner's syndrome*. Atrophy of the testes may follow unskillful manipulation during surgical procedures for correction of cryptorchidism. Signs of hypogonadism become apparent only when both testes are damaged. The eunuchism in these conditions is due to deficiency of androgen resulting from absence of Leydig cells. Testicular biopsies and determination of urinary gonadotropins are valuable diagnostic aids. These patients have excessive gonadotropin excretion because of the absence of inhibitory action of testicular hormone.

**Treatment.** Treatment with gonadotropic extracts is ineffective in primary hypogonadism. Substitution therapy with testosterone preparations must not be begun before puberty and not before the diagnosis of primary hypogonadism has been established. Otherwise, harm may be done to testes that are capable of development and function. Testosterone can be administered by intramuscular injection, orally or by implantation of crystalline pellets. Testosterone propionate is injected intramuscularly three times weekly in doses of 25 mg. until the desired genital growth is obtained. Thereafter the dose is reduced to maintenance levels of 10 mg. three times weekly. Methyl testosterone is used for

oral administration in doses of 20 to 50 mg. daily. Methyl testosterone or testosterone propionate in pellet form is recommended for subcutaneous implantation when prolonged and uniform therapy is attempted.

#### HYPOGONADOTROPIC EUNUCHOIDISM

In this condition there is a deficiency of FSH. This group may be subdivided according to etiology: (1) The deficiency may be secondary to organic lesions in or near the pituitary. Such patients usually show other signs and symptoms of pituitary deficiency, and the extent of testicular failure is roughly proportional to the completeness of the pituitary destruction. (2) More commonly the deficiency of gonadotropic function of the pituitary is a selective one not involving its other tropic hormones. There is no known cause for this disturbance, which is believed to be due to a congenital defect in the pituitary. Familial occurrence of this form of hypogonadism has been recorded. The term "idiopathic eunuchoidism with low FSH" has been applied to this group. In one series of eunuchoids it was estimated that 62 per cent of them fell into this category.

Testicular biopsy reveals typical *histologic changes*, consisting of small tubules without lumens, absence of germ cell proliferation, undifferentiated Sertoli cells and spermatogonia, but no well defined Leydig cells. The histologic picture is that of a prepuberal testis. These patients theoretically should have low levels of both FSH and ICSH. Some of them, however, may show spermatogenesis with deficiency of Leydig cells. It is believed that under such circumstances there is sufficient FSH to stimulate spermatogenesis, but the pituitary secretion of ICSH, which is essential for Leydig cell differentiation and function, is deficient.

Clinically, these patients present the classic stigmata of hypogonadism because of failure to produce androgenic hormone. It has been estimated that 20 to 25 per cent of these cases have cryptorchidism. Urinary assays of gonadotropins after puberty remain at low prepuberal levels.

*Replacement therapy* is indicated. Administration of ICSH in the form of chorionic gonadotropin induces a satisfactory development of secondary sex characters by stimulating the Leydig cells. Reports that spermatogenesis has followed this treatment seem to support the assumption that chorionic gonadotropin stimulates all elements of the



testis. Chorionic gonadotropin in oil and beeswax appears to remain effective longer than the aqueous solution.

Delayed sexual development resulting merely from physiologically slow maturation may be confused with this condition. If therapy is instituted and puberty initiated, it is difficult to assess the parts played by therapy and by endogenous hormones. If, however, the signs of puberty regress after therapy has been stopped, one can attribute the maturation to the gonadotropin injected.

#### KLINEFELTER SYNDROME

(SCLEROSING TUBULAR DEGENERATION, DEFECTIVE TESTES WITH TUBULAR FIBROSIS OR HYALINIZATION, TESTICULAR DYSGENESIS)

This syndrome consists of small testes but otherwise normal external genitals, azoospermia and elevated urinary gonadotropins. In some instances gynecomastia develops at or soon after puberty. Most patients with this disorder undergo normal pubertal changes and attain normal masculinization, but a variable degree of eunuchoidism may occur.

Laboratory studies after puberty show elevated urinary gonadotropin levels and normal or low 17-ketosteroid levels. Testicular biopsies reveal small tubules which are completely or almost completely hyalinized. Occasional tubules contain only Sertoli cells. Leydig cells of variable number and appearance are present.

The recent discovery that a large percentage of patients with Klinefelter's syndrome are chromosomal females came as a startling finding. Warren Nelson proposed the term "true" Klinefelter's syndrome for the chromo-

somal females and "false" Klinefelter's syndrome for the chromosomal males. He established certain histologic criteria by which it is possible to differentiate the two types of the disorder.

These findings have led to reconsideration of the pathogenesis of this disorder, which was formerly thought to begin at puberty. It is now clear that the "true" Klinefelter's syndrome begins early in fetal life. Gonads which should develop into ovaries form structures which appear to be testes, transforming the patient into an apparent male. The disorder may, therefore, be rightfully considered a type of female pseudohermaphroditism. Familial occurrence of the disorder has been reported.

The "false" Klinefelter syndrome, in which the affected person is a genetic male, perhaps may have been caused by a recognized or unrecognized orchitis, although other etiologic factors such as primordial degeneration of the germ cells cannot be ruled out.

These patients appear perfectly normal during childhood, but are detected at puberty because of the appearance of gynecomastia or because of the small size of the testes. The youngest child thus far reported with the syndrome was ten years of age. Determination of chromosomal sex in children with cryptorchidism or hypospadias or with a family history of the disorder could result in diagnosis prior to puberty.

There is no treatment for the gynecomastia or the infertility; gonadotropic hormones are not effective. In patients with some degree of eunuchoidism replacement therapy with androgenic hormone as outlined for patients with absence of the testes (p. 1196) is indicated.

### PSEUDOPRECOXITY RESULTING FROM TUMORS OF THE TESTES

Tumors of the testes which cause sexual pseudoprecocity are derived from the interstitial cells of Leydig. These cells are sparse before puberty, and tumors derived from them are rare. Only twenty-four cases in children have been reported since the first description of the entity in 1895. The interstitial cells are the source of the androgenic hormone which produces the secondary sex characters of the male.

The first changes, enlargement of the penis and development of pubic hair, are seen usually between the ages of four and six years. Later, but long before the usual age

of puberty, axillary and facial hair appears. Hypertrichosis of the chest and extremities may also be present. The boys grow rapidly; they gain in weight and appear muscular and strong. Roentgenograms reveal precocious osseous development. The voice becomes deep. The blood pressure is usually within normal limits. The tumor of the testis as well as the enlarged prostate gland can be palpated. Erections may occur, and the 17-ketosteroids in the urine may be slightly or markedly increased.

Treatment consists in surgical removal of the testis which contains the tumor. In one

instance the tumor was found in the tunica vaginalis completely separate from the testis. A partial disappearance of the signs of precocity has been observed in some patients. Progression of virilization always ceases after

the tumor has been removed. One instance of a bilateral tumor has been recorded, but there is reason to believe that this represented hyperplastic ectopic adrenal tissue. Leydig cell tumors are usually benign.

## GYNECOMASTIA

Gynecomastia, or unusual enlargement of mammary tissue in the male, occurs frequently in adolescent boys. Although the etiology is not definitely known, some of these boys have abnormally high urinary excretion of estrogens for brief periods of time. Spontaneous regression usually occurs within a few months, but the anomaly may persist for several years after puberal development has been completed. Occasionally the gynecomastia precedes other signs of puberal development, and it is not unusual for the two breasts to enlarge at disproportionate rates, at different times, or for only one breast to be involved. Tenderness of the breast is frequent but transitory. No hormonal treatment is necessary. Surgical removal of the breasts is indicated only if the enlargement is marked,

persists for several years and causes serious embarrassment to the patient.

Gynecomastia is also found in a number of pathologic conditions. It may be associated with testicular neoplasms such as interstitial cell tumors or with feminizing adrenal tumors, and in association with Klinefelter's syndrome (*q.v.*). It has also been reported in association with chorioepitheliomas, hepatic disease and paraplegia. Exposure to a surprisingly small amount of estrogens by inhalation, percutaneous absorption or ingestion may be a cause of breast development in prepuberal males; increased pigmentation of the nipple and areola should always suggest this etiology.

An increased amount of fat in the mammary region of obese children is common and is referred to as *pseudogynecomastia*.

## HYPOFUNCTION OF THE OVARIES

Hypofunction of the ovaries may be due to congenital failure of development or to postnatal destruction (primary hypogonadism) or to lack of stimulation by the pituitary (secondary hypogonadism). Many chronic diseases may result in this latter type.

### PRIMARY HYPOGONADISM

#### PREADOLESCENT CASTRATION

Surgical removal of both ovaries results in primary hypogonadism. Fortunately removal of one ovary for lesions such as tumors or torsion has no adverse effect on sexual development. Roentgen therapy over the pelvic area may result in permanent ovarian deficiency; pelvic exposure to 1300 roentgens has resulted in permanent castration of an infant of eighteen months of age.

The endocrine effects of preadolescent castration do not become manifest before puberty, when there is failure of sexual maturation. The external and internal genitalia remain infantile, the breasts do not develop, axillary and pubic hair is scanty, and there is no menarche. Such females grow tall, and the

span and lower measurements are relatively long. Epiphysial closure is delayed. Urinary estrogens are absent; gonadotropins are elevated, and the 17-ketosteroids are usually normal.

### GONADAL DYSGENESIS

(OVARIAN AGENESIS, TURNER'S SYNDROME, BONNEVIE-ULLRICH SYNDROME)

In 1938 Turner described a syndrome consisting of infantilism, webbed neck and cubitus valgus in females. It was subsequently demonstrated that these women had elevated levels of urinary gonadotropins and that the gonads consisted of rudimentary elongated ridges, appearing like whitish streaks. Histologically these gonads resemble ovarian stroma; for this reason the disorder was termed ovarian agenesis. In 1954 Wilkins and Polani demonstrated that a high percentage of the patients with this disorder are chromosomal males. Since the gonads in such instances are actually rudiments of testes, the term "gonadal dysgenesis" was suggested.



**Pathogenesis.** Jost and other workers have shown in animal experiments that functioning fetal testes are necessary for normal male differentiation and that in the absence of fetal testes the organism develops as a female. Castration of normal female fetuses, on the other hand, does not prevent normal female differentiation.

Patients with gonadal dysgenesis are analogous to animals castrated in the fetal stage. Damage to the testes early in fetal life permits persistence of müllerian duct derivatives and feminization of the fetus. This concept has been substantiated by the finding of testicular elements in the nondifferentiated gonads of some patients. Destruction of the fetal ovary does not interfere with female differentiation, so that patients with gonadal dysgenesis cannot be distinguished genetically as male or female by their physical characteristics, but only by their chromosomal sex pattern. Thus it is apparent that patients with Turner's syndrome and a male chromosomal pattern may be considered an extreme example of male pseudohermaphroditism, whereas patients with a female chromosomal pattern may be regarded as having "ovarian agenesis." When the testes are present in early fetal life and degenerate after sex differentiation is complete, anorchia results.



FIG. 348. A 10-day-old infant with enlarged clitoris and labioscrotal fusion who was erroneously considered to be a male. Chromosomal sex was female. A vagina was demonstrated by a vaginogram. Excretion of 17-ketosteroids was less than 0.5 mg. in 24 hours. Exploratory laparotomy and biopsy of both gonads revealed normal ovaries. The mother had received small doses of progesterone during pregnancy. The relation of this therapy to the genital abnormality is not clear.

**Clinical Manifestations.** Patients with this disorder do not develop sexually. The external genitals remain infantile, and the breasts do not develop. The uterus and cervix are small, and untreated patients remain amenorrheic. Growth in height is usually retarded. Though such patients are ordinarily less than 58 inches tall, they surpass in height most pituitary dwarfs. There is no explanation for the stunted growth, since ovarian hypofunction, per se, does not interfere with growth in stature.

Such patients frequently have other congenital defects. Webbed neck, coarctation of the aorta, cubitus valgus, eye defects, congenital lymphedema of the extremities and unexplained hypertension are some of the more common anomalies, but a wide variety of associated skeletal, cardiac and urinary tract anomalies have been reported. Some of the defects are sufficiently serious to be lethal in early infancy. Mental retardation seems to be more frequent than in the general population. If there is enlargement of the clitoris, one speaks of *gonadal dysgenesis with phallic enlargement*. The presence of nests of Leydig cells in the primitive gonads is thought to be responsible for the phallic enlargement.

**Laboratory Data.** The chromosomal sex pattern can be demonstrated in epithelial cells obtained by scraping the oral mucosa; it is male in approximately 80 per cent of persons with gonadal dysgenesis. In patients over ten to thirteen years of age urinary gonadotropins are elevated, but occasionally elevated values have been found in prepuberal children. Mild to moderate retardation of bone age and osteoporosis are common.

**Differential Diagnosis.** All female infants and children with growth failure, especially when associated with congenital anomalies, should be suspected of having gonadal dysgenesis. A male chromosomal sex pattern will establish the diagnosis. Those that show a female chromosomal pattern must be followed up through puberty before the diagnosis can be established, unless pterygium colli and other associated anomalies betray the nature of the disorder. Shortness of stature and sexual infantilism also occur in *pituitary dwarfism*, but pituitary dwarfs have a low rate of excretion or absence of urinary gonadotropins, whereas postpuberal patients with gonadal dysgenesis have elevated levels. This test, of course, is not applicable to prepuberal children. Pituitary dwarfs are much more retarded in growth than children with the syndrome of gonadal dysgenesis. Stocky

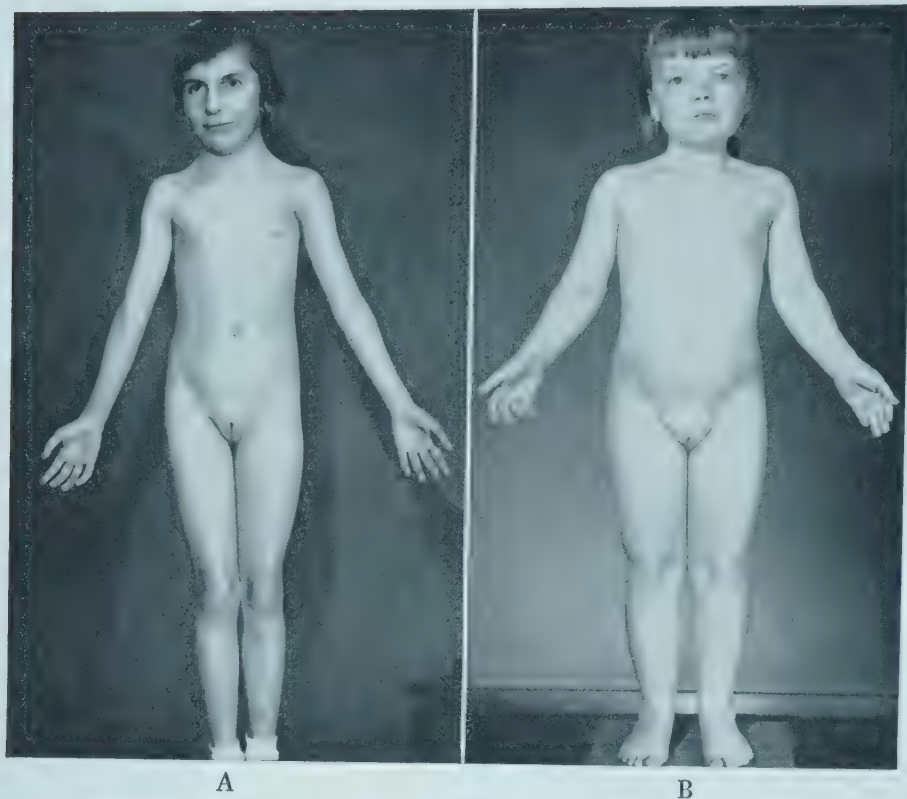


FIG. 349. A, A 9-year-old girl with webbed neck, mental retardation and pulmonic stenosis. She had a female chromosomal pattern and elevated gonadotropins. This girl can be considered to have true ovarian agenesis. B, A 14-year-old girl with height-age of an average child of 6 years. Note broad chest and hypoplastic nipples, cubitus valgus, absence of sexual maturation. Chromosomal sex is male.

body build with a broad shieldlike chest and an almost normal epiphysial development are characteristic of gonadal dysgenesis; gracile figure and delayed bone age, of pituitary dwarfism.

**Treatment.** Replacement therapy with estrogens is indicated for primary hypogonadism. This results in development and function of the secondary sex organs, which then simulate those of normal women. In the absence of ova and ovulation, however, reproduction is impossible, and the affected person remains sterile. Treatment may be started at twelve to fourteen years of age. For the first three to nine months 0.5 to 1.0 mg. of stilbestrol is given daily; this results in mammary development and pigmentation of the areola. The uterus grows to adult size, and the vaginal epithelium shows signs of maturation. When these changes are apparent, cyclic treatment is begun. The schedule of treatment recommended by Wilkins consists of 1 mg. of stilbestrol daily for three weeks. During the third week 10 to 30 mg. of anhydrohydroxyprogesterone is also administered daily by mouth. No treatment is given during the fourth week. Menstrual bleeding usually occurs after withdrawal of treatment. At present

there is nothing to be gained by telling the child or the parents of the chromosomal sex pattern if the child is genetically a male. In spite of the male chromosomal sex, the child should be reared as a female. With adequate replacement therapy such children can lead completely normal lives as females except that they are sterile and may be limited by associated congenital anomalies.

## SECONDARY HYPOGONADISM

Hypofunction of the ovaries which results from pituitary and thyroid deficiency can be recognized, as a rule, by associated symptoms. The differential diagnosis between pituitary dwarfism and the syndrome of gonadal dysgenesis has been discussed. It is difficult to distinguish primary hypogonadism from the clinical picture which develops in girls who have a selective deficiency of pituitary gonadotropin. Since such girls are not dwarfed, but tall, and since they have no great delay of ossification and have long extremities, they resemble clinically castrate girls with eunuchoid proportions. The pituitary origin of their sexual immaturity is revealed only by the absence of gonadotropic hormone in the



urine. This hormone is found in excess in primary hypogonadism. Absence of gonadotropic hormone has also been observed in a girl who resembled those with ovarian agenesis. This indicates that some patients with ovarian agenesis may have a coordinated pituitary defect.

In *treatment*, since there are no follicle-

stimulating and luteinizing hormones of pituitary origin available for substitution therapy, one must resort to symptomatic substitution therapy (see therapy of pituitary dwarfs, p. 1153).

Secondary hypogonadism due to thyroid deficiency can be treated successfully with thyroid extract (p. 1167).

## PSEUDOPRECOCITY DUE TO GRANULOSA CELL TUMORS OF THE OVARY

The dominant cell type in feminizing ovarian tumors in children is usually the granulosa cell. There is increasing evidence that histogenetically the granulosa cell and the theca cell are both derived from the ovarian mesenchyma (Novak). This explains the frequent finding of theca cells in granulosa cell tumors and granulosa cells in thecomas. Tumors consisting almost completely of theca cell elements are extremely rare in children.

In spite of variable morphology, granulosa cell tumors produce a similar clinical picture because they secrete estrogens. In the majority of instances they are unilateral and of low malignancy, so that recurrence after removal is infrequent.

As a rule enlargement of the abdomen is the first symptom, and a mass in the lower portion becomes palpable. This is followed by precocious development of isosexual (female) secondary sex characters. The breasts become enlarged, rounded and firm, and the nipples are prominent. Axillary and pubic hair appears. The external genitals resemble those of a normal girl at puberty, and the uterus is

enlarged. At first a white vaginal discharge, followed by irregular bleeding, is noticed. Finally, regular, cyclic menstruation is established. However, ovulation does not occur (pseudoprecocity). As a rule, growth is accelerated and osseous development advanced. Such tumors produce enormous amounts of estrogens, the urinary excretion of which may be increased several thousand times the usual rate. The urinary 17-ketosteroids are only moderately increased.

*Meigs' syndrome* of ascites and hydrothorax has been observed with this tumor in a nine-year-old child. The effusions disappeared after surgical removal of the tumor. Such manifestations should not be confused with metastases, and hence the primary tumor mistakenly considered inoperable.

The tumor should be removed as soon as the diagnosis has been established. The prognosis is good, since metastases are a late manifestation in children and recurrence is rare. Signs of precocious puberty may disappear within a few months after operation. The excretion of urinary estrogens returns to normal values.

## OTHER ENDOCRINE TUMORS OF THE OVARY

(See page 1358.)

### STEIN-LEVENTHAL SYNDROME

This syndrome consists of secondary amenorrhea, a male type of hirsutism, hypoplasia of the uterus and bilaterally enlarged polycystic ovaries. In married women the most frequent complaint is infertility. The disorder is most commonly found in women seventeen to

thirty years of age, but the diagnosis has been established as early as ten years of age. The diagnosis should be considered in adolescent girls with secondary amenorrhea and hirsutism. The enlarged ovaries can often be detected by combined rectal and abdominal palpation. Pneumoperitoneum utilizing carbon dioxide is useful diagnostically. Bilateral wedge resections of the ovaries are indicated.

## HERMAPHRODITISM (INTERSEXUALITY)

In recent years the scope of recognized intersexuality has been increased. In the past hermaphroditism implied a discrepancy between the morphology of the gonads and of the external genitals. Some ambiguity of the external genitals was usually expected. However, the ability to establish the chromosomal sex of the individual has revealed many instances in which it is inconsistent with the apparent sex or even with the gonadal sex. Some hermaphrodites have normal external genitals; only recently have they been recognized as examples of gonadal dysgenesis (p. 1197) or Klinefelter's syndrome.

### CHROMOSOMAL SEX

In 1950 Barr noted that it was possible to identify the sex of an animal by the morphology of the nuclei of the nerve cells of the brain. It was soon found that all somatic cells, including the circulating polymorphonuclear leukocytes, could be used for determination of sex. Identification of sex is based on a mass of sex chromatin in cell nuclei which is present in normal females and absent or insignificant in males. The sex chromatin is typically located on the inner surface of the nuclear membrane. Procedures have been developed for the study of chromosomal sex by fixation and staining of easily available cells such as those of the buccal mucosa or of the vagina. Chromosomal sex is determined at the moment of fertilization and is not influenced by hormones. Its recognition has made possible the diagnosis in early infancy of gonadal dysgenesis without an exploratory laparotomy.

### EMBRYONIC SEXUAL DIFFERENTIATION

In normal differentiation all sexual structures are consistent with the chromosomal sex. Intrauterine castration of rabbit fetuses by Jost showed that differentiation of most secondary characters is not under direct genetic control, but is influenced by secretions of the embryonic gonad. Absence of either ovaries or testes in the embryo results in regression of the wolffian (mesonephric) duct and in the development of the female secondary sex structures (müllerian duct derivatives and the external genitals). It is apparent that

normal male differentiation requires the presence of the fetal testis, whereas female differentiation does not require any gonad. Patients with gonadal dysgenesis who are chromosomal males, but have female external genitals and secondary sex structures, owe this discrepancy to absence of a normal fetal testis (*q.v.*).

One of the last phases of sex differentiation consists in the development of the external genitals. The male external genitals differ from the female in that there is fusion in the midline of the labioscrotal folds and greater development of the phallus. This phase of genital development can be affected, especially in the female, by excess of androgen. Labioscrotal fusion and enlargement of the phallus are seen in infants with adrenal hyperplasia. The increased amounts of androgens from the abnormal fetal adrenal cortex at the stage of external genital development give rise to this abnormality.

### FEMALE PSEUDOHERMAPHRODITISM

The most common disorder of sexual differentiation is female pseudohermaphroditism due to congenital adrenal hyperplasia. It affects female infants who have been masculinized as a result of increased androgenic steroid secretion by the fetal adrenal cortex (pp. 1187, 1188). *Female pseudohermaphroditism not associated with adrenal hyperplasia* has been considered rare. However, in recent years it appears that there has been an increase in this disorder attributable to administration of various steroids to women during pregnancy for the treatment of habitual or threatened abortion. One of the therapeutic agents administered during pregnancy with which the disorder has been repeatedly associated is 17-ethinyltestosterone (Pranone, Progesterol and Lutocylol). Since these substances are widely used, it remains to be explained why they are only occasionally associated with masculinization of the female fetus. Administration of androgens such as 17-methyltestosterone during the first trimester of pregnancy has been reported as the masculinizing agent in some instances. In one instance an arrhenoblastoma in the mother was the cause of female pseudohermaphroditism in her infant. In some instances the masculinizing factor cannot be



identified, an indication that a variety of unrecognized factors may be involved in the etiology.

The appearance of infants with female pseudohermaphroditism at birth is the same as that described for congenital adrenal hyperplasia on page 1187. The principal deviations are phallic enlargement and labioscrotal fusion. Occasionally the fusion is complete and a penile urethra is present. The chromosomal sex is always female. A urethrovaginogram or endoscopic examination reveals a cervix and a uterus. Normal urinary 17-ketosteroids distinguish the nonadrenal cases from those with adrenal hyperplasia.

**Diagnosis and Treatment.** These infants may resemble and be mistaken for cryptorchid, hypospadiac males. The diagnosis of cryptorchidism associated with hypospadias can be made with certainty only by exploration and biopsy of the gonads. Every effort should be made to establish the diagnosis in hermaphroditic infants during the neonatal period so that the child can be reared according to the proper sex. An elevated 17-ketosteroid level in association with the above-described genitals is diagnostic of adrenal hyperplasia. If the 17-ketosteroids are not increased, an exploratory laparotomy and gonadal biopsy are indicated. Irrespective of the external genitals, these infants should be reared as females. The treatment for infants with congenital adrenal hyperplasia is outlined on page 1189. Infants without adrenal hyperplasia require no treatment except for plastic procedures which are best performed between eighteen months and four years of age. When the diagnosis is established in infancy, and there is no attempt to change the adopted sex status after the age of eighteen months to two years, the prognosis is excellent. Female pseudohermaphrodites have a normal potential for fertility.

### MALE PSEUDOHERMAPHRODITISM

All patients in this group are chromosomal males. One type of male pseudohermaphroditism (gonadal dysgenesis) has been described (p. 1198). It may be regarded as the extreme form of male pseudohermaphroditism.

A second group consists of patients with normal female external genitals who are reared as women. The vagina ends blindly, and only rudimentary müllerian duct derivatives are present. At puberty there is normal development of the breasts. The gonads are

testes which consist largely of seminiferous tubules and are located intra-abdominally or in the inguinal canal. Prepuberal children with this disorder have usually been recognized because of inguinal masses which proved to be testes or because of an accidental finding of the testes during herniorrhaphy in apparent females. In adults the amenorrhea may be the only complaint. This disorder has a tendency to re-occur in families.

Psychosexual orientation of such persons is entirely feminine, although they are chromosomal males. The sex of rearing should always be female. It is usually recommended that the testes be removed and that replacement therapy with estrogens be given after puberty.

A third group of male hermaphrodites consists of those who have predominantly masculine or ambiguous external genitals. These persons may or may not have müllerian duct derivatives, and they do not develop breasts, but tend to masculinize at puberty. Sex of rearing has been both male and female. It is highly desirable that "sex" be assigned only after careful study of the patient. The principal determining factor should be the potential for surgical construction of the external genitals even though it may be contradictory to the gonadal or chromosomal sex. Structures contradictory with the "sex" of rearing should be removed. It is not advisable to reverse the sex of rearing of a child with hermaphroditism after the age of two years.

### TRUE HERMAPHRODITISM

True hermaphroditism is a condition in which both ovarian and testicular tissue is present in the same patient. Jones and Scott have accepted sixty cases as proved and divided them into six groups. The clinical features are not characteristic and include those described for all other types of hermaphroditism. The chromosomal sex may be male or female. Definitive diagnosis can be established only by biopsy of both gonads. True hermaphroditism must be considered in the differential diagnosis of all types of intersexuality except congenital adrenal hyperplasia. Treatment is the same as described for male pseudohermaphroditism.

ANGELO M. DiGEORGE  
JOSEF WARKANY

## REFERENCES

## General

- Jones, H. W., and Scott, W. W.: Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. Baltimore, Williams & Wilkins Company, 1958.
- Paschkis, K. E., Rakoff, A. E., and Cantarow, A.: Clinical Endocrinology. 2nd ed. New York, Paul B. Hoeber, Inc., 1958.
- Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. 2nd ed. Springfield, Ill., Charles C Thomas, 1957.

*Hypofunction of the Testis*

- Biben, R. L., and Gordan, G. S.: Familial Hypogonadotropic Eunuchoidism. *J. Clin. Endocrinol.*, 15:937, 1955.
- Bunge, R. G. and Bradbury, J. T.: A Sex-Chromatin Positive 10 Year Old Boy. *J. Urol.*, 78:775, 1957.
- Grumbach, M. M., Blanc, W. A., and Engle, E. T.: Sex Chromatin Pattern in Seminiferous Tubule Dysgenesis and Other Testicular Disorders: Relationship to True Hermaphroditism and to Klinefelter's Syndrome. *J. Clin. Endocrinol.* 17:703, 1957.
- Howard, R. P., Sniffen, R. C., Simmons, F. A., and Albright, F.: Testicular Deficiency: A Clinical and Pathologic Study. *J. Clin. Endocrinol.*, 10: 121, 1950.
- McCullagh, E. P.: Sex Hormone Deficiencies. Some Clinical Considerations. *Recent Prog. Hormone Res.*, 2:295, 1948.
- Nelson, W. O.: Sex Differences in Human Nuclei, with Particular Reference to the "Klinefelter Syndrome," Gonadal Agenesis and Other Types of Hermaphroditism. *Acta Endocrinol.*, 23:227, 1956.
- Sougin-Mibashan, R., and Jackson, W. P. U.: Turner's Syndrome in the Male. *Brit. M. J.*, 2:371, 1953.

*Pseudoprecocious Puberty Due to Tumor of the Testis*

- Dalgaard, J. B., and Hesselberg, F.: Interstitial Cell Tumours of the Testis. *Acta path. et microbiol. Scandinav.*, 41:219, 1957.
- Jolly, H.: Sexual Precocity. Springfield, Ill., Charles C Thomas, 1955.

*Gynecomastia*

- Green, M.: Gynecomastia and Pseudoprecocious Puberty Following Diethylstilbestrol Exposure. *A.M.A. Am. J. Dis. Child.*, 95:637, 1958.
- Steiner, M. M.: Enlargement of Breasts during Childhood. *Pediat. Clin. North Am.*, 2:575, 1955.
- Wheeler, C. E., Cawley, E. P., and Gray, H. T.: Gynecomastia: A Review and an Analysis of 160 Cases. *Ann. Int. Med.*, 40:985, 1954.

*Hypofunction of the Ovaries*

- Grumbach, M. M., Van Wyk, J. J., and Wilkins, L.: Chromosomal Sex in Gonadal Dysgenesis (Ovarian Agenesis): Relationship to Male Pseudohermaphroditism and Theories of Human Sex Differentiation. *J. Clin. Endocrinol.*, 15:1161, 1955.
- Hoffenberg, R., and Jackson, W. P. U.: Gonadal Dysgenesis: Modern Concepts. *Brit. M. J.*, 2: 1457, 1957.
- Portmann, U. V., and McCullagh, E. P.: Developmental Defects Following Irradiation of the Ovaries in a Child. *J.A.M.A.*, 151:736, 1953.

*Tumors of the Ovary*

- Costin, M. E., and Kennedy, R. L. J.: Ovarian Tumors in Infants and in Children. *A.M.A. Am. J. Dis. Child.*, 76:127, 1948.
- Knaus, W. E., Camps, J., and Rose, W.: Meigs' Syndrome: A Report of a Case in a Child. *J. Pediat.*, 43:88, 1953.
- Morris, J. McL., and Scully, R. E.: Endocrine Pathology of the Ovary. St. Louis, C. V. Mosby Company, 1958.

*Stein-Leventhal Syndrome*

- Stein, I. F.: The Stein-Leventhal Syndrome. *West. J. Surg.*, 63:319, 1955.

*Hermaphroditism*

- Barr, M. L.: Cytologic Tests of Chromosomal Sex. *Prog. in Gynecol.*, 3:131, 1957.
- Jost, A.: Embryonic Sexual Differentiation (Morphology, Physiology, Abnormalities); in Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. Baltimore, Williams & Wilkins Company, 1958, Chap. 2.
- Money, J., Hampson, J. G., and Hampson, J. L.: Hermaphroditism: Recommendations Concerning Assignment of Sex, Change of Sex, and Psychologic Management. *Bull. Johns Hopkins Hosp.*, 97:284, 1955.
- Rosenthal, I. M., Kiefer, J. H., McGrew, E., and Bronstein, I. P.: Unilateral True Hermaphroditism. Two Cases with Sex-Chromatin Positive Cellular Pattern. *Pediatrics*. 20:1006, 1957.
- Segal, S. J., and Nelson, W. O.: Developmental Aspects of Human Hermaphroditism: The Significance of Sex Patterns. *J. Clin. Endocrinol.*, 17: 676, 1957.
- Wilkins, L., Jones, H. W., Jr., Holman, G. H., and Stempfel, R. S., Jr.: Masculinization of the Female Fetus Associated with Administration of Progestins during Gestation: Non-adrenal Female Pseudohermaphroditism. *J. Clin. Endocrinol.*, 18: 559, 1958.
- Witschi, E., Nelson, W. O., and Segal, S. J.: Genetic Developmental and Hormonal Aspects of Gonadal Dysgenesis and Sex Inversion in Man. *J. Clin. Endocrinol.*, 17:737, 1957.



# Metabolic Disorders

## DIABETES MELLITUS

Diabetes mellitus is a disorder of carbohydrate metabolism characterized by hyperglycemia and glycosuria and associated with abnormal metabolism of fat and protein. In the untreated state there is loss of weight and the development of acidosis.

**Incidence.** The incidence of diabetes in childhood has been estimated to be from 5 to 8 per cent of all cases. There is no strong sex factor, although in some series there is a slight preponderance of females.

**Etiology.** Diabetes mellitus is a hereditary disease and in most instances appears to be transmitted as a recessive character. Evaluation of the genetic pattern is complicated by the variability in the clinical expression of the disease. This situation is pointed up by such factors as (1) the wide age range in which the disease may become manifest (infancy to old age), (2) the variability in clinical severity, some cases being clinically inapparent, perhaps at times indefinitely, and (3) the similarity of clinical patterns in newborn infants of diabetic mothers and prediabetic mothers. Diabetes occurs more frequently in both members of identical twins than in those who are not identical.

Whether certain factors may precipitate manifest disease in the potentially diabetic person is of some importance. It is thought that obesity may be such a factor in the adult, but there is no evidence that either overindulgence in eating or obesity is related to the onset of diabetes in childhood.

The relationship of endocrine glands other than the pancreas to the metabolism of carbohydrates is recognized but incompletely understood. Diabetes can be produced in the experimental animal by the appropriate injection of anterior pituitary extract, and diabetic-type glucose tolerance curves can be produced more often in persons of a diabetic kinship than in those of a nondiabetic one. Hyperglycemia is occasionally associated with such endocrine disturbances as acromegaly,

Cushing's syndrome, hyperthyroidism and pheochromocytomas. These disturbances of carbohydrate metabolism usually disappear if the endocrine disturbance is controlled.

Attempts have been made to incriminate infection as a cause of diabetes. The evidence does not support such a relationship; however, it does indicate that acute infection may be a frequent "trigger mechanism" activating a latent state of diabetes mellitus in children.

**Pathologic Physiology.** Diabetes mellitus is the manifestation of a deficiency of insulin. The metabolic pattern which evolves from this deficiency is far more complicated than simple interference in the utilization of sugar, and many aspects of the total disrupted metabolic pattern are not understood. What follows is merely an attempt to enumerate some of the metabolic defects which contribute to the clinical expressions of this disease.

Most significant is the fact that, when there is insufficient insulin or when its effect is inhibited, a sequence of events is set up which terminates in diabetic acidosis, coma and death. In the absence of an adequate supply of insulin there is (1) impaired glycogen formation in the liver and in the muscles, (2) increased glycogenolysis, and (3) deficient utilization of glucose by the peripheral tissues. As a result there is hyperglycemia, which, when it exceeds the renal threshold, is responsible for glycosuria. The diuresis initiated by the hyperglycemia accounts not only for the excretion of excess glucose, but also for excessive losses of electrolytes and water.

The loss of water and electrolytes is from both intracellular and extracellular compartments. The breakdown of tissue and the consequent freeing of potassium and phosphates result in abnormally high levels of these electrolytes in the blood at a time when the total body stores of them are being significantly depleted. The loss of body water results in hemoconcentration and dehydration, which in turn are responsible for de-

creased renal function. The shift of electrolytes from the intracellular to the extracellular spaces, the hemoconcentration and the renal dysfunction create a state of relative hyponatremia which, except as it is interpreted in the light of the altered physiology, may create a false impression of the body stores.

The tissue breakdown results in part from osmotic forces, in part from tissue catabolism secondary to the inability to use glucose for fuel. Both protein and fat are oxidized at abnormally rapid rates. The increased rate of breakdown of fat in the liver results in overproduction of ketones and in discharge of them into the blood at a rate exceeding the capacity of the peripheral tissues to oxidize them and of the kidneys to excrete them. Ketonuria may occur at blood levels which do not disturb the acid-base equilibrium, but the accumulation of ketone bodies in the blood of the uncontrolled diabetic does become sufficient to be a substantial factor in the development of acidosis. The other factors in the development of acidosis are dehydration, renal dysfunction secondary to anhydremia and loss of fixed base. Late contributory factors are loss of water through the hyperpnea caused by the acidosis and accumulation of lactic acid during cardiac failure.

The specific causes of coma are not apparent, but cerebral cellular activity is probably adversely affected by all the various metabolic derangements. Whether anoxia is a cause or merely an accompaniment is not known, but Kety's observation of diminished cerebral oxygen uptake during coma is one of the strong arguments in favor of the correction of excessively low pH levels early in the course of therapy of diabetic acidosis. Acidosis also inhibits restoration of the disrupted metabolism in the uncontrolled diabetic state in other ways. Guest and his co-workers showed that lowering of the pH and alkali reserve of the body fluids leads to hyperglycemia, hemoconcentration, losses of intracellular labile phosphates and potassium and inhibition of insulin action.

Thus in the uncontrolled diabetic patient there are severe losses of body water and electrolytes, depletion of fixed base, lowering of the plasma carbon dioxide content, a shift of the pH of the blood to the acid side and depletion of the glycogen stores in the liver and muscles.

Therapy, to be rational, must be directed toward restoration of metabolic equilibrium.

**Pathology.** The outstanding feature is the

lack of correlation between the pathologic changes and the severity of the diabetes. In some instances the changes are so slight that their significance is doubtful. There is at times diminution in the size of the pancreas, and a decrease in the number of the islands of Langerhans has been observed. The most characteristic lesion of the islands in children is lymphocytic infiltration, believed to be a response to a pre-existing injury rather than a primary change or cause. Hydropic degeneration may be present, but hyalinization, a common finding in adults whose diabetes was of long duration, is rare in children. Hepatomegaly is not an uncommon finding, and chemical studies reveal a depletion of glycogen. Histologic studies reveal little or no glycogen in the cytoplasm, but deposition of it in the nuclei. Arteriosclerosis and other degenerative changes occur with increasing frequency in young adults after fifteen years of clinical diabetes.

**Clinical Manifestations.** In general the symptoms of diabetes mellitus in children are similar to those in adults. The principal differences are that the onset is likely to be more rapid in children, and the diabetic child at the time of onset is more likely to be underweight in contrast to the frequency of obesity in adults. The chief symptoms are wasting, increased thirst and appetite and polyuria. The symptoms are somewhat more variable than in adults, and not infrequently the onset is so rapid that none of them has been noticed, or their existence is brought out only by leading questions. The child may be brought for medical attention because he has failed to gain weight in spite of a voracious appetite. One of the more frequent evidences of polyuria is bedwetting in a previously trained child. In untreated and long-standing cases dryness of the skin and pruritus are not uncommon, and there may be hypertrichosis. In infants and small children the hair on the body has a soft texture not unlike that of lanugo. Skin infections are common, but the converse—a high incidence of diabetes in association with chronic infections of the skin—is not the case. Intertrigo and secondary skin infections are particularly common about the genital region in small children.

The presenting symptoms are often those of coma or stupor (diabetic acidosis), particularly when there is an existing acute infection or if there has been a recent one. In the precomatose state there is drowsiness, dryness of the skin, flushed cheeks, cherry-red lips, acetone breath, hyperpnea, nausea



and vomiting, abdominal pain and often general body pains. In complete coma the hyperpnea becomes greater (Kussmaul breathing), the eyeballs are soft and sunken, the abdomen is rigid, the pulse is rapid and weak, and the temperature and blood pressure are subnormal.

**Chemical Changes.** The characteristic changes in the nonacidotic state consist in glycosuria, with or without ketonuria, and hyperglycemia. The absence of a fasting hyperglycemia does not rule out the possibility of diabetes mellitus. In rare instances the fasting blood sugar of an infant or young child who has only recently acquired diabetes may not be above the normal level, and a glucose tolerance test will be required to establish the diagnosis. Ketonuria may exist without measurable disturbance of the acid-base equilibrium, and there is no consistent relation between the degree of hyperglycemia and the absence or presence of ketonuria or its degree. Blood sugar levels as high as 800 to 1000 mg. per 100 ml. have been observed without an associated ketonuria in children who have eaten large amounts of carbohydrate. The blood cholesterol and lipid levels may be elevated in untreated diabetics; there does not appear to be a relationship with the duration or the severity of the disease.

With the development of acidosis there is a lowering of the carbon dioxide content of the blood, and a shift of the pH to the acid side. There is often an elevation of the non-protein nitrogen. Albumin and casts are frequently present in the urine at such times, but disappear when the acidosis is corrected.

**Diagnosis.** Children in whom the diagnosis of diabetes mellitus must be considered may be divided into three general categories: (1) those who have a history suggestive of diabetes; (2) those who have a transient or persistent glycosuria; and (3) those who have clinical manifestations of acidosis with or without stupor or coma. In all instances the diagnosis depends upon laboratory data. Glycosuria associated with a fasting hyperglycemia is for practical purposes diagnostic of diabetes mellitus. However, it is necessary to eliminate the rare possibilities of Cushing's syndrome, hyperthyroidism and pheochromocytoma. Transitory glycosuria may be the result of emotional disturbances, of overeating (alimentary glycosuria), of acute infections, of cerebral injuries, of lead poisoning and of the ingestion of certain drugs. Salicylates may be responsible for a reduction of Benedict's solution which may simulate that by sugar.

Renal glycosuria is the result of a lowered renal threshold for sugar, but there is no hyperglycemia, and the glucose tolerance curve is either within or below the usual range. The level of the renal threshold for sugar can be established by the sugar clearance test. It is important to bear in mind that not all urinary sugar is glucose, and steps should be taken to ensure that the unusual instances of pentosuria and galactosemia are not diagnosed as diabetes mellitus.

Whenever sugar is detected in the urine, a blood sugar determination should be obtained. If there is only a small amount of sugar in the urine, a fasting blood level may be obtained the following morning. If, however, there is considerable urinary sugar and/or if acetone is also present, a blood sugar determination should be obtained immediately. If the blood sugar is more than 200 mg. per 100 ml., a tentative diagnosis of diabetes mellitus is justified; if it is under this level, a fasting specimen of blood should be obtained the following morning; if the level is then within the normal range, a glucose tolerance test should be performed. The glucose tolerance test should be reserved for questionable cases; fasting and postprandial blood sugars will usually serve both for diagnosis and for evaluation of treatment.

**Diabetic acidosis** with or without coma must be differentiated from acidosis and/or coma resulting from other causes, such as hypoglycemia, uremia, gastroenteritis, lead poisoning, salicylate poisoning, encephalitis, cerebral hemorrhage and other intracranial lesions. The symptoms previously described aid in differentiation, but the diagnosis must be based on laboratory analyses. Abdominal pain, tenderness, muscular rigidity, vomiting and leukocytosis are commonly present in diabetic acidosis. Though it is possible that acute appendicitis or other intra-abdominal infection may be the inciting cause of diabetic acidosis, it should be recognized that the differential diagnosis cannot be made until the symptoms of acidosis have been relieved. High white blood cell counts may exist in association with diabetic acidosis, and do not in themselves indicate an infection.

**Complications.** Except in cases of long duration or in inadequately treated ones, complications are uncommon. Gangrene is a rare complication, but has been observed even in newborn infants. Stunting of growth, lack of development, failure to develop secondary sexual characteristics, and amenorrhea are seen in children whose diabetes has been un-

controlled over long periods of time. Hepatomegaly, though not a frequent complication, apparently occurs more often in inadequately treated children than in adults. Cataracts may occur at any age, but their incidence increases with duration of the disease; arteriosclerosis is seen with frequency only after the disease has existed for ten to fifteen years. Xanthomatous deposits in the skin occur occasionally in uncontrolled diabetes in association with hyperlipemia. *Necrobiosis lipoidica diabetorum* is an uncommon cutaneous lesion characterized by elevated red papules 1 to 3 mm. in diameter, which eventually develop a yellowish tint. Carotenemia with resultant discoloration of the skin is more frequent in diabetics than in nondiabetics, and apparently is a reflection of hepatic dysfunction in the conversion of the provitamin A, carotene, to vitamin A. In poorly treated diabetic children infections not only are common, but also show less tendency to heal; among the more frequent are dental caries, infections of the respiratory and lower urinary tracts, skin infections and tuberculosis.

Complications associated with the injection of insulin are lipodystrophy (atrophy of the subcutaneous fat), lipomatosis (a lipoma-like swelling) and allergy to insulin. Lipomatosis and possibly also lipodystrophy are the results of repeated injections of insulin into the same area, and perhaps of too superficial injection.

**Course and Prognosis.** Prior to the introduction of insulin in 1922 the life expectancy of diabetic children was only about two years after the onset of the disease. What the expectancy is for the insulin-treated patient is not known, but in recent years the outlook has become less bright than it seemed in the earlier years of the "insulin era." The reason for this apparent change is based primarily upon the relative frequency with which serious degenerative lesions are appearing in young adults who have had diabetes for ten to twenty years. These complications consist principally in arteriosclerosis with hypertension, retinal and lenticular changes and nephropathy, the characteristic lesion being intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome). The incidence of complications in persons who have had diabetes for twenty years or more is as high as 85 per cent in a large series (White). The high incidence of vascular degenerative disease constitutes the most important problem in juvenile diabetes. There are those who are inclined to the view that these complications

are manifestations of a phase of diabetes which is not affected by presently available therapy. Some attach causal significance to deviations in clinical control sufficient to result in high blood cholesterol levels and frequent episodes of ketosis and acidosis. There is less agreement about the significance of hyperglycemia, per se, or of adherence to a prescribed diet.

Physical growth and development are related to control of the diabetes. To what extent they are related to a degree of control which approximates normoglycemia is not known. Beal's data on a group of children whose diabetic control was probably well above average show a slight delay in growth in stature, but a tendency to approximate average adult heights after a somewhat prolonged growth period. Some diabetic children whose disease is kept under adequate control are small in stature and continue to remain well below the average physical development of their age group. In such instances deficiency of other endocrine glands has been postulated but not established.

The so-called *Mauriac syndrome*, the underlying problems of which are not understood, consists of dwarfism, hepatomegaly and obesity in association with diabetes mellitus.

Comparatively little difficulty is encountered in management of the average pre-adolescent diabetic child, provided both the child and his family are properly instructed in the technique of diabetic care and assisted in making the necessary psychologic adjustments. The adolescent child, however, has a natural inclination to rebel against authority and restraint, which is often reflected in breaks in diabetic control. At such times both the physician and the parents must take care that they do not lose the confidence and cooperation of the child.

**Treatment.** The aims of treatment are restoration of the diabetic child to average physical status and health, and subsequent maintenance of them. Control of the metabolic aspects of diabetes is merely a means to an end. The child who is not physically and socially able to compete with his colleagues cannot be considered an adequately treated diabetic child.

The essentials of treatment are (1) insulin in an amount adequate to maintain or approximate glycemic equilibrium; (2) a diet adequate for normal growth and activity and sufficient to satisfy the child's appetite; (3) instruction of the child and his parents in the ordinary routine care of diabetes so that



may be satisfactorily managed in the home; and (4) acceptance on the part of the child and his family that he is a "normal" healthy person able to compete with children of his own age.

Treatment may be divided into four phases, depending upon the state of control of the diabetes at the moment: (1) acidosis; (2) postacidotic stage; (3) establishment of glycemie equilibrium; and (4) supervision of the controlled diabetic child.

**Diabetic acidosis.** Diabetic acidosis is a medical emergency requiring constant attention and teamwork among doctor, nurse and laboratory. Recovery from diabetic acidosis is directly related to its duration, its degree, and the state of consciousness of the patient on the one hand and of the quantitative aspects of treatment on the other. When it is not known that the patient is diabetic, the diagnosis can be established only by laboratory means. A sample of blood should be taken immediately for determinations of the blood sugar level and the carbon dioxide-combining power or content, and a specimen of urine should be obtained, by catheterization if necessary, for examination for sugar and acetone.

A plan of fluid and insulin therapy is detailed on page 189. The plan of therapy in our clinic differs in only one feature. For the patient who is in a severe state of acidosis (pH less than 7.1; carbon dioxide less than 6 mEq. per liter) we administer sodium bicarbonate after the initial expansion of the vascular volume with saline solution. This policy is based on clinical experience and on the physiologic considerations stated previously. In comparative observations in children and in animals recovery as based on return of consciousness and ability to take and retain oral feedings has been more rapid when bicarbonate was administered early in therapy. Further, we have not observed any untoward results from such therapy. It should be clearly understood that only enough bicarbonate is given to raise the carbon dioxide level to 10 to 12 mEq. per liter (p. 191).

Potassium is administered relatively early as indicated on page 189. Our usual practice is to add potassium chloride to the glucose-saline solution being administered intravenously in an amount so that its concentration does not exceed 0.15 per cent rather than administering it as a separate solution subcutaneously. This latter method may have advantages.

*Gastric lavage* is invariably beneficial in

the acidotic patient. It will not only avert subsequent vomiting in the majority of instances, but will also shorten the time until fluids and foods can be taken by mouth. After the stomach has been thoroughly emptied of its contents, which often contain digested blood, several grams of sodium bicarbonate in solution may be introduced. The lavage may be delayed until after the parenteral fluid therapy has been started.

**Postacidotic stage.** Parenteral fluid therapy can usually be terminated in less than twenty-four hours. For the next twenty-four to forty-eight hours the child will require special attention. As soon as he is ready to take fluids by mouth, sips of water or chilled ginger ale may be given for a few hours or until it is evident that vomiting or gastric distention is not likely to occur. A soft or liquid diet consisting chiefly of carbohydrate may then be started and given to the child at approximately three-hour intervals during the day hours. Such foods as fruits, fruit juices, skimmed milk, fat-free ice cream, and gelatin desserts are taken well. The insulin dosage during this time is entirely empiric and is based on urine analyses for sugar. It is best to give small doses of regular insulin at frequent intervals rather than large doses at infrequent intervals. Careful check should be maintained at this time to avoid insulin shock or the return to hyperglycemia. After a day or two on this regimen the child should be ready for an average diet.

**Establishment of glycemie equilibrium.** The suggestions made here are also applicable to the child who has not been in acidosis, but is not in satisfactory diabetic control. There are no hard and fast rules, and each child must be regarded as an individual problem for whom a satisfactory diet must be arranged and the insulin dosage determined. No attempt should be made to avoid the use of insulin. Rarely after the initial period of stabilization, insulin may be dispensed with for a time, but in such instances the patient and his parents should be advised that insulin will be required again within a comparatively short time.

**Diet.** There has been a gradual transition in types of diets prescribed for diabetic children. The prescription of low carbohydrate diets has for practical purposes ceased, and the tendency now is to provide a diet which approximates that of the average child and conforms to the family's dietary pattern. Principal differences exist now in whether the diet is measured or is unrestricted ("free

diet"). The so-called free diet is usually restricted to the extent that the children and their parents are cautioned against dietary excesses, especially of "sweets" and food-stuffs of high carbohydrate content. There is no doubt that one of the essentials in the management of the diabetic child is complete acceptance of the disease and its management without the sense of undue restriction or of being "different" from other children. Such an ideal situation is usually not attained; if the use of the "free diet" could be the determining factor in attaining it, its use would be justified. In our experience, however, we have felt that most often both child and parent felt more secure and profited initially from a guided dietary program.

It is our practice to prescribe the initial diet for the child while he is in the hospital. After the first week or so of the insulin adjustment period the child is consulted about his satisfaction with his diet and requested to participate in planning his "home diet" both qualitatively and quantitatively. The method devised by Stare is used, and the child and his mother are given a copy of the "Exchange Lists" (p. 1409). They should know that the diet is not a rigid one, that gross household measures are adequate, and that occasional quantitative deviations are of no great consequence. Though the diet is not an entirely unrestricted one, it can be a self-determined one. The goals of such a plan are (1) to ensure a qualitatively satisfactory intake; (2) to secure an adequate distribution of caloric intake at the various meals; and (3) to teach the child by experience the "self-serving" of meals at a later age. The essentials of an adequate diet are (1) sufficient caloric value for activity and growth; (2) a protein intake not less than 1.5 gm. per pound of body weight for children under three years of age, and 1 gm. per pound for older children; (3) 40 to 50 per cent of the calories as carbohydrate; (4) optimal intake of vitamins and minerals; and (5) participation of the diet by the entire family.

A reasonable distribution of calories can be obtained by the use of one of the following formulas:

	Carbohydrate		Protein		Fat		Cal./Kg.	Cal./Lb.
	Kg.	Lb.	Kg.	Lb.	Kg.	Lb.		
Grams per								
unit of	9	4	3	1.5	2.5	1.5	70	35
body	9	4	2	1.0	2.5	1.5	66	33
weight	7	3.5	3	1.5	2.0	1.0	58	29
	7	3	2	1.0	2.0	1.0	54	25

See page 100 for average caloric requirements at different age levels.

"Stabilization" should be carried out, if at all possible, while the patient is normally active. Even in the hospital the child may be permitted considerable activity. The initial diet should subsequently be adjusted on the basis of the appetite and the growth response (as indicated by the weight curve). If growth is normal and appetite is satisfied, the diet remains as planned; if growth is not proceeding and appetite is not satisfied, the diet is increased; if there is no gain in weight, but the appetite is satisfied, more food is prescribed and more concentrated foods are substituted for relatively bulky ones; or, if the patient is gaining, but the appetite is not satisfied, the bulk of the diet is increased without increasing the caloric value. There is no need to use commercial diabetic foods.

**Insulin.** Insulin is the sine qua non of diabetic therapy. No juvenile diabetic can be treated without it. The principal question is the degree of control of hyperglycemia which is attempted. A few clinicians believe that, except as hyperglycemia is sufficient to cause excess diuresis, it is not harmful; otherwise their only concern is ketosis. Others hold that a reasonable attempt should be made to achieve a normoglycemic status; we subscribe to this goal, but only so far as it can be attained without the occurrence of hypoglycemic attacks, other than as rare occurrences, and without too great dietary rigidity. Practically all children excrete small amounts of sugar daily on this plan.

The sulfonylureas, as orally administered hypoglycemic agents, are being widely used as substitutes for insulin in adults with mild diabetes. To date it is the consensus that they do not provide a reliable replacement for insulin in the treatment of juvenile diabetes. However, the possibility that effective usage of available agents or that more effective ones will be found justifies continued clinical investigation in this aspect of diabetic control.

There are now available at least five different forms of insulin: (1) regular or unmodified insulin; (2) protamine zinc insulin; (3) NPH insulin; (4) globin insulin; and (5) Lente insulin. The effect of unmodified insulin upon the blood sugar is apparent within twenty or thirty minutes after injection and is maintained for six to eight



hours. The effect of protamine insulin is apparent within an hour or so, but its full effect is delayed for about three hours after injection; if sufficiently large doses are injected, its effect may be prolonged for twenty-four hours or more. The actions of Lente, NPH and globin insulins are somewhat between these two: The initial effect is delayed beyond that of unmodified insulin, but is more rapid than that of protamine, and the effect is maintained for a longer period than that of unmodified insulin, but for a shorter period than that of protamine.

However, if sufficient Lente or NPH insulin is administered as the prebreakfast dose, an effect can be secured for twenty-four hours or so. In this respect they are similar to protamine zinc insulin. They have the added advantage that their quicker action will, in many cases, provide sufficient insulin action to avoid significant glycosuria during the day hours, and still maintain nocturnal control without hypoglycemia. More often, however, unmodified insulin will have to be administered along with Lente or NPH insulin to avoid significant diurnal glycosuria if diurnal control without insulin shock is desired. The majority of our diabetic children receive a combination of Lente and unmodified insulin. One of the advantages of Lente and NPH insulin over protamine zinc insulin is that regular insulin can be included in the same syringe without being altered; it thus behaves as if it were a separate injection. Lente insulin contains no protamine, so that the slight possibility of induced allergy to it is eliminated. For infants and children up to four or five years of age unmodified insulin for the prebreakfast and prelunch injections and Lente insulin for the evening injection are preferable.

The insulin dose is estimated from qualitative tests of the urine for sugar. Specimens of urine should be collected four times a day: (1) before breakfast (7 to 8 A.M.), (2) before the noon meal (11:30 A.M. to 12 noon), (3) before the evening meal (5 to 6 P.M.), and (4) before retiring (7 to 9 P.M.). The results of analyses of these specimens will be of greater aid in estimating insulin dosage if the child voids (discarding the specimen) from one-half to one hour before each of the three latter specimens is obtained.

After the first day or two of the postacidotic stage as described above, an average diet is provided, and unmodified (regular) insulin is given before each meal. Individual doses

are usually in the range of 10 to 15 units; estimates can be made from the experience of the preceding days, and adjustments made daily on the basis of the qualitative urine test for sugar in specimens voided about three hours after each meal, as noted above. After two days or so a reasonable estimate of the total daily dose of insulin which is sufficient to effect a reduction in the urinary sugar without causing insulin shock can be made. At this time one may initiate the permanent plan for insulin therapy. It is our practice to give about 75 per cent of the previous day's total dose of insulin as Lente insulin and the remainder as unmodified insulin before breakfast. Subsequent adjustments of the dose of each insulin are made on the basis of the presence or absence of sugar in the urine and/or by the occurrence of insulin shock: The dose of Lente insulin is adjusted so that the urine of the following morning contains little or no sugar and so that the child does not have insulin shock during the night or prebreakfast hours. The dose of the unmodified insulin is estimated on the basis of the urinalyses preceding the noon and evening meals and/or the occurrence of insulin shocks during this portion of the day. Under such a plan an attempt is made to secure an average blood sugar level the following morning and urine tests at noon and in the afternoon which indicate only small amounts of glycosuria. Occasionally, satisfactory glycemic equilibrium is obtained with only Lente insulin, but most often unmodified insulin will also have to be continued in the prebreakfast injection. Rarely is an additional dose of unmodified insulin given before the evening meal to avoid glycosuria during the evening hours. If there is only a transitory spilling of sugar after the evening meal and if, on the following morning, the blood sugar level is within the normal range or the urine does not show sugar, there does not appear to be any need for injection of insulin before the evening meal.

The urine can be made essentially sugar-free within about a week by this regimen. In the majority of instances, however, the dose of insulin at this stage does not represent the child's maintenance dose. During the next three to six weeks it will usually have to be decreased. The need for decreasing it is determined on the basis of blood sugar levels below the normal range or by hypoglycemic shock. A general metabolic adjustment appears to take place gradually, and there is no known

way to shorten this period. There are distinct advantages in keeping the child hospitalized but not inactive for at least the first two or three weeks of the initial adjustment period. The latter part of this period can then be managed in the child's home, provided instruction of the patient and his family has been adequate and careful records of urine analyses for sugar will be kept.

Insulin should be administered subcutaneously, care being taken that it is not injected too near the skin. Definite instruction should be given for changing the site of injection: e.g., successively into the right upper arm, the left upper arm, the left thigh, the right thigh. Each extremity may be used for several weeks without making two injections into the same site, provided a systematic plan is followed. Thus, starting at the inner and upper corner of an area to be used, each succeeding injection is made  $\frac{1}{2}$  inch below the preceding one, and when each vertical line is complete, the site selected is moved outward  $\frac{1}{2}$  inch at the upper level, and injections then proceed downward in a similar vertical manner. Other sites which may be used are the upper part of the buttocks, the back and the abdomen. If signs of induration appear at the sites of injection, these areas should be carefully avoided for several weeks after all evidences of local irritation have disappeared. In case of allergic reactions to insulin, the commercial brand or the type of insulin should be changed. Patients receiving insulin should bathe at least every other day, and sterile technique should be practiced in preparing the needle, syringes, bottle caps and the skin at the site of the injection.

*Among the factors which vary the need for, or utilization of, insulin are diet, physical activity, infection and, to a less extent, growth.* No definite rule can be stated about the possible need for increased insulin with increase in diet or body weight. Many children require gradual increases in insulin dosage up to puberty, and then often further but temporary increases during early adolescence, whereas others do not. Increased dietary intake usually does not require proportionate increase of insulin dosage, often none at all.

Exercise tends to lower the blood sugar level of children receiving otherwise adequate amounts of insulin and may thus initiate insulin shock. Diabetic children should, however, be encouraged to be normally active; so far as possible, exercise should be regulated in quantity and time so that allowance may

be made for it in the adjustment of insulin dosage. The child should be instructed to carry sugar with him at all times and to take it whenever the first symptoms of shock are noted. When it is known that there is to be an increase in physical activity, the dose of insulin for that day can be reduced by an amount determined by experience to be satisfactory.

Infection increases the requirement for insulin and is the most potent factor in initiating acidosis. During mild infections, such as those of the upper respiratory tract, the only treatment required for the diabetic condition is sufficient extra insulin to prevent glycosuria. In more severe infections the fat should be decreased in the diet, extra carbohydrate should be administered if the child's appetite requires it, and additional insulin should be injected as needed. An adequate plan for adjustment of insulin dosage during infection in children receiving a combination of Lente and unmodified insulins is to maintain the quantity of Lente insulin at the previous dose and to add extra unmodified insulin at breakfast, lunch and dinner in amounts estimated from the results of Benedict's test of the urine. It is important to bear in mind that the dose of insulin must be reduced again during convalescence.

*Insulin shock* may result from an overdose of insulin, from reduction in diet or from increase in exercise without a corresponding reduction in insulin. Early symptoms are sudden hunger, weakness, restlessness and nervousness, pallor, sweating, and dilated pupils; if carbohydrate is not administered, there will occur tremor, vertigo, unconsciousness, convulsions and in rare instances even death. In shock from overdose of protamine insulin and to a less extent of Lente and NPH the onset is less abrupt, and the reactions usually, but not always, less severe. Vomiting during and after shock from the long-acting insulins may occur, but it practically never occurs in shock from unmodified insulin. The slower onset of shock from the long-acting insulins, together with the vomiting, may lead to an incorrect diagnosis of diabetic acidosis.

The time of occurrence of hypoglycemic shock after injection of insulin may aid in the differential diagnosis of shock from coma. Shock from unmodified insulin occurs usually three to eight hours after injection, that from Lente, NPH and protamine insulins usually eight to twenty-four hours after injection. If,



however, it is not clear whether unconsciousness is the result of hypoglycemia or diabetic acidosis, 20 to 10 ml. of 20 to 50 per cent glucose should be injected intravenously. If unconsciousness is the result of hypoglycemia, consciousness will be quickly restored, and no harm will be done by the injection of glucose if the child is in diabetic acidosis. The emotional response of the diabetic child to insulin shock usually tends to follow a stereotyped pattern characteristic of the individual. The variations in response are somewhat similar to those of different persons to alcoholic intoxication. Thus one child may become despondent and cry readily, whereas another one is exuberant and even hilarious, and an occasional child becomes belligerent.

Insulin shock is, under ordinary circumstances, such a transient affair, and the disappearance of symptoms is so complete, that there is often failure to recognize that it may have serious consequences. When insulin shock of an extreme degree is allowed to persist, there may be cerebral damage responsible for permanent motor defects, mental deficiency and even death.

**Supervision of the diabetic child.** Diabetic children can be normally healthy and active, and it is the physician's responsibility to assist the child and his family in making an adequate psychologic adjustment. Instruction in the daily care should be given to the patient and his family so that they can be essentially independent of the physician for the ordinary care of diabetes. These instructions should include (1) construction of a diabetic diet and especially variation of menus to avoid monotony; (2) administration of insulin and minor adjustments in dosage which are required by changes in activity and even minor infections; (3) examination of the urine for sugar; (4) the keeping of daily records; (5) the need for personal cleanliness; (6) recognition of early signs of shock and method of treatment; and (7) recognition of early signs of acidosis and of the need for immediate medical assistance. The diabetic child should assume his share of family responsibilities and compete on an equal basis with his schoolmates. He should not look upon his diabetes as a handicap or as a reason for asking for quarter.

Unfortunately a truly adequate psychologic adjustment by the child and his family is frequently not attained. In some instances this is largely due to the physician, owing to his failure to provide early guidance and particularly to his failure to permit the child and

his parents to achieve a sense of sufficiency for the ordinary management of the diabetes. The daily management can become as routine as other features of personal hygiene. No attempt should be made to hide the fact that the child has diabetes; on the other hand, it should not be used as a "crutch" or defense mechanism. The child should be permitted and encouraged to develop his natural talents, but the *sense of direction* should exist in him. The differences in the attitudes and adjustments of diabetic children in various clinics attest to the importance of guidance by medical and ancillary personnel—or in certain respects, perhaps, to lack of it.

During adolescence the problems of the diabetic child are likely to be accentuated. Rebellion at the regularity of insulin injections may result in lapses of medication and hence acidosis, or rebellion may be expressed in other ways, such as aggressiveness or withdrawal and even delinquency. Parents and doctors require a fine understanding, and above all they must have the confidence of the child if he is to be brought to maturity adequately adjusted to compete on an equal basis with his peers.

### THE DIABETES MELLITUS SYNDROME IN THE NEWBORN INFANT

A few instances of a transient state of diabetes mellitus developing in the newborn period, persisting for weeks or months and terminating apparently in complete recovery, have been reported. Clinically, the syndrome fulfills the diagnostic requirements, viz., hyperglycemia, glycosuria and clinical control with exogenous insulin. The only minor variant is the absence of marked ketonuria; in the infant reported by Arey there was none, and in the one observed in our clinic only small amounts of acetone on isolated occasions. This response, however, is in keeping with Heymann's observation that the production of ketones in very young infants is much less than in older infants and children. Infection has not seemed to be an important instigating factor. The management is that of diabetes mellitus, but extreme care must be taken to avoid hypoglycemia and to determine when administration of insulin is no longer required. By contrast with the true disease, complete recovery occurs and, so far as is known, is permanent.

True diabetes mellitus is also rare in newborn infants, but it does occur. Differentiation from the transient state can be made only

after sufficient time has elapsed to determine whether the diabetic state is permanent.

WALDO E. NELSON

## REFERENCES

- Arey, S. L.: Transient Diabetes in Infancy. *Pediatrics*, 11:140, 1953.
- Beal, C. K.: Body Size and Growth Rate of Children with Diabetes Mellitus. *J. Pediat.*, 32:170, 1948.
- Behrer, M. R., Goldring, D., and Hartmann, A. E.: The Treatment of Diabetic Acidosis: Comparison of Treatment Regimes with and without Parenteral Potassium. *J. Pediat.*, 49:141, 1956.
- Bell, E. T.: Renal Vascular Disease in Diabetes Mellitus. *Diabetes*, 2:376, 1953.
- Danowski, T. S.: *Diabetes Mellitus*. Baltimore, Williams & Wilkins Company, 1957.
- Darrow, D. C., and Pratt, E. L.: Retention of Water and Electrolyte during Recovery in a Patient with Diabetic Acidosis. *J. Pediat.*, 41:689, 1952.
- Guest, G. M.: The Mauriac Syndrome. *Diabetes*, 2:415, 1953.
- Guest, G. M., Mackler, B., and Knowles, H. C., Jr.: Effects of Acidosis on Insulin Action and on Carbohydrate and Mineral Metabolism. *Diabetes*, 1:276, 1952.
- Jackson, R. L., and others: Degenerative Changes in Young Diabetic Patients in Relation to Level of Control. *Pediatrics*, 5:959, 1950.
- Keidan, S. E.: Transient Diabetes in Infancy. *Arch. Dis. Childhood*, 30:291, 1955.
- Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F.: The Blood Flow and Oxygen Consumption of the Human Brain in Diabetic Acidosis and Coma. *J. Clin. Investigation*, 27:500, 1948.
- Klein, R., and Laron, Z.: Current Problems in Diabetes. *Pediatrics*, 18:983, 1956.
- Lichtenstein, A.: Diet in Diabetes Mellitus; in *Advances in Pediatrics*. Chicago, Year Book Publishers, Inc., 1949, Vol. IV, p. 1.
- Mirsky, I. A.: The Etiology of Diabetic Acidosis. *J.A.M.A.*, 118:690, 1942.
- Nelson, N., Elgert, S., and Grayman, I.: Production of Permanent Hyperglycemia and Glycosuria by Prolonged Administration of Insulin. *Science*, 95:583, 1942.
- Stadie, W. C.: Recent Advances in Insulin Research. *Diabetes*, 5:263, 1956.
- Wagner, R., White, P., and Bogan, I. K.: Diabetic Dwarfism. *Am. J. Dis. Child.*, 63:667, 1942.

## INFANTS OF DIABETIC MOTHERS

The high fetal and neonatal mortality rate of infants of diabetic mothers has long been known, but to date no complete satisfactory explanation for it has been presented. Numerous theories have been proposed; one which has received widespread attention is that the neonatal mortality rate is due to hypoglycemia. Numerous workers have claimed, however, that the blood sugar levels of infants of diabetic mothers differ in no way from

those of infants of comparable gestational age born of nondiabetic women. Recently the problem was reopened by Reardon and her co-workers, who maintain that infants with clinical disturbances have sustained low values for blood glucose as compared to healthy infants of nondiabetic mothers delivered either by the vaginal route or by elective cesarean section. In addition to the hypoglycemia they find a respiratory and metabolic acidosis in many of the infants and hyperphosphatemia and hyperkalemia in some.

Infants of diabetic mothers may show a completely normal course or may exhibit a typical clinical disturbance. This consists in respiratory distress which may be marked immediately after delivery or may be minimal at birth and becomes severe in a few hours following delivery. The respiratory distress consists in rapid respirations with or without cyanosis, inspiratory retractions of the soft tissues of the chest and a constant irritable cry. These signs increase in severity during the first two or three days of life and end in respiratory failure or gradually decrease over the same period of time. Physical examination reveals poor aeration of the lungs and inconstant rales throughout the lung fields. A roentgenogram of the chest reveals a generalized fine granular atelectasis.

Other striking findings on physical examination are the large size of the infant, which is inconsistent with his gestational age, and edema which is generalized and nonpitting.

Miller suggests that the respiratory difficulties of these infants are due to cardiac enlargement and failure. The author, however, has not observed cardiac failure frequently and attributes the respiratory signs to pulmonary hyaline membranes, which are present more frequently in infants of diabetic mothers than in infants of normal mothers. It is possible, however, that cardiac failure may play a role in the production of pulmonary hyaline membranes.

Warren and LeCompte have reviewed the autopsy findings of a series of fifty infants of diabetic mothers and have re-emphasized the large size and visceromegaly of these infants. The most characteristic finding was hyperplasia of the islets of Langerhans and infiltration of the pancreas with eosinophilic leukocytes. Miller and others have pointed out that these findings are not only characteristic of the infants of mothers with clinical diabetes, but that they may also be found in infants born as long as fifteen years before



diabetes becomes clinically evident in their mothers. For these reasons it is wise to investigate for potential diabetes mellitus any woman giving birth to an unusually large baby.

Because the peak of fetal mortality of infants of diabetic mothers is reached after the thirty-sixth week of pregnancy, it is recommended that delivery of these infants be effected at or before this time. Since spontaneous delivery may be impossible, cesarean section is often required. Hormonal therapy to diabetic mothers during pregnancy has been stressed by White, but is still a highly controversial subject.

**Treatment.** It is recommended that a pediatrician attend the delivery of infants of diabetic mothers and be responsible for the immediate care of the infant. In view of the large amount of amniotic fluid in the stomachs of these infants, especially when delivered by cesarean section, the stomach should be emptied after clearing the upper airway.

The infant should be followed up closely after birth. A rising respiratory rate indicates early distress and may soon be accompanied by retractions. If oxygen is needed, a high humidity is recommended. It is now felt that antibiotics should not be given prophylactically, but administered only if infection occurs or is suspected. The author has delayed the initial feeding of infants with respiratory distress and has not treated hypoglycemia except in the presence of convulsions. Reardon et al., however, claim excellent results from the administration by stomach tube or intravenous infusion of 30 ml. per pound per day of 5 per cent glucose in 0.45 per cent sodium chloride solution. Further controlled studies are needed to evaluate these findings.

If signs of distress do not develop during the first twenty-four hours of life, they are unlikely to occur subsequently. Infants with respiratory distress have increasing difficulty, death occurring in forty-eight to ninety-six hours, or, over the same period of time, there is gradual improvement in aeration with disappearance of abnormal signs. The basic cause or causes of the high incidence of pulmonary hyaline membranes in these infants are not clear.

Although the incidence of lethal congenital abnormalities in infants of diabetic mothers is about three times higher than in infants of nondiabetic mothers, malforma-

tions account for only a small proportion of the deaths.

SYDNEY S. GELLIS

## REFERENCES

- Arey, J. B., ed.: Pulmonary Hyaline Membranes. Report of the Fifth M and R Pediatrics Research Conference. Columbus, Ohio, M and R Laboratories.
- Farquhar, J. W.: The Significance of Hypoglycemia in the Newborn Infant of the Diabetic Woman. *Arch. Dis. Childhood*, 31:203, 1956.
- Gellis, S. S.: The Care of the Newborn Infant of the Diabetic Mother. Proceedings of the Special Committee on Infant Mortality of the Medical Society of the County of New York, 1950-51.
- Gellis, S. S., White, P., and Pfeffer, W., Jr.: Gastric Suction: A Proposed Additional Technic for the Prevention of Asphyxia in Infants Delivered by Cesarean Section. *New England J. Med.*, 240: 533, 1949.
- Miller, H. C., Hurwitz, D., and Kuder, K.: Fetal and Neonatal Mortality in Pregnancies Complicated by Diabetes Mellitus. *J.A.M.A.*, 124:271, 1944.
- Miller, H. C., and Wilson, H. M.: Macrosomia, Cardiac Hypertrophy, Erythroblastosis and Hyperplasia of the Islands of Langerhans in Infants Born to Diabetic Mothers. *J. Pediat.*, 23:25, 1943.
- Reardon, H. S., Field, S. H., and Baumann, M. L.: Acidosis and Hypoglycemia in Infants of Diabetic and "Prediabetic" Mothers. *Am. J. Dis. Child.*, 90:648, 1955.
- Reardon, H. S., and others: Treatment of Acute Respiratory Distress in Newborn Infants of Diabetic and "Prediabetic" Mothers. *Trans. Soc. Ped. Res.*, Carmel, Calif., June, 1957.
- Warren, S., and LeCompte, P. M.: Pathology of Diabetes Mellitus. 3rd ed. Philadelphia, Lea & Febiger, 1952.
- Winter, W. D., Jr. and Gellis, S. S.: Pulmonary Hyaline Membranes in Infants of Diabetic Mothers. *Am. J. Dis. Child.*, 87:702, 1954.

## HYPOGLYCEMIA

Hypoglycemia is an abnormally low level of blood glucose. The concentration of *true* blood glucose\* in normal infants and children after a twelve-hour fast ranges from 80 to 100 mg. per 100 ml. In normal infants during the first five days of life values as low as 20 to 60 mg. are not uncommon. The fasting blood glucose levels may be altered by various physiologic influences, which should be considered in the interpretation of such values. Loud crying or extreme fright may

\* Many reducing substances in addition to glucose are present in blood. Determination of the so-called total true blood glucose value by the Somogyi-Nelson method before and after yeast fermentation has demonstrated that galactose may constitute a considerable portion of the blood sugar value in many normal and sick infants.

elevate the blood sugar as a result of adrenal stimulation—the so-called alarm reaction. Hartman considers any true blood glucose value below 50 mg. as hypoglycemia, whereas Conn regards only values below 40 mg. per 100 ml. as significant. A low blood sugar value may be designated as clinically significant hypoglycemia only when associated with characteristic clinical manifestations which disappear as the blood sugar concentration rises.

**Physiologic Considerations.** The almost constant level of the fasting blood glucose level represents a dynamic balance between the rate of flow of glucose into the blood from the liver and the rate at which glucose is withdrawn from the blood by the tissues to be utilized or stored as glycogen.

The absorption of glucose from the intestinal tract is not a passive process. Glucose is drawn into the cells by the energy of conversion of the inert glucose molecule into the reactive phosphorylated form, glucose-6-phosphate. A constant flow of glucose into the body fluids from the intestinal tract is thus ensured, even when a high blood glucose concentration would act as an osmotic barrier to a more dilute glucose solution in the intestinal lumen. As glucose is discharged into the circulation by the cell, the coupled phosphate is removed. The impaired intestinal carbohydrate absorption associated with hypothyroid states, and the enhanced absorption seen in hyperthyroidism, stem from the regulatory influence which thyroid hormone has on this phosphorylating mechanism.

Absence of glucose from the urine under normal conditions results from a similar activity by renal tubular cells by which glucose is rapidly and completely withdrawn from the glomerular filtrate by phosphorylation. The glycosuria induced by administration of phlorizin is due to depression of the tubular mechanism which reabsorbs glucose.

As glucose enters a cell it is immediately phosphorylated to glucose-6-phosphate by the enzyme hexokinase, utilizing phosphate from adenosine triphosphate (ATP). Depending on the immediate needs of the cell, glucose-6-phosphate may follow one of several metabolic pathways. It may be burned to supply cellular energy in an orderly progression of breakdown which is conveniently divided into two parts: (1) the *Embden-Meyerhof cycle* of glycolysis, a series of phosphorylated compounds to the stage of three-carbon atom compounds (pyruvic and lactic acid); (2) the *Krebs tricarboxylic acid cycle* of reactions

in which phosphate is removed from pyruvic acid by the enzyme transphosphorylase. Following the metabolic pathway of the Krebs cycle of six organic acids, pyruvate is then burned to carbon dioxide and water. The part of the pyruvate which does not enter the Krebs cycle is utilized for the formation of body fat (lipogenesis) by synthesis into fatty acids.

Glucose-6-phosphate in excess of the cell's energy requirement may be stored as glycogen by preliminary change to glucose-1-phosphate, from which the phosphate is removed by the enzyme phosphorylase, and polymerization into inert glycogen occurs. In the reverse process of glycogenolysis, glycogen is broken down to glucose-6-phosphate, which in turn may be burned via the Embden-Meyerhof cycle or be regenerated into glucose by the enzyme glucose-6-phosphatase, which is present in liver, but not in muscle cells. The absence of this specific phosphatase from muscle explains why muscle glycogen does not furnish glucose to the body fluids. In all other aspects the pathways of glucose metabolism are believed to be similar in liver and muscle. The reactions and enzymes involved in the metabolic transformation of glucose are shown in Figure 63 (p. 269).

The hexoses fructose, galactose and mannose have no complete metabolic pathways of their own in the cell, but are utilized for energy or the formation of glycogen by introduction into the stream of glucose metabolism after phosphorylation by hexokinase.

Endocrine influence on glucose metabolism is exerted through direct action on specific enzymes. Hormonal stimulation of the hexokinase system by insulin increases the rate at which glucose is withdrawn from the blood by formation of glucose-6-phosphate in the cells; the effect is hypoglycemia. Hexokinase activity may be inhibited by anterior pituitary growth hormone, perhaps by adrenal glucocorticosteroids and by epinephrine. The action of these three hormones leads to hyperglycemia.

Increased activity of hepatic phosphorylase results in acceleration of glycogenolysis with elevation of the blood sugar by the regenerated glucose. Two hormones, epinephrine and glucagon (the pancreatic hyperglycemic factor), have an enhancing effect on phosphorylase action. Hypoglycemia may therefore have its origin in (1) excess of circulating insulin; (2) lack of anterior pituitary growth hormone, glucocorticosteroids or glucagon; (3) liver damage.



**Etiology.** It is readily apparent that hypoglycemia may result from a wide variety of etiologic factors. Since rational treatment and prognosis vary, depending upon the basic disorder, it is essential to make every reasonable effort to determine the etiology.

**Hypoglycemia due to defective intestinal absorption of glucose.** Unlike most adults, children and especially infants may exhibit lowering of the blood sugar level when carbohydrate is withheld for twenty-four to forty-eight hours. However, fasting by itself is rarely, if ever, a cause of clinical hypoglycemia, but may be a precipitating factor when other defects that may cause hypoglycemia are present. This is also the case when the blood sugar values are lowered by impaired intestinal absorption as is the case in chronic diarrhea, celiac disease, intestinal tuberculosis and the edematous phase of the nephrotic syndrome. Thyroxin influences the rate of intestinal absorption of hexoses by its regulatory effect on the phosphorylation process. The hypoglycemia seen at times in cretins is partially due to this absorptive defect.

**Hypoglycemia due to renal glycosuria.** Glycosuria due to defective tubular reabsorption of glucose occurs in a variety of clinical entities. It is encountered as an isolated hereditary condition, and is also part of the de Toni-Fanconi syndrome, presumably owing to hereditary absence of the tubular enzyme system which phosphorylates glucose. Glycosuria in some patients with lead poisoning and that following administration of phlorizin or dinitrophenol results from poisoning of the renal tubular system. In rare instances renal glycosuria has lowered the blood sugar to hypoglycemic levels.

**Hypoglycemia due to hyperinsulinism.** Hypoglycemia may result from an absolute or relative excess of insulin secretion.

**ORGANIC HYPERINSULINISM.** Secretion of excessive amounts of insulin which occurs in hyperplasia or adenoma of the beta cells of the islets of Langerhans is the organic type of true hyperinsulinism. There is an erroneous concept that hypoglycemia and organic hyperinsulinism are synonymous. This is unfortunate, since most instances of hypoglycemia in childhood are due to causes other than true hyperinsulinism.

The primary adenoma of the islet cells (nesidioblastoma), relatively common in adults, is an extreme rarity in children.

Hypoglycemia resulting from hyperplasia of the islets may occur in newborn infants of diabetic and prediabetic mothers. The fre-

quently encountered symptoms of cyanosis, dyspnea and tachypnea and the high mortality rate of such infants are not solely attributable to the low blood glucose levels (p. 1214). It is of interest that hyperplasia of the islets of Langerhans has been observed in infants dying of erythroblastosis fetalis.

**FUNCTIONAL HYPERINSULINISM.** Nervous impulses through the right vagus originating in the hypothalamic parasympathetic center can stimulate insulin secretion, and a functional type of true hyperinsulinism based on such abnormal nervous stimulation has been postulated.

Fundamentally, the prime factor in the adjustment of the blood sugar concentration is the blood sugar level itself. Thus hyperglycemia, acting as a stimulus to insulin secretion, will, in the presence of hyperreactiveness of this mechanism, result in a functional type of true hyperinsulinism. Such patients have hypoglycemic reactions two to four hours after a meal or a glucose tolerance test, but not after fasting. In organic hyperinsulinism hypoglycemic attacks occur both postprandially and after food deprivation as well as during hyperpyrexia or strenuous muscular exercise, when the increased oxidation of glucose by the tissues is a contributing factor.

Infants with galactosemia frequently have hypoglycemic reactions due to functional hyperinsulinism. Galactose is present in the body fluids of such infants because of a hepatic defect, which may be congenital and permanent or may occur as a temporary abnormality in newborn and young infants. Hypergalactosemia is as effective as hyperglucosemia in evoking an increased secretion of insulin which lowers the blood glucose to hypoglycemic levels, but leaves circulating galactose intact. Since ordinary clinical methods of blood sugar determinations do not differentiate glucose and galactose, this phenomenon accounts for the occurrence of hypoglycemic reactions in infants with seemingly normal levels of blood sugar.

**Hypoglycemia due to pituitary and adrenal cortical insufficiency.** Corticotropin and growth hormone are the principal anterior pituitary hormones with carbohydrate-regulating properties. The effect of corticotropin on carbohydrate metabolism is an indirect one through its control of adrenal secretion of glucocorticosteroids. The principal actions of the glucocorticosteroids on carbohydrate metabolism are to increase gluconeogenesis mainly from protein and to decrease tissue utilization of glucose. The latter may be due

in part to inhibition of hexokinase activity. A deficiency of corticotropin or adrenal cortical secretion results in depression of gluconeogenesis and increased tissue utilization of glucose and hence in hypoglycemia.

The hypoglycemia occasionally noted in congenital adrenal hyperplasia is due to inability of the adrenal cortex to produce adequate amounts of hydrocortisone.

Growth hormone appears to decrease peripheral utilization of glucose, but the mechanism is unknown. Deficiency of growth hormone is partially responsible for the hypoglycemia of hypopituitarism.

**Hypoglycemia due to decreased delivery of glucose into the blood by the liver.** Severe hepatic damage produced experimentally or by disease may involve all three of the hepatic mechanisms of carbohydrate metabolism: viz., impairment of (1) *glycogenesis* results in an inadequate storage of glycogen; of (2) *gluconeogenesis*, in the conversion of fatty acids and amino acids (derived from body fat and tissue protein) to glucose and glycogen; and of (3) *glycogenolysis*, in a decreased ability of the liver to deliver glucose to the blood.

Hypoglycemic manifestations may be produced by such hepatotoxic agents as phosphorus, carbon tetrachloride, chloroform, hydrazine, neoarsphenamine, salicylates and white snake root (milk sickness), and during acute and chronic infectious hepatitis, often as a terminal event.

Extensive infiltration of the liver by neoplastic cells, fibrous tissue, granulomas or fat may lead to hypoglycemia. It is obvious that in the aforementioned conditions hypoglycemic manifestations are secondary to the symptom of hepatic disease.

Hepatic glycogen disease (von Gierke's disease) (p. 268) is a cause of hypoglycemia due to defective glycogenolysis.

The rate of breakdown of hepatic glycogen to glucose is regulated by the enzyme phosphorylase. Both epinephrine and glucagon increase blood sugar levels by increasing the activity of the phosphorylase enzyme system. McQuarrie has described two children in one family in whom hypoglycemia was presumed to be due to a deficiency of glucagon, because no alpha cells could be demonstrated in biopsied pancreatic tissue. There are no known cases of hypoglycemia secondary to absence or failure of epinephrine activity.

**Idiopathic hypoglycemia of infancy.** In most instances of hypoglycemia in the pediatric age group no pathologic lesion can be

identified. The symptoms usually begin in early infancy, and there is a tendency to spontaneous improvement in subsequent years. In the absence of an understanding of the pathogenesis such cases of hypoglycemia have been termed *idiopathic hypoglycemia of infancy*. McQuarrie's observations of absence of the alpha cells of the pancreas in two siblings with hypoglycemia has not been noted in other patients. It has recently been demonstrated that in some instances of this disorder a fall in the fasting blood glucose level follows ingestion of a high protein feeding, a casein test meal or administration of leucine (p. 267).

This group is probably a heterogeneous one consisting of several different defects. Familial tendencies have been observed.

**Clinical Manifestations.** There are no exact relationships between the levels of blood sugar and the development or severity of symptoms. The rate of fall of the blood sugar seems to be a determining factor for the appearance of symptoms; a rapid fall, irrespective of the actual level reached, is most likely to bring on symptoms. The time of occurrence of symptoms in relation to muscular activity, fasting and food intake has differential diagnostic value. Hypoglycemic manifestations which appear only several hours after a meal are due to functional hyperinsulinism. Symptoms occurring in the morning or after vigorous activity are more indicative of organic hyperinsulinism. Even at extremely low blood levels of glucose children show great variability in symptoms. Many become conditioned to repeated hypoglycemic episodes or to hypoglycemia of long duration, so that they cease having symptoms. The symptoms of hypoglycemia are derived chiefly from disturbances of the central nervous system. Nerve tissue has little stored carbohydrate and, unlike other tissues, cannot utilize protein or fat, so that it is dependent upon a continuous supply of blood glucose in adequate amounts to maintain its normal functions.

Hypoglycemic symptoms are protean, but often produce more or less characteristic patterns in individual patients. Some of the more frequent symptoms are fatigue, headache, pallor, sweating, speech and visual disturbances and motor disturbances, such as tremulousness, incoordination, paralyses, syncope and convulsions. Hunger is prominent, and vomiting not infrequent. The temperature is often subnormal. Tachycardia and extrasystoles occur as a result of stimulation



of the sympathetic nervous system. Psychic disturbances such as irritability, negativism, drowsiness and alterations in behavior are seen in older children. In the ranks of emotionally disturbed children there are certainly some unhappy, ill-behaved or maladjusted children requiring, not guidance, but more sugar.

In newborn and young infants recognition and evaluation of symptoms may be difficult except as the possibility of hypoglycemia is considered. Convulsions are often the manifestation recognized initially.

Mental deterioration and demonstrable permanent cerebral damage may result from protracted or repeated hypoglycemic episodes.

**Diagnosis.** Two distinct diagnostic problems are posed: (1) the detection of hypoglycemia, and (2) the determination of the disturbed regulatory mechanism. There is unfortunately no routine and simple laboratory test for the screening of patients with hypoglycemia.

The most effective means for the establishment of the hypoglycemic state are the determination of fasting blood sugar levels and the glucose tolerance test. Patients whose symptoms occur in the fasting state would be expected to have a low blood sugar level before breakfast. If the fasting blood sugar level is normal after a simple overnight fast, then a more prolonged fast period, even as long as twenty-four hours, may be necessary to provoke symptoms and to demonstrate hypoglycemia. When symptoms tend to occur several hours after meals and not before breakfast, a six-hour glucose tolerance test is indicated. In many instances both tests should be performed.

When it is established that hypoglycemia is present, it is necessary to determine the etiology. If there is fasting hypoglycemia, the conditions to be considered in the differential diagnosis are severe renal glycosuria, hepatic disorders, anterior pituitary insufficiency and adrenal cortical insufficiency. If hypoglycemia is evoked by a carbohydrate load as with the glucose tolerance test, functional hyperinsulinism is the most likely explanation. If both fasting and postprandial hypoglycemia are demonstrated, organic hyperinsulinism and "idiopathic spontaneous hypoglycemia of infancy" must be considered.

The *epinephrine tolerance test* is a useful procedure to study the hepatic glycogenolytic mechanism. A flat curve indicates an abnormally rapid rate of glycogen depletion, a failure of glycogen formation by hepatic dis-

ease or hepatic glycogen (von Gierke's) disease.

Talbot recommends that the test be carried out in the following manner: To provide an adequate glycogen supply in the liver, a diet containing 6.5 gm. of carbohydrate per kilogram per day (180 gm. per square meter) is given daily for three days before the test. Omitting breakfast on the fourth day, 0.01 cc. of 1:1000 epinephrine per kilogram (0.3 cc. per square meter) is injected subcutaneously. Sugar determinations are done on blood samples taken at fifteen, thirty and forty-five minutes. A rise of blood sugar of at least 20 mg. per 100 ml. should occur during this time if hepatic glycogenolysis is normal.

The *intravenous glucose tolerance test* as described below evokes the secretion of insulin which brings the blood glucose content to normal levels in about two hours. As the glucose level continues to fall below normal under the influence of continued insulin secretion, the insulin antagonists (epinephrine, glucagon and glucocorticosteroid) cause the blood glucose level to rise and return to a normal value by the third hour. In the patient with hypoadrenocorticism or a deficiency of glucagon insulin continues to act unopposed, and the steadily falling blood glucose reaches hypoglycemic levels within four to six hours.

The patient is prepared for this test by the feeding of a diet containing 6.5 gm. of carbohydrate per kilogram (180 gm. per square meter) for three days. Before breakfast on the fourth day, after a twelve-hour fast, 0.7 gm. of glucose per kilogram (20 gm. per square meter) is administered intravenously as 10 or 20 per cent solution over a thirty-minute period. Blood samples are obtained before and at one-half, one, two, three, four and five hours after the injection.

Although deficiency of glucocorticosteroids as in Addison's disease or Simmonds' disease is frequently associated with hypoglycemic manifestations, hypoglycemia is rarely the presenting complaint. Other signs and symptoms of adrenal insufficiency are often present and lead to recognition of the disorder (pp. 1154, 1183).

The *insulin tolerance test* provides a more direct method of determining the response to hypoglycemia, but its use is not often necessary. Normally there is a prompt fall in the fasting blood sugar followed by a return to the fasting level in two hours. Failure of restoration of normoglycemia in two hours has the same significance as described for the intravenous glucose tolerance test. This test is not without danger in the hypoglycemic child and should never be done without con-

stant surveillance during the procedure and without provision to terminate the hypoglycemia promptly if alarming symptoms develop.

The *insulin tolerance* test is performed by administering 0.1 unit of regular insulin per kilogram after a three- or four-day period on a normal diet and immediately after a night's fast. Blood for sugar determinations is obtained before the injection of insulin and fifteen, thirty, forty-five, sixty, ninety and 120 minutes thereafter. In the normal child the blood sugar drops to about 50 per cent. of the fasting level in fifteen to thirty minutes and returns to normal in sixty to ninety minutes. The child should be observed closely for symptoms of hypoglycemia, which include irritability, faintness, headache, dizziness, sweating, tremor and visual disturbances. Mental confusion is a grave sign and is an indication for immediate termination of the test by the administration of glucose. When an unusual degree of insulin hypersensitivity is suspected, one-half or one-third of the dose of insulin should be used for the initial test.

Abnormal *electroencephalographic patterns* resulting from hypoglycemia are difficult, if not impossible, to differentiate from those occurring in epileptic patients. In patients with infrequent hypoglycemic attacks the abnormalities in the electroencephalogram are usually not present between attacks. It is likely that cerebral defects are the result rather than the cause of hypoglycemia.

**Treatment.** The immediate symptoms of hypoglycemia may be relieved by administration of epinephrine (0.03 ml. or  $\frac{1}{2}$  minim of 1:1000 solution per kilogram of body weight; not to exceed 0.8 ml.) and/or of glucose, orally or intravenously. In patients with hypoadrenocorticism more severe hypoglycemia may recur four to six hours after intravenous administration of glucose. Similarly, reliance should not be placed upon high carbohydrate meals to prevent recurrent attacks of hypoglycemia, for frequently the opposite effect is obtained. The severe postprandial fall in blood sugar is responsible for the symptoms of hypoglycemia. Between-meal lunches and one before bedtime are often effective. An increase in the protein content of the diet at the expense of carbohydrate is strongly advocated by Conn on the grounds that glucose is produced at a slow rate from protein and does not provide the hyperglycemic stimulus which elicits secondary hypoglycemia. However, in hypoglycemia of hepatic origin the diet should be high in both carbohydrate and protein.

An occasional patient with "idiopathic

spontaneous hypoglycemia" may have more severe hypoglycemia with diets high in protein (q.v.). It is probably desirable to test the glycemic response of all patients with idiopathic hypoglycemia after a test feeding of casein or leucine. Feeding small amounts of carbohydrate thirty to forty minutes after the normal feeding may prevent the fall of blood sugar in such patients.

Hydrocortisone restores normal carbohydrate metabolism in patients with corticotropin or adrenal cortical insufficiency. Corticotropin has been effective in maintaining normal glycemic levels in infants with idiopathic hypoglycemia (McQuarrie). Hydrocortisone and other glucocorticosteroids administered orally appear to be equally effective. The dose must be adjusted to the individual needs of the patient, but at the lowest effective level. Every six months or so attempts should be made to discontinue the drug gradually.

In the patient with protracted hypoglycemia, unresponsive to diet, corticotropin or corticosteroids, and in whom no pancreatic adenoma is demonstrable on surgical exploration, more radical measures have been used. Partial pancreatectomy has usually had little, if any, palliative effect. Two such infants have been treated with apparent success with alloxan (mesoxalyl urea).

Psychologic guidance of the hypoglycemic child and his family is of paramount importance.

MILTON RAPOPORT

## REFERENCES

- Bridge, E. M., and Mulholland, W. M.: Intermediary Carbohydrate Metabolism; in McQuarrie, I., ed.: Brennemann's Practice of Pediatrics. Hagerstown, Md., W. F. Prior Co., Inc., 1957, Vol. 3, Chap. 24.
- Cochrane, W. A., Payne, W. W., Simpkins, M. J., and Woolf, L. I.: Familial Hypoglycemia Precipitated by Amino Acids. *J. Clin. Invest.*, 35:411, 1956.
- Conn, J. W., and Seltzer, H.: Spontaneous Hypoglycemia. *Am. J. Med.*, 19:460, 1955.
- Gittleman, I. F., and Pincus, J. B.: Blood Sugar and Citric Acid Levels in New-Born Infants. *Pediatrics*, 9:38, 1952.
- Hartmann, A. F., Grunwaldt, E., and James, D. H.: Blood Galactose in Infants and Children. *J. Pediatr.*, 43:1, 1953.
- McIntosh, R.: Acute Phosphorus Poisoning: Report of a Case with Recovery. *Am. J. Dis. Child.*, 34:595, 1927.
- McQuarrie, I.: Idiopathic Spontaneously Occurring Hypoglycemia in Infants. *A.M.A. Am. J. Dis. Child.*, 87:399, 1954.



Mirsky, I. A., and Nelson, W. E.: Ketosis in Relation to Hepatic Reserves of Glycogen; Study of Normal and of Diabetic Children. *Am. J. Dis. Child.*, 67:100, 1944.

Najjar, V. A.: The Physiology and Disorders of Carbohydrate Metabolism. *J. Pediat.*, 41:804, 1952.

Sherman, H.: Islet Cell Tumor of Pancreas in a Newborn Infant (Nesidioblastoma). *Am. J. Dis. Child.*, 74:58, 1947.

Steiner, M. W., and Lawrence, G.: Rare Dwarfism with Chronic Hypoglycemia and Convulsions. *J. Clin. Endocrinol. & Metabol.*, 13:283, 1953.

Stetten, DeW., Jr., and Topper, Y. J.: The Metabolism of Carbohydrates. A Review. *Am. J. Med.*, 19:96, 1955.

Wyke, B. D.: Brain Function and Blood Sugar: Observations Based on a Case of Islet Cell Adenoma of the Pancreas. *Electroencephalog. & Clin. Neurophysiol.*, 4:339, 1952.

## METABOLIC DISORDERS WITH OSSEOUS LESIONS

See also Parathyroid Disturbances (p. 1175), Cystinosis (p. 263) and Diseases of the Renal Tubules (p. 261).

### VITAMIN D-REFRACTORY (RESISTANT) RICKETS

Vitamin D-refractory rickets may now be the most common form of rickets in the United States. Vitamin D-deficiency rickets—once the scourge of childhood—has almost vanished in this country. In vitamin D-refractory rickets the usual prophylactic doses of vitamin D do not prevent the development of severe rickets, and if adequate therapy is not provided, there are severe bony deformities and dwarfism (Fig. 350). The roentgenographic changes in the long bones are similar to those of vitamin D deficiency rickets. The usual chemical changes in the blood are a high alkaline phosphatase and a hypophosphatemia. In exceptional cases the calcium level has been low, and the patients have had clinical tetany. These patients have responded to extremely large doses of vitamin D, as have those with hypophosphatemia and normal calcium levels. In both types healing of the rickets can usually be obtained even though deformities have occurred; the deformities are persistent, except as they can be partially corrected by orthopedic means.

There appears to be a hereditary factor, although the mode of inheritance has not been satisfactorily established. In a large North Carolina kindred hypophosphatemia was found to be inherited as a sex-linked dominant. Although several members had vitamin D-resistant rickets, there was no clear genetic mechanism to explain the presence of rachitic lesions in this kindred. The basic

metabolic defect is undetermined; an abnormally high renal clearance of phosphorus has been demonstrated. Absorption of vitamin D from the intestine is not impaired.

The basis of *treatment* is administration of large doses of vitamin D; the amount varies in different patients and even in the individual patient. The required dosage ranges from 5000 to 1,000,000 units a day and in general is higher during the infantile and adolescent growth spurts. A practical plan is to start with 50,000 units of vitamin D a day, subsequent adjustments being based principally on roentgenographic observations. Serum calcium and phosphorus concentrations and alkaline phosphatase activity are determined at monthly intervals until stabilized and then at intervals of two to four months. The serum inorganic phosphorus rarely returns to normal levels, but the rickets heals with adequate therapy. The parent or patient is instructed to test the urine two or three times weekly with Sulkowitch's reagent\* in order to detect any tendency to hypercalciuria. If there are several 4 + reactions, the patient should be re-evaluated by measurement of the serum calcium level. Hypercalcemia is an indication for reduction in the dose of vitamin D. Orthopedic correction of deformities should never be undertaken until the rachitic process is inactive. Close supervision is necessary when the child

\* Sulkowitch's reagent:

Oxalic acid, 2.5 gm.  
Ammonium oxalate, 2.5 gm.  
Glacial acetic acid, 5.0 cc.  
Distilled water, qs. ad 150 cc.

The test: To 5 cc. urine add 2 cc. of the reagent. Readings are graded 0 to 4 + on the basis of the presence and extent of a white precipitate.

is immobilized for an appreciable time to avoid hypercalcemia and hypercalciuria with their resultant complications; reduction of the dose of vitamin D is usually indicated during this time. Supplemental vitamin D may not be required after growth has stopped, but this is not invariably so, and observation of the patient must be continued into adulthood.

## RICKETS ASSOCIATED WITH AMINO-ACIDURIA

(FANCONI-DE TONI-DEBRÉ SYNDROME)

The features of the syndrome are rickets, growth retardation, hypophosphatemia, amino-aciduria, glycosuria, normoglycemia and hyperphosphaturia. There is polyuria with in-

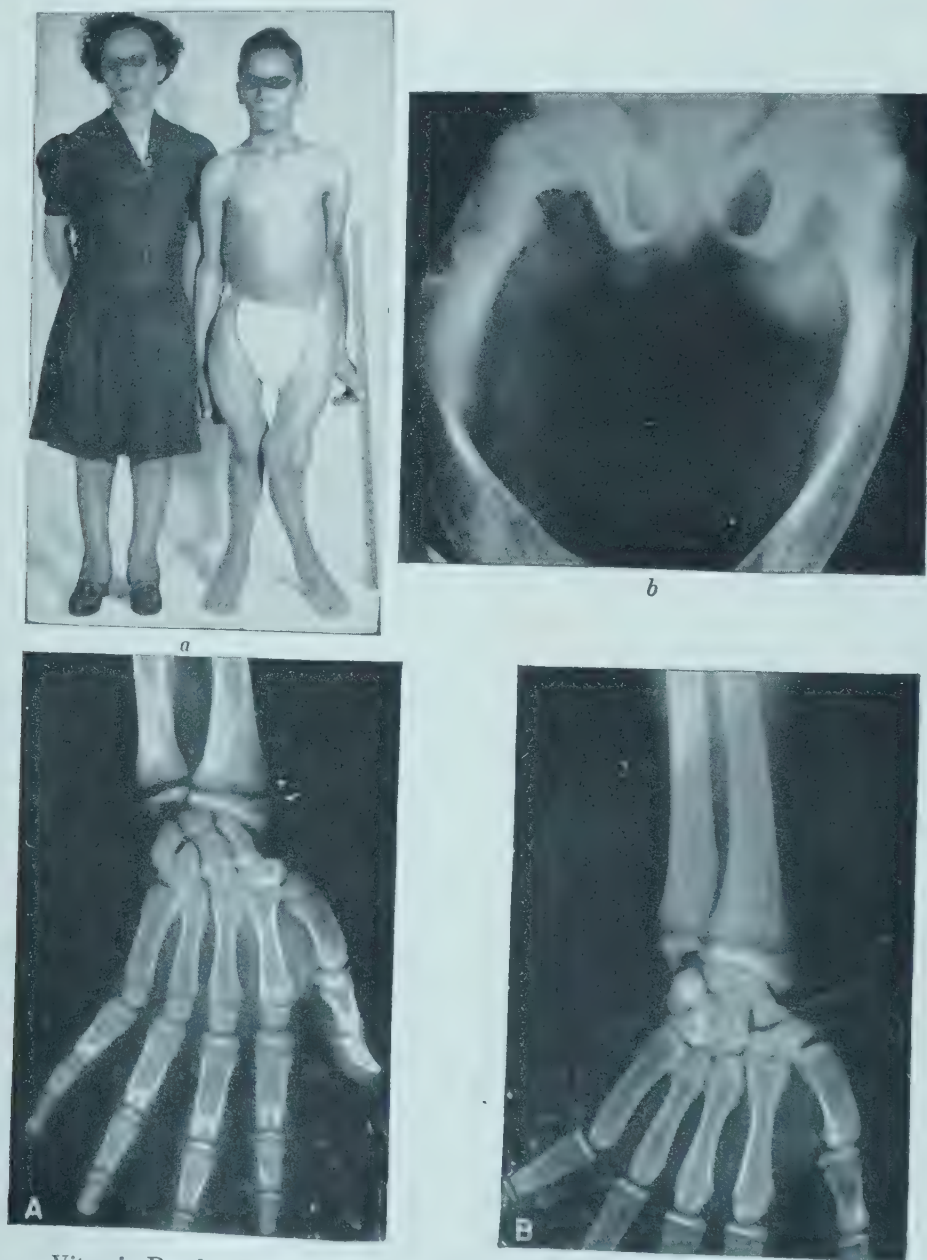


FIG. 350. *a*, Vitamin D-refractory rickets in a mother and her son. The mother's father probably had the same disease. The roentgenograms and the laboratory data refer to the boy: Calcium, 9.6 mg. per 100 ml.; inorganic phosphorus, 2.5 mg. per 100 ml.; serum phosphatase, 34.7 Bodansky units. *b*, Roentgenogram of the femurs showing bowing, thickening and rarefaction. Lower row: *A*, fraying of distal ends of radius and ulna. The distance between epiphyses and diaphyses of the radius and ulna is greater than normal. *B*, Roentgenogram 1½ years later. In the meantime the patient had had 50,000 to 200,000 I.U. of vitamin D daily. Epiphysal clefts show progress in calcification, but the chemical findings in the blood are essentially unchanged. Calcium, 9.6 mg. per 100 ml.; inorganic phosphorus, 2.3 mg. per 100 ml.; phosphatase, 23.7 Bodansky units.



creased excretion of organic acids, and often albuminuria. As in vitamin D-refractory rickets, there is increased renal phosphate clearance. Since hypokalemia has been observed in this syndrome, the possibility of its presence should be investigated prior to therapy. When glomerular function is not impaired, fixed base may be given in the form of sodium citrate, or a mixture of sodium and potassium citrate as described under Rickets Associated with "Base-Losing Nephritis." Fanconi recommends the use of basic sodium phosphate to replace the excessive phosphate loss. Excessive therapy with vitamin D may result in serious anorexia. The prognosis is poor.

There are differences of opinion whether cystinosis (p. 263) is a variant of this syndrome or whether they are two distinct entities. Some would combine the two under the category of de Toni-Fanconi syndrome, with or without cystinosis. Others suggest that amino-acid diabetes (Fanconi syndrome) results from a tubular defect in reabsorption of certain amino acids, whereas cystinosis results from a defect in methionine metabolism.

#### **RICKETS ASSOCIATED WITH HYDROPHthalmos, ORGANIC ACIDURIA AND DECREASED RENAL AMMONIA PRODUCTION**

Lowe identified a syndrome consisting in congenital glaucoma, decreased renal production of ammonia, rickets, organic aciduria and mental retardation. The patients observed were hyperactive and had episodes of fever without obvious cause. The plasma carbon dioxide content and pH were slightly but definitely low. Paper chromatography revealed nine to ten amino acids in the urine; cystine was not among them. The condition was unaffected by large doses of vitamin D alone, but the administration of calcium lactate and sodium citrate resulted in improvement of the rickets.

#### **RICKETS OF CHRONIC RENAL GLOMERULAR AND TUBULAR INSUFFICIENCY**

The classic form of "renal rickets" is that which develops as a result of chronic glomerular and tubular insufficiency. There is elevation of serum nonprotein nitrogen and inorganic phosphate, lowering of serum calcium concentration and systemic acidosis.

*This syndrome is often associated with congenital obstructive lesions of the urinary tract or malformations of the kidneys, or is secondary to severe renal infections. Hyperparathyroidism is a secondary manifestation apparently as a result of phosphate retention (p. 1179). These children usually die of renal failure.*

#### **RICKETS ASSOCIATED WITH "BASE-LOSING NEPHRITIS"**

(RENAL TUBULAR ACIDOSIS, RENAL HYPERCHLOREMIC ACIDOSIS, LIGHTWOOD SYNDROME, ALBRIGHT SYNDROME)

This syndrome appears to be due to a defect of the renal tubules resulting in an inability to excrete an acid urine. One hypothesis is based on a deficiency in the formation of ammonia; another, on a deficiency in the reabsorption of bicarbonate at average plasma concentrations and a deficiency of carbonic anhydrase in the tubular cells. When the defect is severe, symptoms appear in infancy. The principal manifestations are anorexia, vomiting, constipation, failure to thrive, apathy and irritability. Hypotonia, polyuria and dehydration may be manifest. Death may result from dehydration and acidosis. Osseous lesions are usually not found in these infants. Appropriate treatment may result in permanent remission of the disorder.

In mild forms of the disorder the disturbance may be overlooked until the child presents with symptoms referable to the renal or osseous systems. There may be retardation of growth and bony deformities, or pathologic fractures may be the presenting complaint. Roentgenograms reveal changes similar to those of rickets and osteomalacia. These result from excessive loss of cations in the urine. Nephrocalcinosis and/or renal calculi also develop.

The unusual combination of an alkaline urine with a hyperchloremic acidosis is commonly present (Lightwood syndrome). Chemical changes in the serum consist in a low pH, low level of bicarbonate and a high level of chloride. In the patients with nephrocalcinosis the blood urea nitrogen may be elevated, and there may be inability to concentrate urine. Secondary hyperparathyroidism may develop and result in a lowered serum phosphorus level. In all instances the pH of the urine is high in relation to the metabolic acidosis and is often on the alkaline side.

*Therapy for base-losing nephritis consists*

in provision of supplemental sodium and potassium sufficient to more than compensate for the renal loss, supplementary dietary calcium and therapeutic doses of vitamin D to permit rapid remineralization of the skeleton. Although the additional dietary fixed base must be given continuously, the calcium and vitamin D therapy may be relaxed when adequate mineralization is demonstrable roentgenographically. Fixed base can be given in the form of a 30 per cent (w/v) solution of equal weights of sodium citrate and potassium citrate, 10 to 15 cc. per day in divided doses. The administration of sodium salts alone may result in chronic potassium depletion. An electrocardiogram or serum potassium determination should be obtained after the first twenty-four hours of therapy as a check on the possibility of potassium intoxication. The rachitic-like epiphyseal lesions show striking improvement with this therapy.

### RICKETS OF CELIAC DISEASE

(See also p. 721)

Patients with chronic steatorrhea may exhibit hypophosphatemia, hypocalcemia and rickets. Available evidence indicates that this condition is more likely the result of impaired absorption of vitamin D than of the formation of calcium soaps. Celiac rickets should be treated with large doses of vitamin D in a water-miscible vehicle by mouth. It is noteworthy that rickets is not a complication in patients with fibrosis of the pancreas; rickets may occur in association with biliary atresia.

### HYPOPHOSPHATASIA

(LOW PHOSPHATASE RICKETS)

Hypophosphatasia, first described as an entity by Rathbun in 1948, is characterized by abnormal mineralization of bone, diminished alkaline phosphatase activity and increased excretion of phosphorylethanolamine in the urine. The serum phosphorus level is normal, but the serum calcium level may be elevated in severely affected infants. It is an inborn error of metabolism which appears to be inherited as a simple recessive.

The clinical manifestations vary widely in severity. They may be present at birth, appear early in infancy or not become apparent until later. Systemic symptoms such as anorexia, irritability, vomiting, failure to thrive, seizures, recurrent episodes of cyanosis or pneumonia may be presenting complaints in infants. Older children are generally healthy,

and the initial manifestations may be orthopedic deformities such as genu valgum, growth failure or premature loss of deciduous teeth.

Roentgenograms of the bones reveal changes similar to those of rickets. There is disappearance of the zone of provisional calcification due to defective mineralization of osteoid tissue which may extend well into the diaphysis. In severely affected infants the skull is soft, and the fontanels and sutures appear large, owing to large areas of uncalcified osteoid. In older children the osseous lesions are less marked.

When the disorder starts early in infancy, it is usually severe, and a fatal outcome is the rule. Less severely affected patients may have a normal life expectancy, and gradual improvement of the osseous lesions may occur. Vitamin D, even in large doses, has no therapeutic value and may actually be harmful by producing severe hypercalcemia. Cortisone has been reported to benefit some patients, but further experience is necessary for its evaluation.

### IDIOPATHIC HYPERCALCEMIA WITH GROWTH RETARDATION

In 1952 Lightwood and Fanconi separately described a syndrome of idiopathic hypercalcemia in infants with failure to thrive. There appears to be a benign and a severe form. The onset is between two and nine months of age in either sex, with vomiting, anorexia, hypotonia and inadequate gain in weight. About half of the cases exhibited polyuria and polydipsia. Numerous cases have been reported in the British literature, but less than ten cases from North America. In some of the cases the facies has been described as "elf-like," with low-set ears, a thick upper lip and prominent epicanthal folds. The serum calcium concentration may be as high as 18 mg. per 100 ml.; the level of serum inorganic phosphorus is usually normal, except that it may rise with continuation of the severe form of the disease. The serum alkaline phosphatase activity is normal or low. The urinary excretion of calcium is normal or only slightly elevated. Roentgenograms of the bones may not reveal any abnormalities, or there may be some increased density at the ends of the long bones. Hypertension may be associated with increase of the serum inorganic phosphorus and blood urea nitrogen concentrations. Infants with the benign form of the disease may recover spontaneously



after a few months. Infants with the severe form tend to have osteosclerosis, albuminuria, persistent mental and physical retardation and renal failure. In the fatal cases renal calcinosis is common.

The *etiology* of this syndrome is unknown; an idiosyncrasy to vitamin D has been suggested by a number of writers. The great discrepancy between the number of cases reported from Great Britain and from North America has not been satisfactorily explained. The amount of vitamin D in the average infant's diet does appear to be somewhat lower in this country.

*Treatment* of the disease consists in provision of a diet without added vitamin D, and possibly restriction of calcium intake. Versene therapy is not recommended (one child died after intramuscular injection of ethylenediaminetetracetate). In the severe form the administration of 5 to 12.5 mg. of cortisone per day may be helpful.

LYTT I. GARDNER

## REFERENCES

### *Vitamin D-Resistant Rickets*

Winters, R. W., Graham, J. B., Williams, T. F., McFalls, V. W., and Burnett, C. H.: A Genetic Study of Familial Hypophosphatemia and Vitamin D-Resistant Rickets, with a Review of the Literature. *Medicine*, 37:97, 1958.

### *Rickets with Amino-Acid Diabetes*

Worthen, H. G., and Good, R. A.: The deToni-Fanconi Syndrome with Cystinosis. (Extensive Bibliography) *A.M.A. Am. J. Dis. Child.*, 95: 653, 1958.

### *Rickets with Oculo-cerebral-Renal Syndrome*

Lowe, C. U., Terry, M., and MacLachlan, E. A.: Organic-Aciduria, Decreased Renal Ammonia Production, Hydrophthalmos, and Mental Retardation: A Clinical Entity. *Am. J. Dis. Child.*, 83:164, 1952.

### *Rickets of Chronic Glomerular and Tubular Failure*

Albright, F., and Reifenstein, E. C., Jr.: *The Parathyroid Glands and Metabolic Bone Disease*. Baltimore, Williams & Wilkins Company, 1948.

### *Rickets with Base-Losing Nephritis*

Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., and Roos, A.: Osteomalacia and Late Rickets. *Medicine*, 25:399, 1946.

Kunz, H. W., Cheung, M. W., and Pratt, E. L.: Idiopathic Hyperchloremic Acidosis. *J. Pediat.*, 52:434, 1958.

Lightwood, R.: Calcium Infarction of the Kidneys in Infants. *Arch. Dis. Childhood*, 10:205, 1935.

### *Rickets of Celiac Disease*

Parsons, L. G.: Celiac Disease; Rachford Memorial Lecture. *Am. J. Dis. Child.*, 43:1293, 1932.

### *Hypophosphatasia (Low Phosphatase Rickets)*

Fraser, D.: Hypophosphatasia. *Am. J. Med.*, 22:730, 1957.

Rathbun, J. C.: "Hypophosphatasia," New Developmental Anomaly. *A.M.A. Am. J. Dis. Child.*, 75: 822, 1948.

Sobel, E. H., Clark, L. C., Fox, R. P., and Robinow, M.: Rickets, Deficiency of "Alkaline" Phosphatase Activity and Premature Loss of Teeth in Children. *Pediatrics*, 11:309, 1953.

### *Idiopathic Hypercalcemia with Growth Retardation*

Bongiovanni, A. M., Eberlein, W. R., and Jones, I. T.: Idiopathic Hypercalcemia of Infancy, with Failure to Thrive. *New England J. Med.*, 257: 951, 1957. (Reviews earlier literature.)

# The Bones and Joints

A somewhat arbitrary arrangement of the various disturbances of the skeleton has been made on the basis of their etiology and of their management. In the first subsection are grouped the various anatomic defects. Many, but not all, of them are genetically determined, some develop in utero and others after birth. For the majority of these disturbances there is no therapy, but there are exceptions, as, for example, in the craniosynostoses, the

funnel chest deformities associated with cardiorespiratory embarrassment, or basilar impression (platybasia) associated with compression of the brain stem.

The section entitled Orthopedic Pediatrics includes the skeletal disturbances likely to be the joint concern of the pediatrician and the orthopedic surgeon. The remediable congenital dislocations and deformities are included in this division.

## SKELETAL DEFECTS

### DEFECTS IN OSSIFICATION OF THE SKULL

#### ANENCEPHALY

(ACRANIA)

See page 1075.

#### CRANIOSYNOSTOSIS

(STENOCEPHALY)

Premature closure of the sutures of the skull results in deformities of the head and often in damage to the brain and the eyes.

**Etiology.** The frequent association of premature synostoses of the skull with other skeletal defects suggests that the skeleton is adversely affected early in embryonic life.

**Pathology.** In the normal newborn infant the bones of the cranium are still somewhat separated, but soon after birth the definitive sutures are established. In the sutures the edges of the flat bones are separated by a layer of fibrous tissue which represents a remnant of the original membranous skull. Growth of the bones of the vault takes place in this fibrous strip; when the sutures are obliterated, this tissue ceases to grow and disappears. The definitive sutures, such as the coronal, sagittal and lambdoid, do not begin to close before the thirtieth year.

In the various forms of craniosynostosis one or several of these sutures are obliterated

before or soon after birth, and growth of the adjacent bones is inhibited in a direction at a right angle to the obliterated suture. As a result the diameter of the skull is reduced in this direction, and a compensatory growth takes place in regions where open sutures permit it.



FIG. 351. Craniosynostosis in a child 5 years of age who also had mental deficiency and paralysis of the ocular muscles.





FIG. 352. Acrocephalosyndactyly in a boy 12 years of age who also had obesity, hypogenitalism and mental deficiency. (See Laurence-Moon-Biedl syndrome, p. 1232).

**Clinical Forms.** In *scaphocephaly* the sagittal suture is closed prematurely, and a long and narrow head develops. The line of the obliterated suture is usually indicated by a prominent bony ridge. Pressure symptoms develop in many but not in all cases. Although there may be some elevation of intracranial pressure early, symptoms are usually not observed until functional closure of the other sutures occurs by about two years of age. Scaphocephaly affects males more often than females. Associated malformations are observed, and mental retardation occurs in some cases. Ocular complications are not frequent. Craniosynostosis may be found in patients with vitamin D-resistant rickets and affects more than one generation.

In *oxycephaly* there is a premature closure of the coronal suture, with occasionally premature closure of other sutures as well. In some instances the coronal suture is closed in its entire length; in others, in the lateral portions only, so that various types of deformities may develop. One speaks of a towerhead (*turriccephaly*) if the frontal, parietal and occipital bones ascend steeply and the vertex is dome-shaped. In other cases the head is pointed in the region of the anterior fontanel (*acrocephalus*) (Fig. 352). In asymmetry

of a stenocephalic head the term *plagiocephaly* is sometimes used. Premature closure of the coronal suture frequently leads to serious complications, since the brain or adjacent structures may be damaged by compression. The patient complains of headaches; frequently there is loss of vision, and at times there are convulsions. The roofs of the orbits are depressed, and exophthalmos develops. There may be strabismus and nystagmus, and examination of the fundi reveals papilledema or optic atrophy. The base of the skull and the facial bones are often hypoplastic. The palate is highly arched and sometimes cleft. Mental retardation is common. Other malformations such as cardiac anomalies, choanal atresia or defects of the elbow and knee joints and of the parietal bones may also be present. Syndactylism is the most frequently associated anomaly (see below). A familial form of oxycephaly associated with hemolytic jaundice has been reported.

*Acrocephalosyndactyly* is a syndrome consisting of acrocephaly and syndactyly of the hands (Figs. 352, 354) and sometimes also of the feet. A number of cases with syndactyly of the hands and polydactyly of the feet have been reported. As a rule, acrocephalosyndactyly occurs sporadically. Affected persons seldom have children, but an instance of the

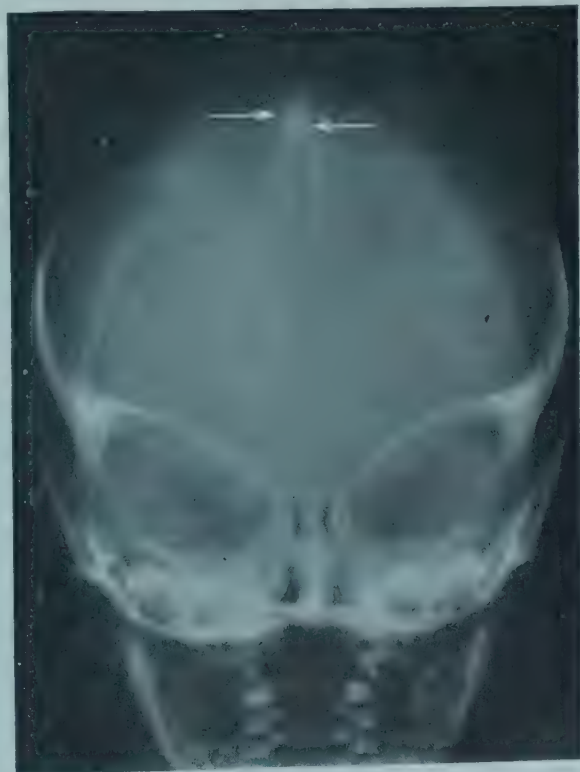


FIG. 353. Craniosynostosis. The sagittal suture is narrow and bridged by bone (arrow). The skull was elongated in its anteroposterior dimension.

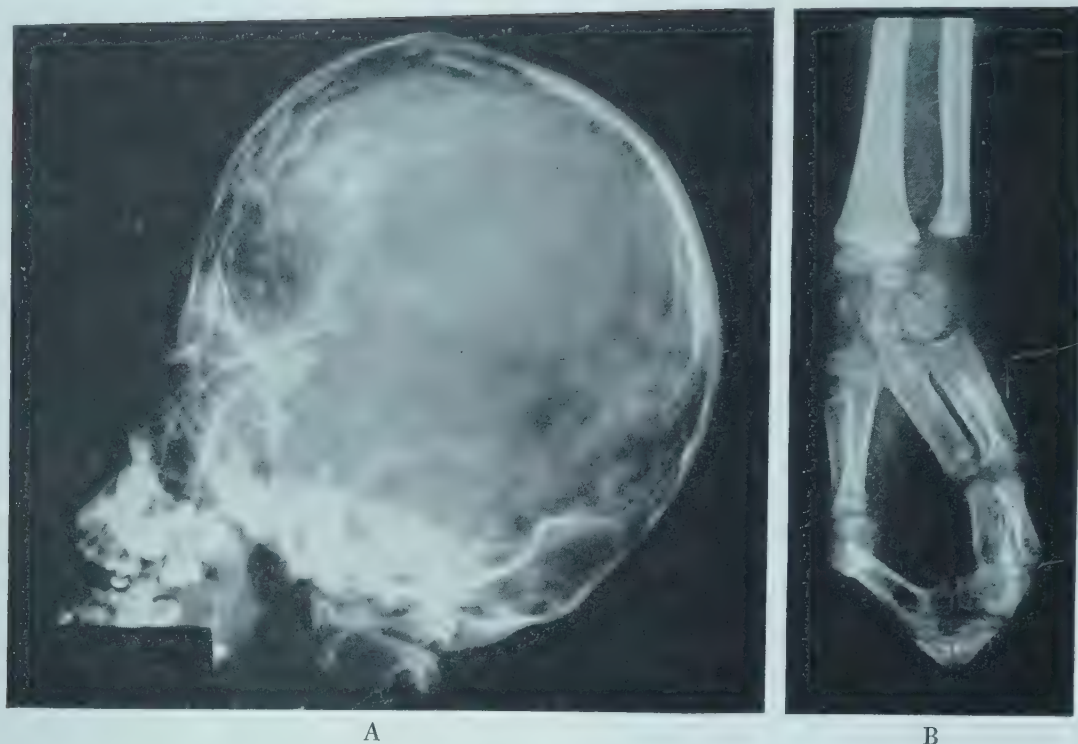


FIG. 354. Roentgenograms showing (A) acrocephalus and (B) syndactyly of the hand.

syndrome in a mother and a child has been observed.

*Craniofacial dysostosis (Crouzon's disease)* is a syndrome characterized by acrocephaly, a beak-shaped nose, hypoplastic maxilla, short upper and protruding lower lips, exophthalmos and external strabismus.

**Differential Diagnosis.** Oxycephaly must be distinguished from a familial form of high skulls in which premature closure of the sutures does not take place. Excessive growth of the adenoids is sometimes associated with a high skull and exophthalmos, but the sutures remain open. In microcephaly the head is small, owing to failure of the brain to grow; there are no evidences of increased intracranial pressure.

In craniosynostosis when there is compression of the brain, roentgenograms reveal convolutional atrophy, absence of one or more sutures, shallow orbits and underdevelopment of the sinuses, in addition to the abnormal shape of the skull. In acrocephalosyndactyly the phalanges are defective and fused with each other or with the metacarpal bones (Fig. 354).

**Prognosis.** During the first few years of life, when rapid growth of the brain may cause a spatial disproportion, the prognosis without treatment is doubtful. If no symptoms of increased intracranial pressure become noticeable in the first decade of life, the prog-

nosis is fairly good, and the chances for loss of vision are not great. In rare instances premature synostosis of the cranial sutures occurs as a hereditary trait which results in deformity of the skull without symptoms of spatial disproportion.

**Treatment.** If surgical repair is performed before there is significant cerebral or visual damage from compression of the brain, it appears that mental and visual defects can often be avoided. Furthermore, elimination of the cosmetic defect may have a significantly favorable psychologic effect. For these reasons operation is now recommended in some clinics as soon as the diagnosis is made in the first year of life.

If there are coronal or multiple synostoses, operation should not be delayed. The decision is more difficult in cases of isolated sagittal synostosis, since some children with this anomaly remain symptom-free. Surgical treatment consists in linear craniectomy along the prematurely closed suture and insertion of polyethylene film over the edges of the bone to prohibit its regeneration.

## PLATYBASIA

(OCCIPITALIZATION OR ASSIMILATION OF THE ATLAS, BASILAR IMPRESSION)

This condition may be primary or secondary. In *primary* platybasia, which is perhaps better



designated as occipitalization or assimilation of the atlas, there is a congenital malformation, with encroachment upon the upper cervical vertebral canal and posterior cranial fossa. For an understanding of this anomaly it is necessary to recall the fact that, embryologically, the occipital condyles and foramen magnum are derived from anlagen which resemble those of the first and second cervical vertebrae, which normally fuse with each other, but not with the upper cervical centers. In primary platybasia the first and second occipital segments and the first and second cervical vertebrae may all be fused into one bony mass, similar to the fusion or failure of segmentation of the cervical vertebrae below the second cervical vertebra in the Klippel-Feil syndrome.

*Secondary platybasia*, or basilar impression, occurs when disease has softened the cranial bones to such an extent that they no longer suffice to support the weight of the head. This may occur in rickets and certain forms of osteomalacia. The posterior cranial fossa is encroached upon as the cranial vertex approaches the occiput.

The importance of both primary and secondary platybasia is due to the effects upon the central nervous system. The medulla may be sharply kinked over the odontoid process of the second cervical vertebra, with resultant pressure upon the various spinal tracts. Localized thickening of the dura at the cranio-vertebral junction is frequently associated with these bony anomalies and contributes to the brain stem constriction. At times the loss of volume of the posterior fossa, through ap-

proach of the tentorium to the occiput, may produce foraminal hernia. A striking feature of platybasia is its tendency to remain asymptomatic in early life, neurologic changes becoming manifest from the fourteenth to the fortieth year.

The encroachment of the osseous structures upon the brain stem may be relieved in some instances by surgical means.

**Hypertelorism.** This condition, characterized by an abnormally large distance between the eyes and a broadening of the root of the nose, is a symptom and not a disease entity. It is often associated with mental deficiency and may be combined with other congenital defects. Mild forms may occur in otherwise normal children. The lesser wings of the sphenoid bone are overdeveloped, while the greater wings are relatively small. Hypertelorism can be transmitted through several generations.

### PARIETAL FORAMINA

These are irregularly shaped congenital defects with well defined margins symmetrically placed on each side of the posterior third of the sagittal suture. They are palpable, but frequently their presence is discovered roentgenographically. They may be inherited or occur sporadically and may be found in otherwise normal persons. At times they are associated with other congenital defects of the skeleton, eye, central nervous system and heart. They must be distinguished from defects of the skull associated with meningo-encephalocele or from defects caused by



FIG. 355. Hypertelorism in a girl 17 months of age (right) who also had a cleft palate and cleft lip. There was no bony deficiency of the forehead. The mother also had hypertelorism, and the father had a harelip. The picture shows contrast with normal child of about the same age.



FIG. 356. A typical example of lacunar skull (age, 18 days). Note the arborizing patterns of bony ridges which sharply delineate and separate rounded defects from one another. This patient had a large lumbosacral meningocele. (Vogt and Wyatt: Radiology, Vol. 36.)

syphilis, xanthomatosis, multiple myeloma or malignant metastases. Parietal foramina do not cause discomfort, and no treatment is indicated.

### LACUNAR SKULL

(LÜCKENSCHÄDEL)

This cranial anomaly is characterized by defects in the vault in the form of shallow depressions or deep cavitations extending to the outer surface and occurring mainly in the frontal or parietal areas. The thinned areas of bone are lined by dura and bordered by ridges of osseous tissue. The outer surface of the skull is smooth, but the inner table is rough, and in the irregular surface are many interlacing columns of bone surrounding oval depressions covered with a parchment-like membrane or a thin layer of bone. The roent-

genographic appearance is diagnostic and shows diminution in the thickness of the skull bones and variations in their density as irregular patches of rarefaction, or lacunas, with interlacing ridges of increased density (Fig. 356). Differentiation must be made from the generalized "hammered silver" or "digital impression" appearance of the skull bones which is observed on occasion without any apparent explanation for it and in other instances in association with increased intracranial pressure.

Meningocele is the most frequently associated defect. Lacunar skull can be detected in roentgenograms of about half of the infants with meningocele, particularly in those who have myelomeningocele or thoracic meningocele. When a meningocele is associated with a lacunar skull, progressive hydrocephalus is a frequent complication.

## DEFORMITIES OF THE EXTREMITIES

Severe defects of the extremities are only rarely compatible with viability. Children with so-called congenital amputations who survive infancy can be greatly benefited by prostheses and physical and psychologic rehabilitation. Minor defects are often encoun-

tered and require treatment as well as interpretation.

### MISCELLANEOUS DISTURBANCES

Complete absence of all extremities (*amelia*) or of one entire extremity (*ectromelia*) is a



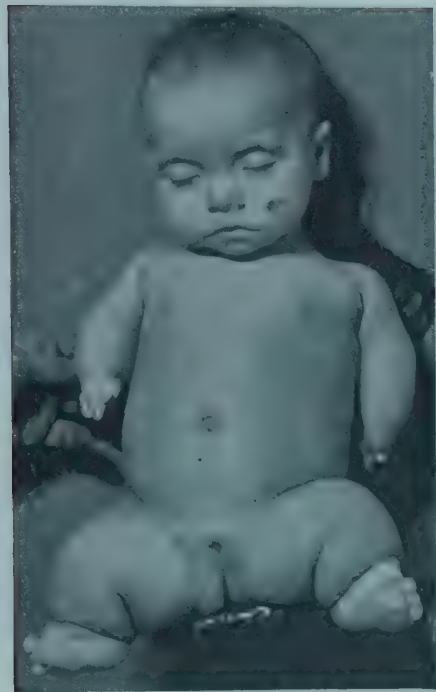


FIG. 357. Hemimelia in an infant 11 months of age; picture taken at autopsy.

rare malformation. The term *hemimelia* is used for a defect of the distal parts of the extremities in which a tapering stump is formed. In *phocomelia* the proximal part of the extremity is defective, and a hand or foot seems to spring directly from the trunk (Figs. 357, 358). Individual bones may be absent. Absence of the humerus and ulna is rare; absence of the radius is usually associated with clubhand. Absence of the fibula is more frequently encountered than absence of the femur or tibia. As a rule, it is combined with pes valgus. Absence of the patella is indicated by a transverse fold of the skin in front of the knee joint during extension.

*Polydactyly* (supernumerary fingers or toes) may be found in a single member of



FIG. 358. Phocomelia and ectrodactyly in a girl 3½ years of age.

a sibship, but there are pedigrees in which polydactyly is inherited as a dominant trait. Polydactyly is sometimes associated with other malformations (see Chondro-ectodermal Dysplasia, p. 1237).

*Syndactyly* (Fig. 359), union of fingers or toes, may consist in fusion of the bones or webbing of the skin (*zygodactyly*). Syndactyly most frequently involves the third and fourth fingers and the second and third toes. It is often seen in children with multiple malformations (*acrocephalosyndactyly*) and in children who otherwise are entirely normal. In the latter, syndactyly is often hereditary.

*Split hand and split foot (lobster claw)* are deep clefts in the anterior part of the hand or foot, and the fingers and toes have different degrees of syndactyly. The foot appears split in the area where the second or third toe should be. The parts of the foot which lie on either side of the cleft are fused



FIG. 359. Syndactyly.



FIG. 360. Split feet (lobster claws) in a child whose mother, maternal aunt and maternal grandfather had similar malformations.

into masses in which terminal digits can be recognized (Fig. 360). Many pedigrees are known in which this malformation is inherited as a dominant trait. *Brachydactyly*, abnormal shortness of the fingers and toes resulting from lack of one of the phalanges, may be inherited as a dominant trait. *Clino-dactyly*, incurving of the little finger, may be inherited as a dominant trait. It is also often seen in mongolism. *Macroductyly* is a hypertrophy of one or several fingers and toes (Fig. 361).

A variety of skeletal defects, of which absence of thumbs and radii is common, occur at times in association with a congenital hypoplastic anemia (p. 935).

#### LAURENCE-MOON-BIEDL SYNDROME

This is a syndrome of retinitis pigmentosa, polydactyly, mental retardation, obesity and hypogenitalism, often with several members affected in a sibship. There is evidence that it is inherited as a recessive trait. The syndrome is not always limited to the five malformations mentioned, and incomplete forms of it are not rare. Dwarfism, acroceph-



FIG. 361. Macroductyly.

aly, oxycephaly, syndactyly, deafness and microphthalmos may also be associated with the syndrome (Fig. 352; see also p. 1162).

### DEFORMITIES OF THE VERTEBRAE, CLAVICLES, SCAPULAS AND STERNUM

#### CLEIDAL AND CLEIDOCRANIAL DYSOSTOSIS

This congenital syndrome is characterized by absence of the clavicles and often by delay of ossification of the skull. The defect is due to a developmental disturbance which is often genetic in origin and transmitted as a dominant trait. Other cases are sporadic and inheritance cannot be proved. Males and females are equally affected. The defective bones are usually membranous in origin. However, the ends of the clavicles, which are often also missing, are derived from cartilage, and other bones of cartilaginous origin are also affected.

**Clinical Manifestations.** The entire clavicle may be absent, or the sternal and acromial ends are present, but the connecting shaft missing. Sometimes the two ends are fairly well developed and joined by a narrow fibrous strip, thus simulating the appearance of a fractured clavicle on the roentgenogram.

In serious clavicular defect the shoulders can be approximated in front to a remarkable

degree (Fig. 362). The muscles which are normally attached to the clavicle may also be defective. At birth ossification of the calvarial bones is so delayed that the fontanels are excessively large and the sutures widely open. Large bosses develop on the frontal, parietal and occipital regions, and the skull assumes a globular shape, at times with a "hot cross bun" type of deformity, owing to depressions along the coronal and sagittal sutures. As the patient grows older, ossification of the calvarial bones progresses slowly, but the fontanels may remain open until adulthood. The sutures frequently close with interposition of wormian bones. The facial bones are underdeveloped, and the sinuses may be absent. The palate is usually highly arched and, in some cases, cleft. The dentition is irregular. Congenital cranial dysostosis may occur without anomalies of the clavicle. Deformities of the vertebrae and of the bones of the fingers and toes and delayed ossification of the pubic bones have also been observed. In hereditary cases the cleidal and the cleidocranial forms have occurred in the same sib-





FIG. 362. Cleidocranial dysostosis in a girl 5 years of age. (Cook: Arch. Pediat., Vol. 51.)

ship. The patients are usually of short stature, but their mentality and general health are unaffected.

**Diagnosis.** Roentgenograms of the chest reveal absence of the clavicles or nonunion of their ends; those of the head show a lack of ossification of the affected bones. The delayed ossification of the calvarium may suggest hydrocephalus, rickets or cretinism.

**Prognosis and Treatment.** The defects rarely cause discomfort or disability. Occasionally a clavicular fragment may press on nerves and cause pain; removal of the disturbing fragment is indicated.

### KLIPPEL-FEIL SYNDROME

In this syndrome there is a reduced number of cervical vertebrae, or there are multiple hemivertebrae formations fused into one osseous mass. Platybasia, spina bifida, scoliosis, torticollis, Sprengel's deformity or other malformations may be associated. External symptoms are shortness of the neck and lowering of the hairline. The motion of the neck is limited. In severe cases neurologic complications may develop.

### PTERYGIUM COLLI

(CONGENITAL WEBBED NECK)

In pterygium colli the skin of the lateral aspects of the neck forms a thick fold extending from the mastoid region to the acromial

process. Large folds of skin are also occasionally seen in the posterior parts of the neck. These anomalies are often combined with congenital lymphangiectatic edema of the hands and feet, high palate, cubitus valgus, deformities of the nails and ears and ovarian agenesis (see Turner's syndrome, p. 1198).

### SPRENGEL'S DEFORMITY

In this condition (Fig. 363) one or both scapulas are in a congenitally high position with the lower angle turned toward the spine. Sometimes a bridge of bone unites the spine to the scapula (omovertebral bone). The arm



FIG. 363. Sprengel's deformity, showing inability to raise the arm completely on the affected side.

on the affected side cannot be raised above a right angle with the body, and the head is inclined toward this side. Scoliosis is present. Sprengel's deformity may occur with the Klippel-Feil syndrome.

### WINGED SCAPULAS

This condition may result from underdevelopment or paralysis of the muscles which are inserted on the vertebral border of the scapula. It is sometimes a manifestation of a *scaphoid scapula*, which is characterized by a concave vertebral border.

### DEFORMITIES OF THE STERNUM

The two halves of the sternum may remain separated (*fissure of the sternum*). Pigeon

*breast* consists in a prominence of the sternum and the cartilaginous parts of the ribs, with lateral depressions of the thorax.

### PECTUS EXCAVATUM

(FUNNEL CHEST)

Funnel chest, or indentation of the lower part of the sternum, may be rachitic in origin or the result of chronic obstruction to respiration. In most instances, however, the condition is congenital. The reason for the defect is not apparent in all instances, but in some it is due to a short central tendon of the

diaphragm. The manubrium sterni is at the normal level, but the inferior parts are depressed, and the xiphoid may approach the vertebral bodies. The volume of the lung is decreased, and the heart displaced to the left. Respiration is paradoxical, since contraction of the diaphragm exerts a pull on the xiphoid and the costal cartilages. The patients appear round-shouldered, hollow-chested, thin and underdeveloped. The deformity may have untoward psychologic effects on the child.

There are differences of opinion as to the best age for repair and also as to the type of surgical procedure.

## DISTURBANCES IN OSTEOGENESIS AND IN ENDOCHONDRAL OSSIFICATION

### CHONDRODYSTROPHY

(ACHONDROPLASIA)

Chondrodystrophy is caused by a disorder of the cartilage which begins in prenatal life and leads to a specific type of dwarfism. Since the long bones of the extremities are affected to a greater extent than the vertebrae and the bones of the head, a disproportion of the extremities and the rest of the body becomes manifest (*micromelia*).

Since the skeletal changes depend upon a disturbance of endochondral ossification, the term *chondrodystrophy* appears appropriate. The term *achondroplasia*, indicating an absence of cartilage formation, is widely used, but does not correspond to the histologic picture.

**Etiology.** Genetic factors play a role in many cases, most pedigrees suggesting a dominant, some a recessive, mode of transmission. Sporadic cases occur. Bleyer considers advanced maternal age a possible etiologic factor. Males and females are equally affected.

**Pathology.** The basic process is a disturbance of endochondral ossification caused by an inability of the epiphysal plate to produce a sufficient amount of columnar cartilage. The result is deficient longitudinal growth of the bone. The rows of columnar cartilage also lack parallel arrangement and are of unequal length. The intercellular matrix of the cartilage has a fibrillar rather than a hyaline structure. The line of preparatory ossification is irregular. The bone trabeculae are short and thick and lack normal orderly arrangement. Sometimes a transverse vascular strip of connective tissue, which originates in the peri-

osteum, grows between the epiphysis and the diaphysis, thus adding another obstacle to longitudinal growth. If this strip affects only one side of the bone, the other side, which grows more rapidly, curves around the stunted half, and the bone becomes bowed. Periosteal ossification is little affected, so that transverse growth of bones is not greatly disturbed.

Short and thick bones are the result of such disproportionate growth. The epiphysal cartilage, which is underdeveloped in the longitudinal direction, may extend well beyond the shaft in the transverse direction, creating a mushroom-like enlargement. This hyperplastic type is more common in young children. In older persons hypoplasia of the cartilage is seen in the transverse as well as in the longitudinal direction, and the enlargement of the metaphysis is less pronounced (hypoplastic type). Owing to insufficient cartilaginous growth, the base of the skull is short, but the bones of the cranial vault which are of membranous origin continue to grow. This disproportionate growth results in a typical profile characterized by a broad nose with a depressed bridge, and a bulging forehead.

**Clinical Manifestations.** The chief characteristic of chondrodystrophy is the combination of short extremities with a head and trunk approximating normal size. The limbs are often curved and their epiphysal junctions enlarged and prominent. The shortness in the thighs and upper arms is greater than in the lower legs and forearms, and the hands, which are short and broad, may not reach below the hips. The plump fingers are not entirely parallel (Fig. 364). The relatively



large head exhibits a prominent forehead, flattening of the bridge of the nose, and a forward projection of the mandible; a slight degree of hydrocephalus is sometimes present. The chest is of normal length, but beading of the ribs and flaring of the costal margins are generally noticeable. The vertebral bodies are usually of normal height, but occasionally a wedge-shaped vertebra may be seen in the roentgenogram.

The thoracic kyphosis and the lumbar lordosis are usually accentuated. Protrusion of the abdomen and the gluteal region results in a characteristic posture (Fig. 364). An umbilical hernia is common. The chondrodystrophic pelvis has a kidney-shaped entrance, the promontory protruding forward. This deformity is an obstacle to delivery in females, often necessitating cesarean section. The gait is waddling, and subluxation of the deformed head of the femur sometimes occurs. Extension of the joints may be impeded by the irregular shape of the epiphyses. The skin is loose and may form transverse folds and pads. The muscular development is good. The mentality is usually normal, and chondrodystrophic dwarfs are reputed to be witty and entertaining.

Associated malformations such as harelip, cleft palate and polydactyly occur occasionally. In general, the endocrine glands function normally, although precocious puberty has been observed in several cases.

**Diagnosis.** The thickness of the bones and their irregular epiphysial ends as visualized in the roentgenogram make the diagnosis possible even in the newborn. The bones of the extremities are short and broad and show a mushroom-like broadening of the ends of the shafts. The fibula appears longer than the tibia. Curving may be seen in various places. At the epiphysial ends of the shafts are such irregularities as cupping, fraying and spurs. The mineral content is good throughout the bones, and there are no periosteal changes. Ossification of the epiphyses and of the carpal and tarsal bones is not delayed, but their outlines are irregular. The metacarpal, metatarsal and phalangeal bones are also short and thick and show irregularities of their epiphysial ends (Fig. 365). On the lateral view the base of the skull appears short. The bones of the vault bulge on all sides beyond the base.

The depressed bridge of the nose may suggest syphilis or cretinism. *Syphilis* can be ruled out by the roentgenogram and by serologic tests; normality in mental development

and of serum protein-bound iodine renders the diagnosis of *cretinism* impossible. A superficial examination of the roentgenograms may suggest *rickets*; however, the intensive calcification of the irregular epiphyses is characteristic of chondrodystrophy (Fig. 365).

Other forms of micromelia can be distinguished from chondrodystrophy by clinical examination or the roentgenogram. The legs of children with *osteogenesis imperfecta* or *osteopsathyrosis* may become shortened and deformed after repeated fractures, but the bones are long and slender. *Hypophosphatasia* resulting in congenital micromelia can be mistaken for chondrodystrophy in the neonatal period, but the deficiency of ossification and low serum phosphatase establish the diagnosis.

**Prognosis and Treatment.** Many children with chondrodystrophy die in utero or soon after birth, particularly when born prema-



FIG. 364. Chondrodystrophy.



FIG. 365. Chondrodystrophy of upper and lower extremities.

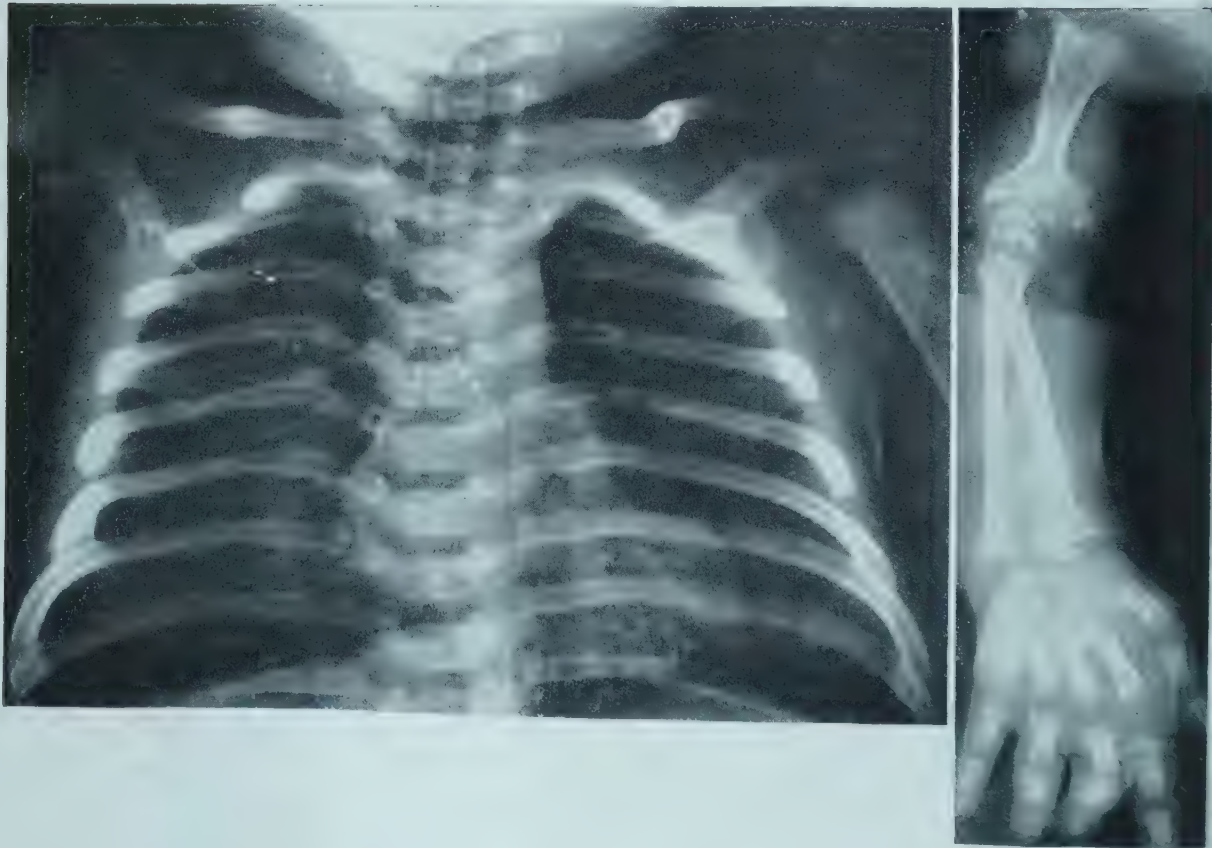


FIG. 366. Chondrodystrophia calcificans congenita. A, There is diffuse calcification of the laryngeal, tracheal and bronchial cartilages. In early infancy the infant had significant dyspnea, presumably due to the constricted tracheobronchial tree. B, Shortening of humerus. Numerous calcifications in the area of the elbow joint. Contractures of finger joints.



turely. Those who survive usually have good general health, and their mental development is satisfactory. Their height rarely exceeds 140 cm. (55 inches).

No specific treatment is known. Early orthopedic correction of developing deformities may improve the appearance.

### ATYPICAL CHONDRODYSSTROPHIES

#### CHONDRO-ECTODERMAL DYSPLASIA

(ELLIS-VAN CREVELD SYNDROME)

The combination of chondrodysplasia, ectodermal dysplasia, polydactyly and congenital heart disease is a rare syndrome. The bones of the extremities are short and thick, and the terminal phalanges of the fingers and toes and the nails are dystrophic. There is a sixth finger on the ulnar side of each hand. Dentition is defective, but the sweat glands and the skin are normal. The syndrome is probably inherited as a recessive trait.

#### CHONDRODYSSTROPHIA CALCIFICANS CONGENITA

This rare form of chondrodystrophy has a typical roentgenographic appearance. The carpal and the tarsal bones are replaced by numerous small but distinctly calcified spots scattered about the affected areas. They represent deposits of calcium in malacic cartilage. The epiphyses may be stippled with similar small calcium deposits. The limbs are short, particularly in their proximal segments (Fig. 366). Contractures are not rare, and cataracts are often present. Calcifications may also occur in the tracheal cartilages (Fig. 366) and be responsible for respiratory embarrassment.

#### MORQUIO'S DISEASE

(FAMILIAL OSSEOUS DYSTROPHY, HEREDITARY OSTEOCHONDRODYSSTROPHY)

The dwarfism produced by this condition clinically resembles that of rickets. The deformities of the spine, chest and extremities are similar to the end results of severe and untreated rickets. This type of chondrodystrophy is genetically determined. Consanguinity of the parents and also of the paternal grandparents was reported in the family described by Morquio. A recessive mode of transmission is suggested; in one unusual sibship the disorder was transmitted as a sex-linked recessive trait. Sporadic cases have also been described.

**Clinical Manifestations.** Development appears to be normal until the infant begins to

walk. The face and the skull are only slightly affected; the neck is short (Fig. 367). In contrast to typical chondrodystrophy, the spine and the chest become severely deformed in Morquio's disease. Fusion of cervical vertebrae and platybasia may occur. The thorax is short and broad; the anteroposterior diameter is increased, and the sternum protrudes. There is an exaggerated thoracic kyphosis of the spine and scoliosis of a varying degree. The abdomen protrudes; genital development is normal. The long upper extremities extend to the knees. The hands and fingers are long and soft. Genu valgum and flat feet are present. The joints are enlarged; the muscles and ligaments are flaccid; the gait is waddling. There are no characteristic chemical or serologic changes in the blood. Mental development is not impaired.

**Diagnosis.** There is an external resemblance to *rickets*, but the absence of hypophosphatemia and the roentgenographic appearance of the bones exclude rickets. In Morquio's disease, basilar invagination and occipitalization (platybasia) may be present in addition to anomalous segmentation of the cervical vertebrae. The vertebrae are flattened, and their cranial and caudal surfaces are uneven. The shafts of the long bones are of

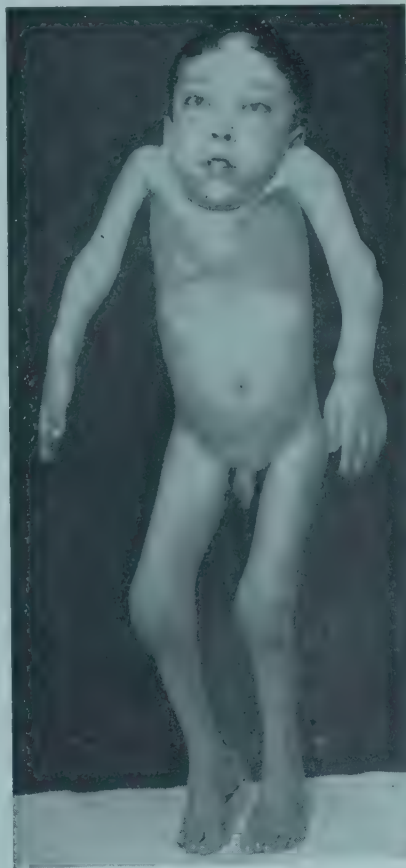


FIG. 367. Morquio's disease.

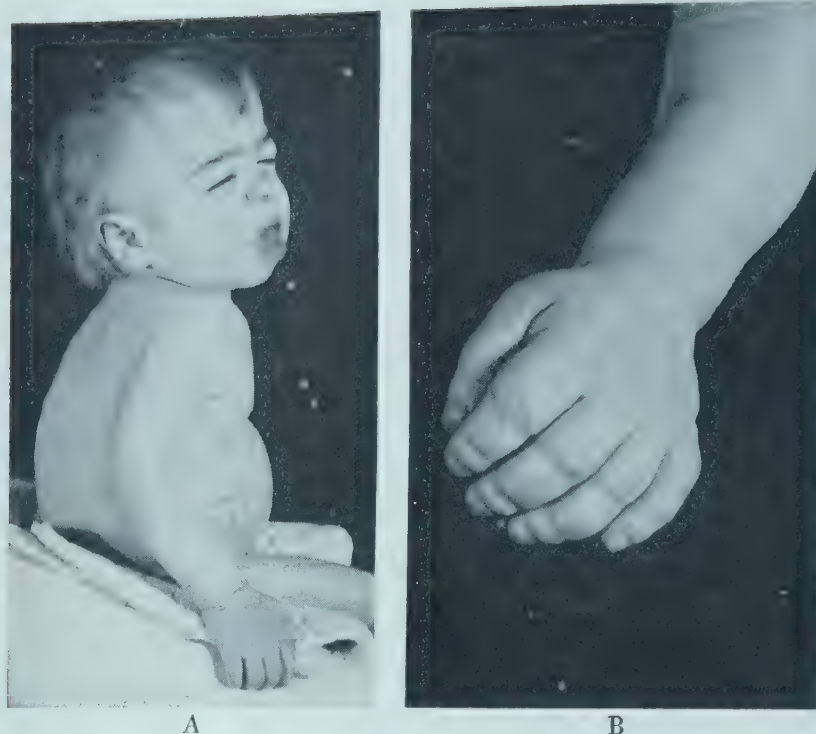


FIG. 368. A, Gargoylism in a child 2 years of age, showing heavy features, depressed nasal bridge, kyphosis and stunting of growth; also outline of the enlarged liver. Child had corneal opacity and was mentally deficient. B, Typical spadelike hand in gargoylism.

normal length and shape. The outlines of their epiphysial ends are irregular, with flattening in some places and abnormal projections in others. The epiphyses are of irregular shape and sometimes fragmented. The ends of the metacarpal bones resemble those seen in typical chondrodystrophy.

In typical *chondrodystrophy* the head and trunk are large and the extremities short, whereas in Morquio's disease the head is of normal size, the trunk is short, and the extremities relatively long. In *gargoylism* the mentality is impaired, and a cloudy cornea and enlargement of the spleen and liver are found. There are, however, many atypical chondrodystrophies which cannot be distinguished with certainty from Morquio's disease.

**Prognosis and Treatment.** As far as physical development is concerned, the prognosis is unfavorable, since the deformities progress and become more pronounced. There is no specific treatment. Orthopedic treatment may prevent or correct the deformities to a certain extent.

#### GARGOYLISM

(HURLER'S SYNDROME, DYSOSTOSIS MULTIPLEX, LIPOCHONDRODYSTROPHY)

This disorder is the result of a metabolic disturbance which affects the skeleton as well as

soft tissues. Although the metabolic disturbance is present at birth, most of the symptoms develop in postnatal life. The fully developed disease exhibits cloudy corneas, hepatosplenomegaly, mental deficiency, skeletal changes and dwarfism. Both sexes may be affected. The disorder is genetically determined, most cases being due to a single recessive gene. Sex-linked recessive transmission has also been observed. The basic metabolic disturbance results in accumulation of an abnormal intracellular material which affects the cells and structure of many organs. The nature of the stored substances has not been determined, but they are thought to be mucopolysaccharides.

**Clinical Manifestations.** The skull is frequently malformed and may be scaphocephalic, oxycephalic or hydrocephalic. The closure of the anterior fontanel may be delayed. The supraorbital ridges are prominent, and the bridge of the nose is depressed. A profuse nasal discharge is usually present. The tongue is enlarged and the neck short. There is a kyphosis in the dorsolumbar region (Fig. 368, A). The heart is frequently enlarged, and a systolic murmur can be heard (p. 896). Dyspnea occurs on slight exertion, and cyanosis in advanced stages. The abdomen is prominent; the spleen and liver are





FIG. 369. Gargoylism. A, Lateral view of spinal column; B, hand.

enlarged; an umbilical hernia is frequently present. Externally, the sex organs appear normal, but sexual maturation does not occur. The joints show limited extensibility, particularly in the fingers. The appearance of the hands is characteristic (Fig. 368, B): the breadth is greater than the length; the fingers are maintained in a "clawing" position, and the fourth and fifth fingers are incurved. Coxa valga and genu valgum of a moderate degree may be present. The combination of the clawlike hands, the large head, the grotesque, inhuman facies and deformed limbs accounts for the designation of "gargoylism." The thickness of the skin contributes to the characteristic picture. Corneal opacities and mental retardation occur in a large percentage of these children. In the white blood cells abnormal granulations (Reilly bodies) may be found, but laboratory studies show no other characteristic changes. Several atypical forms of this disorder have been described.

**Diagnosis.** The stunted growth, the thickness of the skin and the mental retardation suggest *cretinism*, but the laboratory data and the roentgenographic changes are adequate for differentiation. Roentgenograms show the sella turcica to be elongated in many cases. The changes of the spinal column are best seen in the lateral view. The vertebral bodies

are shortened in the sagittal direction, their anterior and posterior outlines appear concave, and the spinous processes are directed downward. The first or second lumbar vertebra is small and displaced backward, resulting in deformity of the spine (Fig. 369, A). The lower ribs are club-shaped. The humerus is long and thick, the ulna and radius short and thick; their epiphysial ends and their epiphyses have irregular outlines. The metacarpal bones are bottle-shaped, the basal phalanges cylindrical (Fig. 369, B). The femur, tibia and fibula are moderately thickened, and their epiphyses are angular.

The disproportionate shortness of the extremities of classic *chondrodystrophy* is absent in gargoylism. The deformities of the head, the appearance of the hands and the mental retardation distinguish this disorder from *Morquio's disease*.

**Prognosis and Treatment.** The prognosis is unfavorable, since the patients remain retarded in mental and physical development. Orthopedic treatment may aid in correcting the deformity of the spine.

### OSTEOPETROSIS

(OSTEOSCLEROSIS FRAGILIS, ALBERS-SCHÖNBERG'S DISEASE)

Osteopetrosis is a rare disorder characterized by hardness and brittleness of the bones.

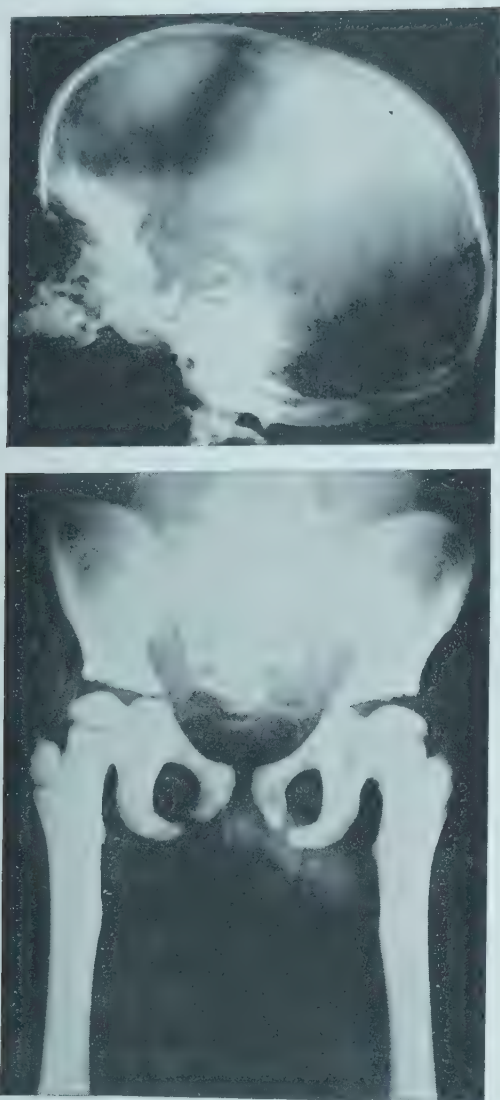


FIG. 370. Osteopetrosis of skull, pelvis and femurs.

**Etiology.** In the majority of cases the mode of inheritance appears to be recessive; in some cases, dominant. Males and females are equally affected.

**Pathology.** The cortex of the bones, as well as the trabeculae, is thickened. The endochondral ossification is disturbed by lack of resorption of cartilaginous intercellular ground substance. Islands of this partly calcified ground substance, which under normal conditions is replaced by bone, persist and are found in the shafts of the bones. The trabeculae are unusually crowded and numerous. At the ends of the long bones, as well as in the scapulas and pelvic bones, zones of increased and decreased density alternate. The zones of decreased density consist of areas of bone marrow. In the dense parts of the shaft the marrow spaces are reduced in volume; the marrow may contain abnormal cells or may undergo fibrous changes. In the mem-

branous bones the trabeculae are also densely arranged and thickened. The foramina for the cranial nerves are often constricted by an overgrowth of bone. The chemical composition of the bones is normal.

**Clinical Manifestations.** This condition probably always begins in utero, although clinical symptoms may be absent in infancy. Brittleness predisposes the bones to fracture, and roentgenograms taken on occasion of a fracture often reveal the underlying process for the first time. Although the fractures as a rule heal satisfactorily, deformities frequently develop during childhood. The head is square and somewhat enlarged, and deformities of the chest and spine may be present. Vision is usually disturbed early in life and diminishes progressively; the movements of the eyes may be impaired. Cataracts and optic atrophy may develop. A progressive deafness has frequently been described. The teeth develop abnormally and have a tendency to decay. The patient often has a hypochromic anemia and, in the final stage of the disease, a myelophthisic one. Hepatosplenomegaly and enlargement of the lymph nodes have been observed. Osteomyelitis is a frequent complication, particularly in the mandible or maxilla. General growth is retarded, and some of the patients are dwarfed. The mentality is normal, but chronic illness, blindness or deafness may interfere with its development.

**Diagnosis.** Roentgenographic demonstration of increased density of the entire skeleton is the essential feature and is diagnostic. No distinction can be made between the cortex and marrow. There are heavy shadows at the base of the skull, the bones of the vault appearing less dense (Fig. 370). The long bones, particularly the femur and tibia, are club-shaped, and transverse bands are seen near their ends. Similar bandlike stratification may be found in the os ilium and in the scapula, where they run parallel with the outlines of the bones. Skeletal maturation is normal.

Localized sclerotic processes as seen in *siphilis* and *sclerosing osteitis* are easily distinguished from osteopetrosis. A generalized *osteosclerosis* may result from fluorine poisoning, but in such cases calcification of muscles and ligaments is also often present.

**Prognosis and Treatment.** The prognosis is unfavorable in the majority of cases observed during childhood. Accidental detection of osteopetrosis in a number of apparently healthy adults is evidence that the



disorder may exist for a long time without causing significant symptoms.

There is no treatment. The complications are treated symptomatically.

## OSTEOGENESIS IMPERFECTA

This disease is characterized by increased fragility of the bones, which are easily fractured by slight trauma. Patients suffering from this disorder usually have blue scleras and flaccid ligaments; some of them become deaf later in life.

In severe cases fractures occur in utero, and the infant is born with deformities (*osteogenesis imperfecta congenita*). In other instances fractures do not occur until several years after birth, and the tendency to break bones easily disappears after puberty (*osteopsathyrosis*, *osteogenesis imperfecta tarda*). This latter form usually has a milder course, but often occurs repeatedly in the same family or sibship. Whether the two forms are identical is a matter of dispute.

**Etiology.** The disorder is determined before birth. Osteopsathyrosis is often transmitted as a dominant hereditary trait, but the different manifestations (blue scleras, fragility of the bones, deafness, and the like) may be dissociated in various members of the family (p. 237). The congenital form is usually not familial, although rarely it may alternate with the late form (osteopsathyrosis). Whether the congenital cases are nonhereditary (phenocopies) or hereditary on a recessive basis has not been determined.

**Pathology.** Osteogenesis imperfecta is a systemic disease in which a defect of the mesenchyma and of some of its derivatives (scleras, bones and ligaments) is considered responsible for the various symptoms.

The cortex is invariably diminished in thickness, owing to the disturbed formation of periosteal bone. Inactivity of the patient contributes to the atrophy of the bones. Osteoblastic activity is defective, and the osteoid and mature bone are of fetal quality. The generalized mesenchymal involvement in the congenital form of the disease is demonstrable in sections of the skin and scleras by a failure of the reticulum to differentiate into mature collagen. In some cases the abnormally thin scleras allow the underlying pigment to show through. In others increased transparency, but not thinness, of the sclera is observed. Occasionally cataract, coloboma and embryotoxon are associated with this disorder. Deaf-

ness may be due to otosclerosis or labyrinthine disturbance.

**Clinical Manifestations.** In *osteogenesis imperfecta congenita* fractures may occur early in utero, and the infant is born with deformed extremities, since the bones generally heal in abnormal positions. Fractures also occur frequently during the process of delivery. The skull has wide membranous spaces between the bones of the vault, and crackling is often felt on pressure. Many wormian bones are found within the occipital, parietal and temporal bones (Fig. 371, A). The eyes are often prominent, the scleras blue. The neck is short. The chest and the spine are deformed in severe cases. Many children with the severe congenital form die soon after birth. In those who survive, fractures of the extremities may result from otherwise inconsequential trauma. Callus usually forms rapidly, and the process of healing is considered satisfactory. The callus, however, is often replaced by inferior and rarefied bone which is prone to bend and breaks easily. Most of the fractures occur in the legs, where bizarre deformities develop (Fig. 372). Many patients with osteogenesis imperfecta are unable to learn to walk, since every attempt to stand or walk results in fractures.

The levels of calcium and phosphorus in the blood serum are normal.

In *osteopsathyrosis* (*osteogenesis imperfecta tarda*) the child appears normal at birth, and fractures usually do not occur until after the first year of life. There is great variation in the time of the first fracture. Occasionally osteopsathyrosis is so severe that it resembles the congenital form in the development of early and numerous fractures. In the majority of instances, however, only a moderate number of fractures occurs, and the fragility ceases with puberty. The bones of the extremities are long and slender (Fig. 373, A); 70 per cent of the fractures are in the lower extremities. Healing takes place rapidly, but deformities may develop. As a rule all the affected members of a family can be recognized by their blue scleras. Only about two thirds of the members with blue scleras suffer from increased fragility of the bones, and only about one fourth from deafness. The flaccidity of the ligaments and muscles may result in repeated dislocations. Deafness is usually a late manifestation and hence is rarely found in children.

A clear distinction between osteogenesis imperfecta congenita and tarda cannot always

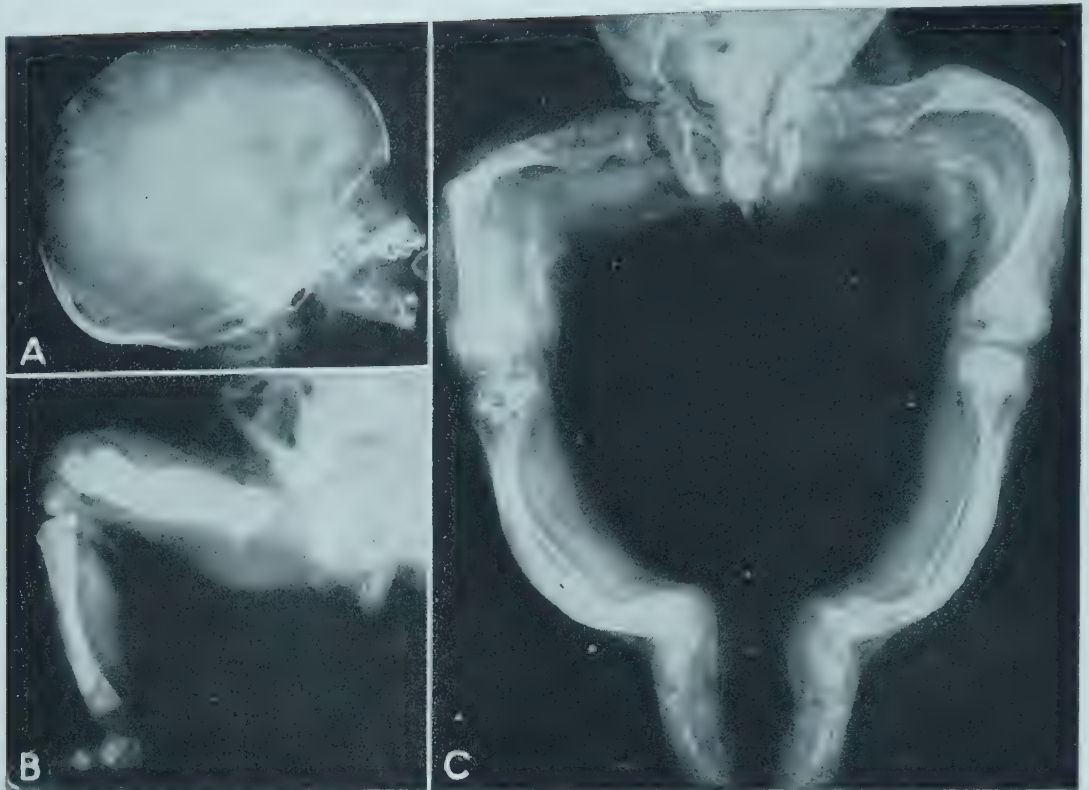


FIG. 371. Osteogenesis imperfecta. A, Skull showing wormian bones. B, Roentgenogram of lower extremity at birth. C, Roentgenogram of lower extremities at 5 years of age.

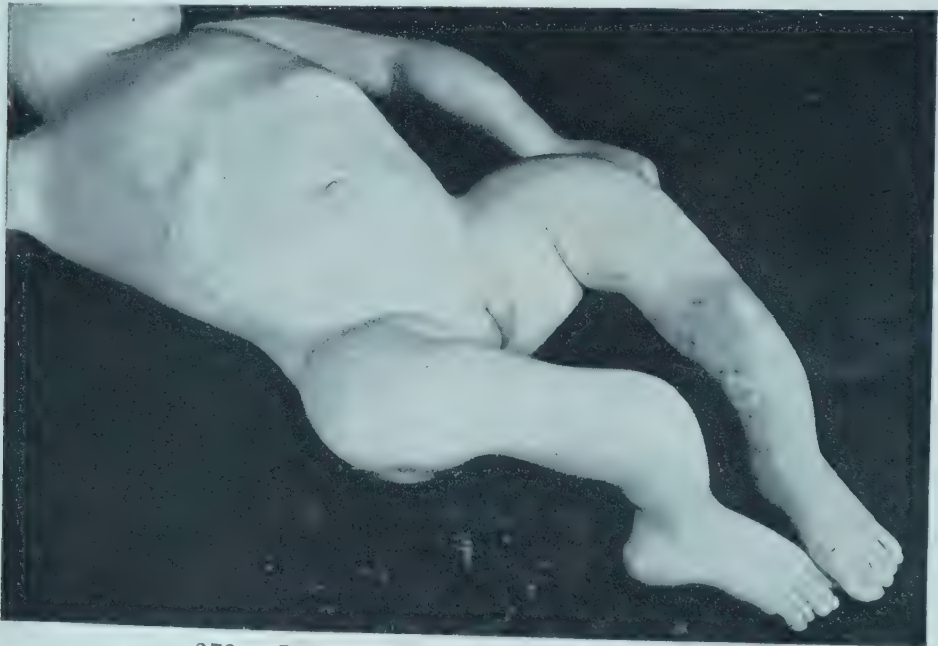


FIG. 372. Osteogenesis imperfecta in a 5-year-old girl.

be made, and intermediate forms may be encountered.

**Diagnosis.** In roentgenograms of the newborn infant the unbroken bones in *osteogenesis imperfecta congenita* are thin, but otherwise appear normal. The previously fractured bones appear irregularly thickened, curved or angulated (Fig. 373, B); the epiphysial ends

are usually normal. The skull is characterized by thinness of the bones and by the osseous islands, the wormian bones, which are separated from each other by numerous sutures of irregular shape. The mineral content of the bones seems reduced, but the bone age corresponds to the child's chronologic age. As the child grows older and the processes of



fracturing and healing continue, the shafts of the bones assume grotesque shapes.

In *osteopsathyrosis* roentgenograms show the unbroken long bones to be slender and elongated. Their epiphyses are normal. Improper healing of fractures may result in deformities; demineralized areas are frequent.

*Syphilis* may be suspected in the newborn infant if the movements of the extremities are limited and painful. However, the destructive processes in the metaphysis frequently present in syphilis are absent in osteogenesis imperfecta. *Chondrodystrophy* and osteogenesis imperfecta result in micromelia, but otherwise the two disorders have little in common. In the former the bones are thick and short, and the epiphysal ends are irregular. The epiphysal changes in *rickets* are an adequate distinguishing factor. The diagnoses of osteogenesis imperfecta and of osteopsathyrosis are facilitated by the presence of blue scleras; and in osteopsathyrosis a typical family history is often obtained. *Hypophosphatasia* in the newborn may resemble osteogenesis imperfecta congenita, but is readily distinguished (p. 1224) by the low serum phosphatase values and by fraying of the ends of the bones.

**Prognosis and Treatment.** Many children with *osteogenesis imperfecta* are stillborn or die soon after birth. Those who survive usually become severely deformed.

Children with the late form, *osteopsathyrosis*, may also become deformed, but the deformities can be lessened by orthopedic treatment. Frequently they can live fairly normal

lives. The prospect of developing deafness and of transmitting the disorder to part of their offspring, however, must be considered in relation to the prognosis.

No effective treatment is known for osteogenesis imperfecta. Good nutrition and correct treatment for the fractures are essential. Vitamin D should be given in usual amounts, but massive doses may be harmful.

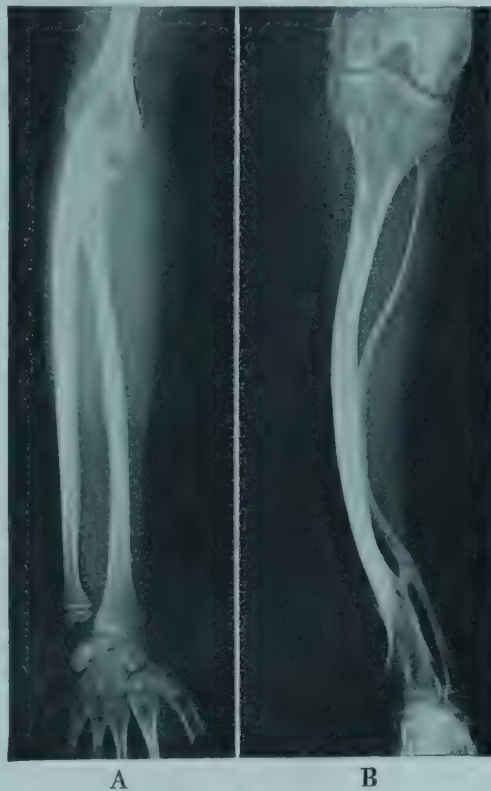


FIG. 373. Osteopsathyrosis.

## MISCELLANEOUS DISORDERS

### ARACHNODACTYLY

(DOLICHOSTENOMELIA, MARFAN'S SYNDROME)

Arachnodactyly, abnormal length of the extremities, particularly of the fingers and toes, represents a congenital anomaly which is frequently combined with luxation of the lens (Marfan's syndrome) and other malformations.

**Etiology.** The disorder is considered a general "mesodermal dystrophy." In many families the syndrome is inherited as a dominant trait, but there are sporadic cases in which the etiology is doubtful.

**Clinical Manifestations.** The patients tend to be tall and underweight, and their extremities are long and thin (Fig. 374). The

fingers are characterized by the term "spider-fingers." The phalanges, metacarpals and metatarsals are unusually long. The muscles are usually flaccid, so that the joints are hyperextensible, but occasionally the syndrome is combined with arthrogryposis. The skull is long and narrow, the palate high. The external ears are frequently deformed. Luxation of the lens may be combined with cataract, megalocornea, coloboma and other defects of the eye. Myopia, strabismus and nystagmus are frequently present. The spine sometimes shows scoliosis and kyphosis. Deformities of the chest and cardiovascular disease develop as the children grow older. Cardiac hypertrophy, valvular deformities, aortic cystic medionecrosis, aortic aneurysm (sometimes dissecting) and other anomalies



FIG. 374. Arachnodactyly.

have been found at autopsy. Imperfect lobation of the lungs, renal ectopy, dislocation of the hips and other malformations are also occasionally associated with the syndrome. The mentality is normal in the majority of instances.

**Prognosis and Treatment.** The patients have a tendency to respiratory disease, but the prognosis depends chiefly upon the cardiac lesions. Some children reach maturity and transmit the disorder to some of their children.

Appropriate treatment of the deformities of the spine and of the eye defects is required.

## MULTIPLE EXOSTOSES

(DIAPHYSIAL ACLASIS, DYSCHONDROPLASIA, ECCHONDROSIS OSSIFICANS)

In this disorder hard, irregular prominences appear in the region of the metaphyses of bones. The condition is hereditary in the majority of instances, a dominant mode of transmission being the rule. If a person appears to be "skipped" in a pedigree, roentgenographic examination may reveal small exostoses which have escaped external inspection. A sporadic instance may represent a

phenocopy or a member of a sibship in which the disorder had not been noticed before. Males are affected more often than females.

**Pathology.** The exostoses consist of spongy bone covered by a layer of compact bone and a shell of hyaline cartilage. The excrescence enlarges by endochondral, periosteal and perichondral ossification. Exostoses develop only on parts of the skeleton previously cartilaginous. They develop from intraperiosteal or subcortical cartilaginous rests, whereas the enchondromas sometimes associated with them arise from cartilaginous islands situated in the spongiosa. Exostoses occur chiefly on the long bones, but occasionally the base of the skull, the vertebral column, the ribs, the scapulas and the pelvis are affected. The growth of exostoses stops when general growth of the skeleton ceases.

**Clinical Manifestations.** Although exostoses are frequently present at birth, they are usually not noticed before the second year of life, when osseous elevations become prominent near the ends of bones. Growth of the affected bones is retarded, and deformities may develop. The radius is often longer than the ulna and bends around the end of this bone, resulting in ulnar deviation of the entire hand. Genu valgum and pes planus frequently develop. Metaphysial enlargement may be seen in the fingers and toes, and functional disturbances may be present. The exostoses are usually bilateral and often symmetrical. Occasionally a large osteochondroma develops from an exostosis; it may interfere with free movements of the limbs or press on nerves or blood vessels (Fig. 375, B).

**Diagnosis.** On the roentgenogram exostoses appear as small or large spurs or as pedunculated, truffle-shaped excrescences (Fig. 375, A). They originate within the metaphysis and always grow away from the epiphysis. The structure of the entire metaphysis is abnormal; the irregular ossification is indicated by rarefied areas in which striation or abnormal trabeculation can be seen. Exostoses frequently cause curving of the affected or neighboring bones, and the spaces between radius and ulna and between tibia and fibula are often enlarged.

Osteochondromas have been mistaken for malignant tumors; exostoses in other parts of the skeleton suggest the benign state of the tumor. When there is doubt, a biopsy should be obtained.

**Prognosis and Treatment.** Exostoses and the osteochondromas developing from them are not malignant; rarely they may be trans-



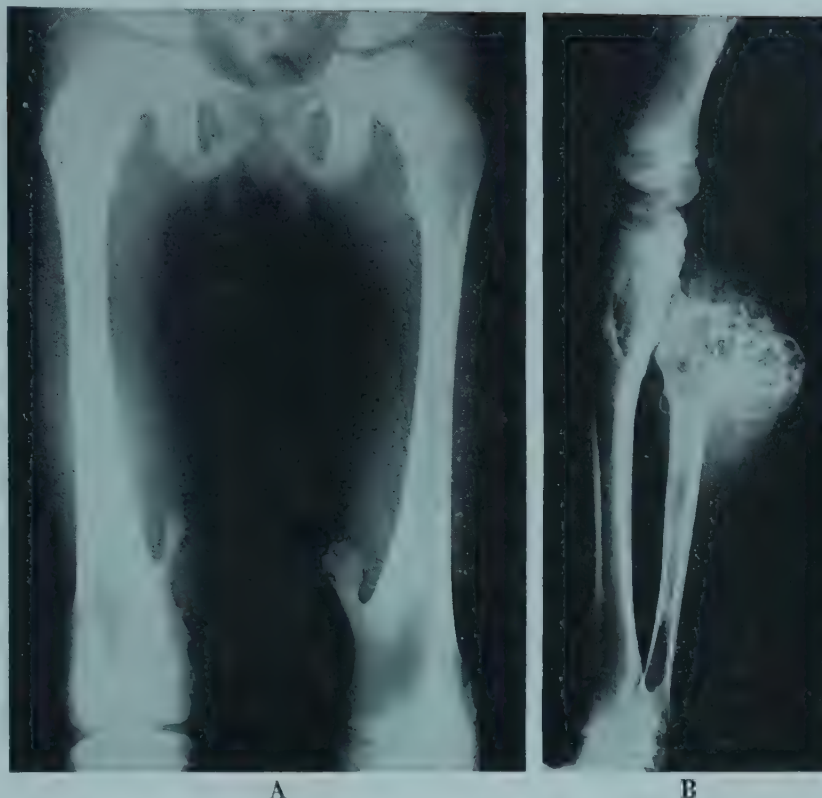


FIG. 375. A, Exostoses of both femors. B, Osteochondroma in the fibula of the same patient.

formed into chondrosarcomas. Exostoses and osteochondromas become quiescent when growth of the patient is complete. Surgical intervention may be required for limitation of movement or for the relief of pressure symptoms on nerves or blood vessels.

### OLLIER'S DISEASE

(CHONDRODYSPLASIA, DYSCHONDROPLASIA)

This malformation of the ends of the shafts is characterized by the presence of nonossified cartilage in the diaphysial ends of bones. The disorder is usually unilateral, but occasionally lesser changes of the same sort are found on the opposite side. Since facial asymmetry is often present, a relationship to hemiatrophy seems probable. There is no evidence that this disorder is genetically determined.

**Pathology.** The cartilaginous islands consist of hyaline cartilage upon which bone is deposited. The cells are larger and more irregularly distributed than in normal epiphyseal cartilage. The cartilage is calcified in parts of its periphery, but it does not ossify normally.

**Clinical Manifestations.** There is a gradual onset of symptoms during the first few years of life. It may be noticed that one limb is shorter than the other, or an external

deformity may appear near a joint. In many cases the disease affects the arm and the leg of the same side, and the pelvic and facial bones may also be involved. There may be deformity, shortening of the limbs and limitation of movement. The process as such is not painful, but use of the deformed extremities may cause discomfort.

**Diagnosis.** The disorder is easily recognized when the lesions are unilateral. In the roentgenogram the upper end of the humerus appears thickened; the cortex of the diaphysis is defective; rarefaction is seen in the interior of the bone. The distal ends of the radius and ulna show similar defects at times; the epiphyses are also affected (Fig. 376). The central parts of the shafts are not rarefied, but the shafts may be shortened and thickened. An abnormal bony structure is sometimes found in the acromial end of the scapula and in the pelvic bones of the affected side. In the proximal and distal ends of the femur and tibia there are areas of rarefaction through which dense lines pass either parallel or obliquely to the long axes of the bones. The affected diaphyses may stand at an angle to the center of the shaft and thus contribute to the deformity of the limb.

Isolated lesions may resemble those of *sypilis* or *leukemia*, but the unilateral involvement and absence of other diagnostic

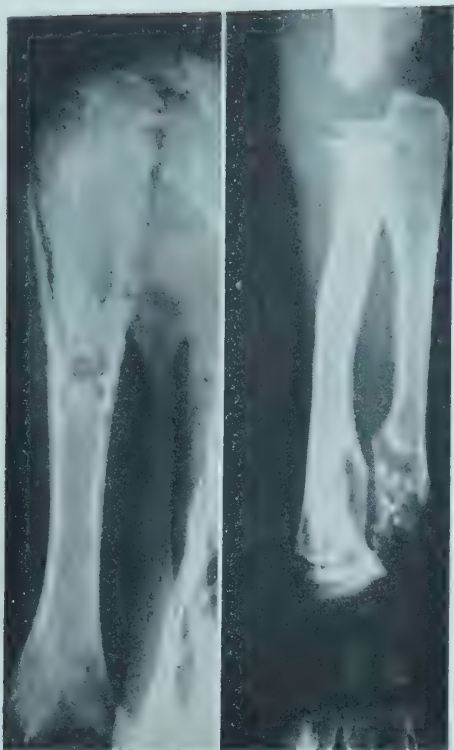


FIG. 376. Humerus and forearm in Ollier's disease.

features of these two diseases suffice for differentiation. Intrametaphysal areas of rarefaction in bones with *multiple exostoses* may resemble Ollier's disease, but the bilateral occurrence of exostoses permits differentiation.

**Prognosis and Treatment.** The process is not progressive, but shortening becomes manifest as the rest of the body increases in size. Infrequently sarcoma has developed in an affected bone. Fractures may occur in the rarefied areas. Orthopedic treatment for the correction of malformations and the prevention of further deformities is indicated.

## MELORHEOSTOSIS

(LÉRI)

This skeletal disorder is a form of hyperostosis which begins in infancy or childhood and progresses slowly on one side of the bones of a single extremity; for example, from the shoulder to the fingers or from the hip to the toes. Thus in the arm the ulnar side may be affected and the radial side remain normal. Enlargement, swelling and curving of the fingers or toes and deformity of the proximal bones of the same limb are clinical manifestations. Roentgenograms reveal a characteristic hyperostosis limited to one side of the bone. Melorheostosis is probably a developmental disorder, but infection and disturb-

ance of sympathetic vasomotor control have also been considered etiologic factors.

## FIBROUS DYSPLASIA OF BONE

(OSTEITIS FIBROSA DISSEMINATA, POLYOSTOTIC FIBROUS DYSPLASIA, OSTEODYSTROPHIA FIBROSA)

Osseous fibrous dysplasia may affect one or many bones of the skeleton. In polyostotic cases the distribution tends to be unilateral; if both sides are involved, one side is affected more than the other. Fibrous dysplasia is probably due to a developmental error of early embryonic life, but there is no proof that the disorder is hereditary. The lesion consists of a fibrous matrix studded with trabeculae of immature bone with varying degrees of calcification. Monostotic cases may be free of symptoms or show only a local swelling. Sometimes a fracture, pain or functional impairment leads to recognition of the disease. If several bones of a limb are affected, clinical complaints are more frequent, and bowing and fractures are common manifestations. Flat bones sometimes become distended into tumor-like masses, while long bones become shortened, curved and thickened. Roentgenographic changes consist in diffuse and cystic osteoporosis, sclerosis, evidence of fractures and abnormal outlines of the bones (Fig. 377). In the severest form of the disease several limbs may be involved, and the skull, vertebral column and pelvis may be included in the pathologic process. In such cases the osseous changes are often associated with brown pigmentation of the skin and with precocious osseous development and precocious puberty, which is seen more often in girls than in boys (McCune-Albright's syndrome) (p. 1159). The blood calcium and phosphorus are normal, but the serum phosphatase is elevated.

## LEONTIASIS OSSEA

In this disease there is an overgrowth of the facial and cranial bones. A few cases have been reported with involvement of the long bones, but most often the disorder is limited to the face and cranium. Leontiasis ossea is probably not an etiologic entity, but a syndrome which may occur in various osseous disorders.

It usually begins insidiously in childhood or early adult life and gives rise to a diversity of symptoms. The skull may increase symmetrically in size, or there may be one or





FIG. 377. Osteitis fibrosa disseminata. Roentgenogram showing extensive fibrous dysplasia of the sacrum, left ilium and femur. Note the irregular demineralization and expansion of the cortex. (Stauffer, Arbuckle and Aegerter: *J. Bone & Joint Surg.*, Vol. 23.)

more prominences. Headache, most severe in the involved part of the skull, is usually the first complaint. Eye symptoms may include exophthalmos, epiphora and optic atrophy. Facial paralysis may result from pressure on the seventh nerve; nasal obstruction from bony overgrowth is common. Convulsions with or without paralysis have been described.

### MANDIBULOFACIAL DYSOSTOSIS

(TREACHER-COLLINS SYNDROME)

The chief manifestations of this syndrome are abnormal (antimongoloid) position of the palpebral fissures, coloboma in the outer portion of the lower lids, hypoplasia of the malar and of other facial bones, malformations of the ears, macrostomia, high palate, blind fistulas opening between the angles of the mouth and the ears and atypical hair growth extending towards the cheeks. Facial clefts, diseases of the ears and deafness occur often in affected persons. The syndrome is often incomplete. The disorder is hereditary and transmitted as a dominant trait attributed to a pleiotropic gene. In many cases the expressivity is reduced.

### ARTHROGRYPOSIS

The term "arthrogryposis" denotes congenital contraction of joints in flexion. It may occur

as a clinical entity or be associated with other malformations such as arachnodactyly and premature synostoses of the bones of the skull (p. 1243).

**Pathology.** The pathologic changes involve thick, inelastic articular capsules and atrophic muscle fibers with some fibrosis and fatty infiltration. Degeneration in the cells of the anterior and posterior horns of the spinal cord with thickening and increased vascularity of the meninges has been reported, but the relationship to the lesions in and about the joints has not been established.

**Clinical Forms.** *Arthrogryposis multiplex congenita* is the term for a special form of this disorder in which there is a congenital stiffness of one or more joints associated with a hypoplasia of the attached muscles. It is the result of incomplete fibrous ankylosis. Dislocation of the hips and of other joints occurs frequently in children with this disorder. Since ankylosis of some joints occurs in extension, the term "arthrogryposis" is not entirely justified, and *multiple congenital articular rigidities*, a name also used, is more adequate. The disorder has been attributed to prolonged intrauterine pressure, but the frequent association with malformations such as defects of the palate, vertebrae, and absence of the sacrum and fibula indicates origin early in

embryonic life before intrauterine pressure becomes a teratogenic factor.

**Clinical Manifestations.** The disorder appears sporadically, but two cases in one family have been observed. The arms are rotated inward; the thighs, outward. The elbows and knees, which are described as cylindrical, are usually ankylosed in extension, although fixation of the knees in flexion also occurs. The wrists and the fingers are flexed, and clubfeet are present. Certain muscle groups may be underdeveloped or absent (amyoplasia congenita). The skin appears thickened, and there may be dimples in the skin near the joints. Roentgenograms show only atrophy of the bones.

**Treatment.** Treatment consists in massage, passive movements, gradual correction of deformities by splints and plaster casts, and orthopedic surgery. According to Chapple, intermittent treatment with a combination of progesterone and an estrogenic substance has been effective in relaxing the joints in some instances.

## HEMIHYPERTROPHY

In hemihypertrophy, a congenital malformation, one side of the body is larger than the other (Fig. 378).

**Etiology.** The most credible explanation of this malformation is a faulty cell division of the zygote resulting in two daughter cells of unequal size; it has been considered a form of incomplete twinning. Females are more often affected than males; the right side of the body, more frequently than the left.

**Clinical Manifestations.** The difference in the two sides is usually greatest in the extremities, the genitals and the trunk. Facial and palatal inequality may also be present. The paired internal organs are sometimes of unequal size. In true hemihypertrophy the bones of the larger side are longer and thicker than the corresponding ones of the other side. There may also be a difference in maturation as seen in the development of the centers of ossification in roentgenograms. There may be associated malformations such as polydactyly, hypospadias, cryptorchism, nevi and hemangiomas. Rare instances of association with tumors or calcification of the adrenal gland have been reported. The mentality may be normal, but retarded development has been observed.

**Differential Diagnosis.** Differentiation from *hemiatrophy* may be difficult, but hemiatrophy is frequently associated with such



FIG. 378. Hemihypertrophy in a girl 4 years of age. The hypertrophy was of the entire left side of the body, including the face, teeth and tongue.

nervous symptoms as paralysis and athetosis. A congenital arteriovenous fistula may result in overgrowth of one extremity, and a similar effect can be caused by a low grade nondestructive infection near an epiphysis. In *Milroy's disease* the soft tissues only are involved.

**Prognosis and Treatment.** The differences in the two sides often become less as the child grows older. Treatment is symptomatic; orthopedic corrections should be instituted early in life.

## HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

This condition, sometimes termed "Marie-Bamberger disease" or "hippocratic fingers," occurs in association with chronic pulmonary conditions and with congenital cyanotic heart disease. The lesions are an ossifying periostitis, effusion into the joints, erosion of the cartilages and hypertrophy of the soft tissues. In mild cases there is only clubbing of the fingers, the nails being broad and curved both transversely and longitudinally. In well developed cases there is also enlargement of the ends of the long bones and of the hands and feet, with pain and swelling of the joints. Clubbing of the fingers does not appear until several weeks to a year or longer after development of the causative disease.

A hereditary type of clubbing of the fingers,



not dependent upon circulatory or pulmonary disease, has been described.

JOSEF WARKANY

## REFERENCES

### *Craniosynostosis*

McLaurin, R. L., and Matson, D. D.: Importance of Early Surgical Treatment of Craniosynostosis. *Pediatrics*, 10:637, 1952.

### *Acrocephaly and Scaphocephaly*

Park, E. A., and Powers, G. F.: Acrocephaly and Scaphocephaly with Symmetrically Distributed Malformations of the Extremities. *Am. J. Dis. Child.*, 20:235, 1920.

### *Platybasia*

Chamberlain, W. E.: Basilar Impression (Platybasia). *Yale J. Biol. & Med.*, 11:487, 1939.

### *Lacunar Skull*

Vogt, E. C., and Wyatt, G. M.: Craniolacunia (Lückenschädel). *Radiology*, 36:147, 1941.

### *Laurence-Moon-Biedl Syndrome*

Cockayne, E. A., Krestin, D., and Sorsby, A.: Obesity, Hypogenitalism, Mental Retardation, Polydactyly, and Retinal Pigmentation: The Laurence-Moon-Biedl Syndrome. *Quart. J. Med.*, 4:93, 1935.

### *Arachnodactyly*

McKusick, V. A.: Heritable Disorders of Connective Tissue. St. Louis, C. V. Mosby Company, 1956.

### *Cleidal and Cleidocranial Dysostosis*

Anspach, W. E., and Huepel, R. C.: Familial Cleidocranial Dysostosis (Cleidal Dysostosis); Preosseous and Dental Dysostosis. *Am. J. Dis. Child.*, 58:786, 1939.

### *Klippel-Feil Syndrome*

Shoul, M. I., and Ritvo, M.: Clinical and Roentgenological Manifestations of the Klippel-Feil Syndrome. *Am. J. Roentgenol.*, 68:369, 1952.

### *Funnel Chest*

Gross, R. E.: The Surgery of Infancy and Childhood. Philadelphia, W. B. Saunders Company, 1953.

### *Chondrodystrophy*

Caffey, J.: Achondroplasia, in McQuarrie, I., ed.: *Brennemann's Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 4, Chap. 28.

Rischbieth, H.: Dwarfism; in *Treasury of Human Inheritance*, VII and VIII. Francis Galton Laboratory for National Eugenics, University of London, 1912.

### *Chondro-ectodermal Dysplasia*

Ellis, R. W. B., and Van Creveld, S.: A Syndrome Characterized by Ectodermal Dysplasia, Polydactyly, Chondrodysplasia and Congenital Morbus Cordis. *Arch. Dis. Childhood*, 15:65, 1940.

### *Morquio's Disease*

Jacobsen, A. W.: Hereditary Osteochondrodystrophia Deformans; Family with 20 Members Affected in 5 Generations. *J.A.M.A.*, 113:121, 1939.

Morquio, L.: Sur une forme de dystrophie osseuse familiale. *Arch. de méd. d. enf.*, 32:129, 1929.

### *Gargoylism*

Hurler, G.: Ueber einen Typ multipler Abartungen, vorwiegend am Skelettsystem. *Ztschr. f. Kinderh.*, 24:220, 1919.

Jervis, G. A.: Gargoylism (Lipocondrodystrophy), a Study of 10 Cases, with Emphasis on the Formes Frustes of the Disease. *Arch. Neurol. & Psychiat.*, 63:681, 1950.

Strauss, L.: The Pathology of Gargoylism: Report of a Case and Review of the Literature. *Am. J. Path.*, 24:855, 1948.

### *Osteopetrosis*

Clifton, W. M., and Frank, A.: Osteopetrosis (Marble Bones); in McQuarrie, I., ed.: *Brennemann's Practice of Pediatrics*. Hagerstown, Md., W. F. Prior Company, Inc., 1957, Vol. 4, Chap. 23, Section 2.

### *Osteogenesis Imperfecta*

Bell, J.: Blue Sclerotics and Fragility of Bone; in *Treasury of Human Inheritance*, 2, III. Francis Galton Laboratory for National Eugenics, University of London, 1928.

Follis, R. H.: Osteogenesis Imperfecta Congenita: A Connective Tissue Diathesis. *J. Pediat.*, 41:713, 1952.

### *Multiple Exostoses*

Jaffe, H. L.: Hereditary Multiple Exostosis. *Arch. Path.*, 36:335, 1943.

### *Ollier's Disease*

Ollier, M.: De la dyschondroplasie. *Bull. Soc. de chir. de Lyon*, 3:22, 1899.

### *Melorheostosis*

Hall, G. S.: A Contribution to the Study of Melorheostosis: Unusual Bone Changes Associated with Tuberos Sclerosis. *Quart. J. Med.*, 12:77, 1943.

### *Mandibulofacial Dysostosis*

Franceschetti, A., and Klein, D.: The Mandibulofacial Dysostosis. Copenhagen, Ejnar Munksgaard, 1949.

### *Arthrogryposis*

Stern, W. G.: Arthrogryposis Multiplex Congenita. *J.A.M.A.*, 81:1507, 1923.

### *Hemihypertrophy*

Ward, J., and Lerner, H. H.: A Review of the Subject of Congenital Hemihypertrophy and a Complete Case Report. *J. Pediat.*, 31:403, 1947.

### *Osteitis Fibrosa Disseminata*

Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females; Report of Five Cases. *New England J. Med.*, 216:727, 1937.

McCune, D. J., and Bruch, H.: Osteodystrophia Fibrosa; Report of a Case in Which Condition Was Combined with Precocious Puberty, Pathologic Pigmentation of Skin and Hyperthyroidism, with Review of Literature. *Am. J. Dis. Child.*, 54:806, 1937.

# ORTHOPEDIC PEDIATRICS

## RESPONSE OF BONE TO LOCAL AND GENERAL DISTURBANCES

Bones are living tissues composed of constantly changing molecules. They are not solid substances of inert matter, but are alive, responsive and changeable. "Tagged" calcium molecules in a particular bone at the time of one examination may be in another bone at a subsequent examination or may have been excreted.

Careful photoelectric comparisons of roentgenograms have been reported by Mack to reveal measurable changes in density after a starvation period of only a few days, and discernible change during short illness and with variations of exercise or bed rest. Perhaps bone would remain relatively constant in its component molecules, and perhaps a certain calcium molecule deposited in bone would remain stationary for an indefinite time, if its environmental conditions were not changed. But they are changing continuously, even in the normal person, and these changes are accentuated during infectious and metabolic diseases and starvation.

The structure of bone can be changed also by alteration of mechanical stresses upon the bone or of its blood supply.

Bone may overgrow in length and in diaphysial diameter as a result of such different causes as hemangiomas, venous obstruction and lymphatic blockage; failure to grow adequately in diameter may be a result of curtailment of passive activity.

## RELATION OF INTRAUTERINE POSITION TO ORTHOPEDIC DISTURBANCES

Congenital malformations are discussed on page 1226.

Different etiologic factors can be responsible for identical structural defects in the fetus. Thus cleft palate in the rat may be genetic in origin or may be an environmental congenital defect resulting from infection, poisoning or vitamin deficiencies in the pregnant rat. It may also be that intrauterine posture can produce the same deformity. The "position of comfort" of the newborn with severe brachygnathia suggests that this may be the case. When the mandible is extremely small or posteriorly subluxated, it is commonly

accompanied by cleft palate. The tongue, which is rarely, if ever, proportionately small, must be accommodated in the nasopharynx, since the mouth does not provide ample space for it. Additional suggestive evidence is supplied by prenatal roentgenograms of infants with brachygnathia showing their heads to be constantly flexed on their chests in utero.

**Intrauterine Postural Effects.** Normally the fetus floats freely for the first half of the gestational period. Until the midpoint of the second trimester it has had unimpeded movements. About this time it begins to impinge on the uterine wall, and the mother translates these collisions as "feeling life." The fetus continues to grow, but the amniotic fluid diminishes relatively in amount. During the latter half of gestation the fetus becomes increasingly restricted until it cannot extend any part without encountering the muscular wall. When it changes its position in relation to its mother, it is unable to alter its own posture.

In order to achieve maximal flexion, the fetus must have a minimum of tension in its stretched joint capsules. This degree of relaxation may be achieved by absorption of a "relaxing factor." After birth the infant retains excessive pliability for approximately the same length of time that other maternal hormonal influences are evident.

The intrauterine position can be reconstructed after birth by "folding" the infant into his most comfortable position. Infants who have been subjected to marked capsular stretch in the uterus are likely to be fretful in the unaccustomed position in which they find themselves after birth. When such an infant is "folded," his fretting ceases immediately, and he falls asleep in his "position of comfort."

To reconstruct the fetal posture, the infant's mouth should be inspected first, since asymmetry of the lips and an angulation of the mandible are among the most common minor abnormalities. These are caused by pressure of the chin against a shoulder when the head was flexed laterally. This position can be responsible for disturbances in respiration and/or swallowing through pressure on the recurrent or superior laryngeal vessels and nerves. These can be pinched between the cartilaginous and osseous structures in the





FIG. 379. A-1, The "position of comfort" of an infant with torticollis and deviated jaw, illustrating one mechanism by which these may be produced. The right sternocleidomastoid is elongated and has been thinned by the stretch (A-2), while the left remains contracted and short. A-3, An effect of pressure against the jaw, and (A-4) a position of the fetal head which can cause it.

B-1, B-2, Sitting on the feet in utero presses them against the soft buttocks. This produces no bony deformity, but causes a mild medial deviation of the feet (metatarsus varus). B-3, B-4, A thigh twisted to bring the knee across the body is difficult to release in utero. Breech deliveries result from this position and others from which the fetus cannot disengage itself.

C-1, The "position of comfort" when the normal release from embryonic cephalic flexion does not occur. C-2, Posture of C-1 in utero. C-3, Brachygnathia ("Andy Gumpism") resulting from this fetal position. The mandible may be pressed up or back and the larynx compressed. Pressure marks on the chest and an angulated manubrium are usual accompaniments. Dyspnea and stridor are among the symptoms. C-4, The gingival ridge is flattened and indented. Fascia is visible at the pressure points. The palate is almost entirely absent. When the forced position of the head prevents withdrawal of the tongue from between the palatal buds where it originated, the tongue develops within the nasopharynx.

D-1, Deformity can result when bone is forced against bone by uterine pressure. D-2, The fetal position by which this deformity (D-1) was caused. D-3, Prenatal roentgenogram of curvature of the fetal spine. D-4, The newborn infant, shown in utero in D-3, prefers to lie curved toward his right side, but, other than facial asymmetry from pressure against the uterine wall, he is normal.

neck if the head is immobilized in lateral flexion against the uterine wall. The face is weakened or paralyzed on the side exposed to the wall, and the laryngeal nerve and vessel are affected on the opposite side. The respiratory disturbances are those of laryngeal obstruction; the digestive ones are regurgitation, aspiration and air swallowing. The prognosis depends on the severity; in the common mild form the facial asymmetry and noisy breathing last only weeks to months.

When a foot has been maintained beside the head, it may be rounded and the over-straight leg may assume the "back-knee" position. In the milder forms this deformity is not unusual and can be demonstrated by passive hyperextension through the neonatal period. When the knee was hyperextended beyond 45 degrees, it may persist in such a position; and in the rare instances when hyperextension has been greater, there is likely to be an associated posterior dislocation of the hip.

Many fetuses are confined in a kneeling position with feet pressed against the buttocks. Occasionally the legs are crossed. The molding is severe when they are pressed against other bony parts, but is mild to negligible when they are pressed against soft parts.

"Positions of comfort" are of infinite variety. They include hands hyperflexed along the forearms or grooving the thorax, heads indented by an arm, heads hyperflexed against the sacrum, feet pressed tightly against the tibias, and many others. Reconstruction of the "position of comfort" frequently explains clubfeet, torticollis, dislocated elbows, and asymmetries, as well as other deformities (Fig. 379).

After the first week of life the relaxation diminishes rapidly but selectively. Muscles and joint capsules which were not stretched or strained during fetal life retain considerable pliancy throughout infancy, whereas those affected by fetal position become restricted in their range of motion. The jaw which was pressed against the sternum cannot be opened wide, and the thighs of an infant whose hip joint capsule was stretched cannot be abducted (p. 1254). In other stretched joints this stiffness is present for only a few months, but in the jaw and in the hips it may last longer. The muscles closing the mouth are stronger than those opening it, and those adducting the hip are stronger than those abducting it. In the stiffened jaw the attached muscles are limited in their exercise by the restricted movement of the mandible. In the

relaxed hip the muscles splint an unstable joint and continue to do so until ossification is established or dislocation occurs.

## THE FOOT

### NORMAL FOOT

The normal foot of the infant and young child appears grossly abnormal if judged by adult standards. The infant's foot is fatter and wider than that of the adult. It seldom has a distinct longitudinal arch and never a transverse one. Fat pads may create a fullness which suggests flatfoot. This is accentuated by the normally soft and pliable muscle of infants. The line of the Achilles tendon, straight in the adult foot, may be moderately angulated in the child, and the foot slightly everted.

### PRONATION OR FLATFOOT

The term *flatfoot* as applied to the infant most often indicates that the medial longitudinal arch does not *look* as high as the parents or physician would like to see it. In most children it is not an abnormality, requires no treatment and does not call for orthopedic corrective shoes.

To decide whether a foot is normal or abnormal requires examination of its component parts and evaluation of its functional status—not merely a casual inspection of the weight-bearing foot. If the child with the suspected "flatfoot" is asked to stand on his toes, a definite longitudinal arch will usually appear. Next the child is asked to stand on his heels with the front of the foot off the floor. If these two maneuvers are successfully accomplished, there is high probability that the feet are well within normal limits.

The joints are examined by checking their motions. The ankle joint moves in dorsiflexion and plantar flexion; the joints of the foot in eversion and inversion. After the physician has examined a few children with normal feet he will have learned the normal range of motion. The length of the heel cord must be tested with the knee straight and the foot inverted; then when the ankle is dorsiflexed, the lateral border of the foot should make an acute angle with the tibia of 80 degrees or less. A short heel cord is an indication for orthopedic examination and usually requires treatment.

The muscles which activate the joints are as follows: tibialis anticus, to produce dorsiflexion and inversion; tibialis posticus, to produce plantar flexion and inversion; perone-



us tertius, to produce dorsiflexion and eversion; peroneus longus and brevis, to produce plantar flexion and eversion; and gastrocnemius and soleus, to produce plantar flexion. The child should carry out each of these motions actively, and the strength of the muscles should be tested. The strength of extension and flexion at the metatarsophalangeal joints should be carefully examined, since the integrity of the anterior arch depends on the flexibility of these joints.

The dorsalis pedis and posterior tibial pulses are palpated, and the tendo achilles and plantar reflexes tested. Sensation is checked on the dorsal and plantar surfaces.

If this systematic examination reveals no abnormalities, the feet are "normal," and no treatment for the "flatfoot" is required. Specifically, so-called orthopedic shoes with Thomas heels are not indicated.

Occasionally a child will complain of pain or fatigue in the feet after play, and neither the examination described nor a roentgenographic examination of the foot will reveal any abnormality. Foot strain is the usual cause of such complaints, and exercises to improve the tone of the muscles supporting the foot are indicated. The young child should be instructed to walk "tip-toe" for five to ten minutes daily; the older one, to stand slightly pigeon-toed with the weight thrown on the lateral border of the foot for five to ten minutes daily. Mechanical support for the arch is not required and is contraindicated in the absence of abnormal findings.

#### PIGEON TOE

Pigeon toe is a frequent presenting complaint. There are three common causes for toeing-in. Metatarsus adductus is the most common of the congenital foot deformities. It consists in adduction of the forefoot with no deformity of the hindfoot. Treatment is required as early as possible and before the infant walks. The deformity is easily corrected by passive stretching, reverse shoe, or casts and wedging, depending on its severity. There is rarely a tendency for it to recur, as is the case with congenital clubfoot. It is frequently associated with congenital dysplasia of the hip, and careful examination of the hip is mandatory.

The second most common cause of pigeon toe is inward tibial torsion. A line drawn from the anterior-superior iliac spine through the center of the patella normally intersects the second toe when the forefoot is neither

abducted nor adducted. In tibial torsion this line intersects the fourth or fifth toe or a point lateral to the fifth one. Tibial torsion is always associated with a tibial bow. The condition requires no treatment such as braces, bars or shoe wedging, but is corrected as the extremity grows. Tibial torsion is frequently associated with metatarsus adductus. When this is the case, the latter should be corrected as described above, but it should be recognized that the pigeon toe will persist until growth has corrected the tibial torsion. The pigeon toe will subsequently be self-corrected.

The third cause of pigeon toe is inward femoral torsion. For examination the child is placed supine, the legs inwardly rotated and then outwardly rotated at the hips. Normally, inward rotation is about 30 degrees and outward rotation 60 degrees. In inward femoral torsion the inward rotation will approach 90 degrees, the patellae will face each other, and outward rotation is practically nonexistent. This condition requires no treatment and is corrected spontaneously during growth.

#### CLUBFOOT

The so-called primary type of congenital clubfoot is exceedingly rare and results from absence of muscles or bones or of fusion of bones. Correction is by orthopedic means.

The usual congenital clubfoot is a secondary deformity of the foot and ankle. The most frequent deformity is that of equinovarus, in which the foot is in plantar flexion and deviates medially. More than 95 per cent of congenital clubfeet are of the equinovarus type. Next most frequent is the deformity of calcaneovalgus, in which the foot is dorsiflexed and deviated laterally. Many children are born with the positional abnormality of equinovarus or calcaneovalgus. If the foot can be passively brought into the opposite position, the infant does not have a clubfoot and requires only simple exercises for correction of the deformity. *The foot which cannot be passively overcorrected is a clubfoot and requires orthopedic treatment.* Conservative treatment with casts and wedgings or the Denis-Browne splint is preferred. Forcible manipulation and surgery are usually unnecessary.

#### SHOES

Before walking, it is unnecessary for an infant to wear shoes; and, while walking is limited

to carpeted floors, the shoes should be the softest obtainable, usually of the moccasin type. Later, when the feet need protection against the pounding received on hard floors and pavements, thicker soles become desirable. These should be as pliable as possible, since stiff-soled shoes limit the range of foot motion and therefore impede development of the supporting muscle. Orthopedic shoes are especially stiff and, on this account, should not be used.

## THE LEG

### BOWLEG AND KNOCK KNEES

Bowleg and knock knees are usually developmental variants and, if acquired lesions—such as rickets—and primary congenital abnormalities—such as achondroplasia—can be ruled out, they must be considered such even though the apparent deformity is marked. Furthermore, it can be expected that they will be corrected by growth within the limits of the heredity pattern. Wedges in the shoes have no effect on bowleg or knock knee.



FIG. 380. Blount's disease. The medial aspect of the proximal end of the left tibia is irregular and "beaked." There is also minimal involvement of medial aspects of the proximal tibial epiphysal center. As a consequence of the proximal tibial deformity, there was abnormal weight bearing, which in turn was responsible for the thickening shown in the medial cortex of the left tibia. The right tibia is normal.

Braces are used only in deformities in which the collateral ligaments of the knees are becoming stretched; they do not correct the deformity and are used only to prevent further relaxation of ligaments.

In developmental bowleg a record of serial measurements between the knees may be kept; in knock knees between the medial malleoli; or, in either, tracings of the legs can be made on wrapping paper to follow the progress of correction by growth. Correction of the deformity may be expected within a year or two in the average case.

*Blount's disease* is an acquired lesion of the upper tibial metaphysis at its medial aspect and may cause bowleg. The lesion may be unilateral or bilateral. It is thought to belong in the category of osteochondroses. Roentgenographically there is a roughening of the medial aspect of the tibial epiphysal center and of the medial aspect of the metaphysis with a beaklike projection. The leg should be braced until the lesion is healed, when osteotomy is usually required to correct the deformity.

### CONGENITAL GENU RECURVATUM

Hyperextension of the knee is not unusual in the newborn period and apparently is a result of positioning in utero. This deformity usually is corrected spontaneously within the first few months of life. Those that persist for more than several months require splinting in slight flexion to permit shortening of the posterior capsule of the knee joint.

## THE HIP

### CONGENITAL DYSPLASIA OR SUBLUXATION OF THE HIP

The infant with dysplasia of the hip only rarely is born with a frank dislocation of the joint. The head of the femur is usually only part way out of the acetabulum, which is more shallow than normal. If the condition is not diagnosed and treated, the joint may become normal; it may remain subluxated throughout life and lead to a degenerative arthritis in later life, or it may go on to a frank dislocation.

The diagnostic signs in early infancy are (1) a persistent limitation of abduction of the hip (Fig. 381): this is the first, the most reliable and often the only sign present as late as one month of age. Knees normally can be abducted more than 45 degrees from the perpendicular, which can be established by the median raphe or vulva. (2) Ortolani's





FIG. 381. Limitation of abduction is an early sign of congenital dysplasia of the hip.



FIG. 382. The Fredjka abduction splint for treatment of congenital dysplasia of the hip. The splint is discontinued when roentgen and clinical studies demonstrate ossification of the acetabular roof and a stable hip joint. Use of the splint is usually required for several months. (Vernon L. Hart: *Congenital Dysplasia of the Hip Joint and Sequelae*. Springfield, Ill., Charles C Thomas.)

jerk of entry or exit: each hip is tested separately. The hips are flexed to 90 degrees, and the hip to be tested is then adducted slowly with slight downward pressure on the knee. A click and a noticeable jerk may be heard and felt as the femoral head moves out of the acetabulum. The thigh is then abducted slowly to its maximum; a click and a slight jerk are noted as the head re-enters the acetabulum. (3) In a true anteroposterior roentgenogram of the pelvis the acetabular roof may be more oblique than that of the opposite side, or the metaphysis of the neck of the femur may be placed more laterally than that of the opposite side with widening of the space between the metaphysis and the acetabulum. Apparently normal roentgenographic findings do not exclude dysplasia of the hip during the first month or two of life. In unusual instances none of the signs described above may be present in the first

two months or so of life (they are usually evident by the first month). Thus it is imperative that the monthly examinations of the apparently healthy young infant should always include tests of hip function.

If any of these signs is present, the child should be treated immediately for congenital dysplasia. Treatment consists simply in maintaining the hips continuously in abduction until the subluxation has been corrected. The constant pressure of the head of the femur in the center of the acetabulum causes it to deepen. This abduction may be maintained in one of several ways; a stiff shell (Fredjka splint, Fig. 382) is effective. It is preferable to treat a normal hip occasionally than to fail to treat an abnormal one, since delay in treatment may permit the hip to dislocate, in which case treatment is prolonged and less certain to produce a normal hip. The use of casts is not recommended when treatment is started early in the first few months of age, since the incidence of Perthes' disease in infants so treated is relatively high.

When complete dislocation of the hip is present, the principal signs are shortening of the affected leg, limitation of abduction, limp if the child is walking and Trendelenburg's sign. (When the child stands upon the dislocated leg and raises the other foot from the floor, the pelvis on the normal side drops.) Excessive mobility of the joint is demonstrable when traction is applied to one leg—so-called telescoping. The roentgenogram demonstrates lateral and upward displacement of the proximal end of the femur in relation to the acetabulum. Appearance of the ossification center of the head of the femur is delayed; it will be smaller than that of the normal side. When there is bilateral dislocation, there is a waddling gait and lordosis.

Treatment requires reduction and immobilization in a plaster cast for six to nine months.

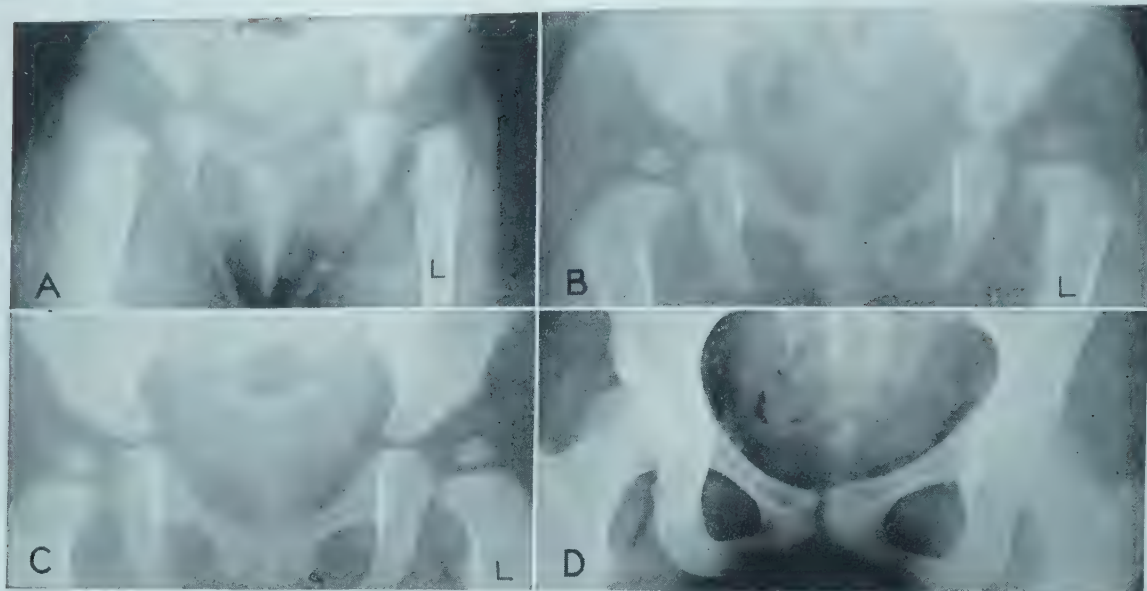


FIG. 383. Bilateral congenital dysplasia of the hip. A, At 2½ months of age the bony roof of each acetabulum is steep, and the left femur is displaced slightly laterally. B, At 10 months of age the left acetabulum is shallow, and there is definite displacement of the left femur laterally and superiorly; clinically there was no apparent shortening of the leg at this time. The left femoral capital epiphysis is smaller than the right. C, At 20 months of age the left hip has a more normal appearance, and at 17 years (D) there is no significant abnormality and both hips were functionally normal. Treatment consisted in maintained abduction until 8 months of age. After this, motion was permitted. No casts were used.

#### ACQUIRED DISEASES OF THE HIP

A variety of lesions of the hip, especially in their initial stage, may produce similar symptoms. These include trauma, acute and chronic (tuberculosis, see p. 1262), infections, Perthes' disease and slipped epiphysis. The common presenting symptoms are those of *synovitis*: limp and pain in the hip, or more often the pain is referred to the knee.

*Infection* is usually manifest systemically by fever and signs of toxemia, as well as by such local signs as muscle spasm and tenderness and pain on attempted passive motion of the joint. In infants the local and systemic signs of infection are difficult to interpret, and paracentesis should be performed whenever the possibility of infection is present. Acute suppurative synovitis is not uncommon, and its possibility must be kept in mind, particularly in the infant with acute cutaneous infections which may serve as the source of the bacteremia. (See Infectious Arthritis, p. 1259.)

*Trauma* is the most frequent cause of suddenly acquired limp and pain in the hip or knee (synovitis of the hip) which brings the child to the physician. Often the trauma has been so slight that it was overlooked or perhaps never known to the parents. A few hours later the joint is full of fluid and painful.

Examination may reveal limitation of motion, muscle spasm and swelling of the joint.



FIG. 384. Untreated congenital dislocation of the right hip demonstrating superior and lateral displacement of the underdeveloped femoral head and capital epiphysis, underdevelopment of the acetabulum and an increase in the slope of the acetabular roof.



The hip is a ball-and-socket joint, and its motions are tested in three planes: flexion and extension, abduction and adduction, and inward and outward rotation. These motions are compared with those of the normal side. In limitation of motion caused by muscle spasm the range of motion gradually increases as gentle pressure is maintained against the leg, and the muscle becomes fatigued. Swelling of the joint is demonstrated by placing the thumb over the femoral artery where it crosses the inguinal ligament and the other four fingers posteriorly over the buttock opposite the position of the thumb. In this way the joint with the soft tissues anterior and posterior to it is grasped between the thumb and the fingers. When the hip joint is swollen with fluid, the involved hip will feel thicker than the opposite one (Gill's sign).

It is impossible to distinguish the joint lesion of trauma from that of early Perthes' disease before roentgen changes have become manifest. If the roentgen examination is negative, the child should be put to bed for three or four days. If the spasm persists, the child should have Buck's traction on both legs for three weeks. If the signs of spasm have then disappeared, as they usually will have if trauma has been the cause, he is allowed gradually increasing activity. If spasm persists, traction is continued for another three weeks, when the roentgen examination is repeated. The characteristic changes of Perthes' disease will usually have appeared by then.

*Perthes' disease* (Legg-Calvé-Perthes disease) is an aseptic necrosis of the capital femoral epiphysis causing signs and symptoms of synovitis as described above followed by characteristic roentgen changes. Three stages are usually described, each lasting about nine months to one year. The first stage is one of aseptic necrosis; roentgenographically there may be no change during the first weeks, after which a relative opacity of the epiphysis becomes evident. The second stage consists in revascularization, and the epiphysis becomes mottled and fragmented. In the third stage there is reossification, and the roentgenogram appears much as it did in the second stage, but serial films demonstrate gradual re-formation of the head of the femur. The principle of treatment is avoidance of weight bearing by any of several methods. The head of the femur tends to flatten and become mushroom-shaped, causing incongruity between head and acetabulum with degenerative changes later in life. The main prognostic factor as far as the eventual shape of the head of the

femur is concerned is the age of the child at time of onset: the younger the child, the better the chance for a spherical rather than a flat head.

*Slipped epiphysis* occurs typically in the adolescent and also is responsible in its early stages for the signs and symptoms of synovitis. The cause is unknown, but the condition occurs mostly in the "overlarge" child. The onset is insidious and characterized by pain in the knee, so that hip disease may not be suspected even though the child limps. Roentgen examination will reveal that the femoral capital epiphysis has slipped posteriorly and inferiorly. This is shown invariably on the lateral projection, but not always on the anterior-posterior one, so that the diagnosis may be missed if a lateral view is not obtained. The anterior bowing of the neck which occurs as the "slip" progresses makes subsequent therapy difficult, so that early diagnosis is of real importance.

The principle of treatment is arrest of the slipping, which is usually attained by internal fixation, followed by avoidance of weight bearing (crutches) until healing has occurred.

## THE SPINE

### SPONDYLOLISTHESIS

In this condition there is an anterior displacement of a lumbar vertebra, usually the fifth, associated with a bilateral defect in its isthmuses. The cause is unknown. In children under ten years of age spondylolisthesis usually does not cause symptoms and is an incidental finding on a roentgenogram. If the vertebral body continues to be displaced forward as shown by serial roentgenograms, spinal fusion is indicated. Symptoms may appear in the adolescent child. Pain in the low-back area is occasionally referred to the sciatic area, and there is an increasing lumbar lordosis. When such symptoms are present, a brace should be provided, and spinal fusion is indicated if the symptoms persist or if the slipping progresses.

### SCOLIOSIS

Scoliosis is an S-shaped lateral curvature of the spine (Fig. 385). If the scoliosis is correctible by bending toward the side of the curvature, the most common cause is a short leg on the affected side. Such a correctible scoliosis may also be the result of poor posture.

A fixed scoliosis, which is not correctible by bending, is most frequently idiopathic, but may be caused by such lesions as hemi-



FIG. 385. Scoliosis in a girl 10 years of age, showing the tilt of the pelvis and shoulders and the deformity of the chest.

vertebrae, fusion of ribs, absence of muscles, neurofibromatosis of the vertebrae, vertebral infections such as tuberculosis and poliomyelitis.

Treatment consists in bracing to prevent increase of the curvature, and spinal fusion after growth has been completed.

### OSTEOCHONDROSIS

(OSTEOCHONDROITIS DEFORMANS JUVENILIS, AVASCULAR NECROSIS)

Osteochondrosis is characterized by the fragmentation of epiphysial centers. Its cause is unknown, but osteochondrosis of the hip has been observed in children after reduction of a dislocation and after long immobilization in a cast. Although almost any epiphysis may be involved, there is a definite predilection for certain ones, and, in the individual child, involvement is usually limited to a single epiphysis. The lesion is known by various names, depending on the affected epiphysis. Among these are Freiberg's disease of a metatarsal head, Koehler's disease of the tarsal navicular, Osgood-Schlatter's disease of the tibial tubercle (Fig. 386), Legg-Calvé-Perthes disease (p. 1257) of the femoral

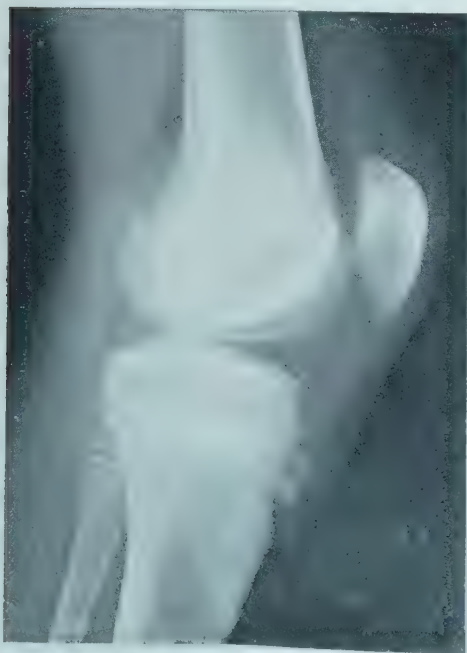


FIG. 386.



FIG. 387.

FIG. 386. Osteochondrosis of tibial tubercle (Osgood-Schlatter's disease) in a boy 13 years of age. Roentgenogram shows irregular ossification of tibial tubercle and associated thickening of infrapatellar tendon.

FIG. 387. Legg-Calvé-Perthes disease of the left hip in a boy 6 years of age. The presenting complaints were limp and pain in the left knee. The lateral roentgenogram reveals sclerosis of the femoral capital epiphysial center, which is also fragmented and flattened. The "joint space" is wider than normal. At this stage there is little deformity of the neck of the femur.



capitular epiphysis (Fig. 387) and Scheuermann's disease of the vertebral epiphyses.

The outstanding symptom is pain in the affected part with voluntary restriction of motion. When the involved epiphysis is in the foot, leg or hip, there is a protective limp.

Roentgenograms show epiphysal irregularities in which there appears to be an area of poorly calcified and rapidly growing bone surrounded by a densely calcified ring. Later there may be fragmentation of the center ending in malformation if weight bearing is continued (Figs. 386, 387).

**Prognosis and Treatment.** The disease is self-limited and, despite bony distortion, usually terminates with restoration of satisfactory function, provided weight bearing is avoided during the active stage.

## SUBLUXATION OF HEAD OF RADIUS

Subluxation of the head of the radius occurs frequently in young children two to five years of age; it is rare after nine years of age. The child has usually been forcibly jerked by the hand by a taller person while the elbow is in full extension; the subluxation occurs with an audible snap.

The *symptoms* are immediate but usually not persistent pain in the elbow, an inability to supinate the hand and a tendency to hold the arm in slight flexion. Palpation and roentgenograms of the elbow do not reveal any abnormality, and there is no edema. The *diagnosis* is confirmed by the easy therapeutic maneuver of reduction of the subluxation. This is accomplished by firmly grasping the hand of the affected arm and holding the elbow with the thumb of the other hand pressed against the head of the radius while forcibly supinating the forearm beyond the point of obstruction. The click of the return of the radial head to position is usually followed by immediate recovery of painless function.

## INFECTIONS OF THE BONES AND JOINTS

### ACUTE INFECTIOUS ARTHRITIS

This condition is most common in the first six months of life. It is usually preceded by an infection elsewhere in the body, often in the upper respiratory tract. The causative organism is usually one of the common pyogens, such as the *Staphylococcus*, *Streptococcus*, *Pneumococcus* and, less commonly, the *Gonococcus*, *Meningococcus*, influenza bacillus, typhoid bacillus or one of the *Salmo-*

nella group of organisms. The shoulder, hip and other large joints are most commonly affected, but any joint may be involved.

**Clinical Manifestations.** The onset is sudden with systemic symptoms of sepsis. Local swelling appears rapidly with pain and muscular rigidity and, if untreated, is followed promptly by suppuration. When the hip is affected, it may become dislocated with astonishing rapidity, even in the absence of demonstrable suppuration.

**Differential Diagnosis.** Acute suppurative arthritis must be differentiated from *acute osteomyelitis*. In acute suppurative arthritis even slight motion of the joint is painful, whereas in osteomyelitis the joint may be moved without pain if done carefully. The tenderness is localized to the metaphysal region of the bone. In the hip the differentiation cannot be made. The roentgenogram is of no value in early diagnosis. *Rheumatic fever* is excluded in infancy since it rarely occurs at this age.

**Treatment.** When an acute pyogenic infection of a joint is suspected, it should be aspirated, and any material obtained cultured. A blood culture should also be obtained, and broad-spectrum antibiotic therapy started immediately. Subsequently any indicated adjustment should be made on the basis of bacterial susceptibility tests in vitro and the clinical response. If there is no evidence of improvement within twenty-four hours, the joint should be drained surgically.

## OSTEOMYELITIS

This disease occurs most often between five and fourteen years of age and twice as frequently in boys as in girls. In infants under two years of age acute hematogenous osteomyelitis differs in many respects from that in older children.

**Etiology and Predisposing Factors.** The causative organism in the majority of cases in older children is the hemolytic *Staphylococcus aureus*. Predisposing causes are often demonstrable and include furunculosis, impetigo, chickenpox and infected burns and vaccinations.

**Pathology.** Osteomyelitis begins as a hematogenous abscess in the metaphysis, and then, if uninterrupted, the abscess ruptures subperiosteally and spreads along the shaft of the bone. The infection then penetrates to the bone marrow. The separated periosteum forms a shell of new bone around the infected shaft. The pieces of dead bone are known as sequestra, and the new bone formed by the

periosteum as the involucrum. Sinuses may form between the sequestra and the skin surface. In the hip the metaphysial abscess ruptures into the joint and becomes a suppurative arthritis.

**Clinical Manifestations.** The onset is usually abrupt with fever, malaise, and pain with sharply localized tenderness in the affected bone. Shortly thereafter, swelling and redness over the affected bone may be present. These signs appear earlier in infants than in older children. The patient is toxic and extremely weak and irritable.

When osteomyelitis follows an infection which has been treated with an antibacterial agent, the clinical course may be modified sufficiently so that the true nature of the lesion may not be suspected until it is well advanced. In addition, inadequate antibacterial therapy of an acute osteomyelitis infection may temporarily abolish the clinical manifestations, but permit the infection to continue in a temporarily suppressed state only to become evident some days or weeks later.

**Diagnosis.** There is a leukocytosis of 15,000 to 25,000 or more, and the blood culture is usually positive. Roentgenographic examination does not reveal the process for at least five days in small children; in older children this period may be as long as eight to ten days. Initially there is rarefaction of the involved area, and soon there is evidence of the formation of involucrum.

**Differential Diagnosis.** Rheumatic fever, sprain, cellulitis, erysipelas and scurvy, in particular, are likely to require differentiation. The presence of great toxicity and localized pain suggests osteomyelitis. Usually this is enough to distinguish the condition from *rheumatic fever*, but a history of involvement of other joints is indicative of the latter disease, as is the response to salicylates. *Scurvy* produces painful and tender swelling along the shaft of the bone, but roentgenograms of the long bones should be diagnostic. See also Acute Infectious Arthritis.

**Prognosis.** The mortality rate from acute pyogenic infections of the bones has decreased markedly since the availability of specific antibacterial agents. The rate is lower in newborn infants than in older infants and children, as is the incidence of chronic and metastatic lesions. Both the course and prognosis depend on early institution of appropriate therapy and continuance of it for an adequate time.

**Treatment.** Acute osteomyelitis requires immediate treatment. When an acute pyogenic infection of a joint or bone is suspected, a blood culture should be obtained, and antibacterial therapy should be started immediately. In view of the frequency with which pathogenic strains of staphylococci are resistant to the available antibiotics, two of those known to be effective against many of the strains should be selected for initial therapy and continued except as the cultural tests in vitro or the clinical course show one or both of them to be ineffective. Whenever antibiotic therapy is instituted for a *possible* osteomyelitis and is apparently clinically effective, it should be considered obligatory to continue it in full dosage for at least two weeks after the temperature has been normal. Less prolonged therapy may only temporarily suppress the lesion and permit it to become reactivated. Surgical intervention may not be needed, but the extremity should be immobilized, and if an abscess forms, it should be drained immediately. If the child is seen while the lesion is still confined to the metaphysis, some clinicians believe that this area should be drilled and drained in the hope of avoiding further extension.

#### INFANTILE CORTICAL HYPEROSTOSIS

This lesion, also known as Caffey's disease, is a hyperplasia of subperiosteal bone (Fig. 388) over which there is soft tissue swelling and at times a brawny discoloration of the skin. Hyperostoses have been observed in the calvarium, mandible, clavicles, scapulas, ribs and the long bones of the extremities, including the metatarsals. The mandible and clavicles appear to be most frequently affected. The clinical features vary considerably, but the symptoms are not severe as a rule. Fever, usually of a low degree, tenderness, hyperirritability, pseudoparalysis, dysphagia, pleurisy, anemia, increased sedimentation rate and elevated serum phosphatase have been observed in variable combinations.

Duration of clinical activity has been observed for as long as nine months. No treatment has been effective. Recovery has occurred in all reported instances, and there are no recorded residuals.

*Hypervitaminosis A* (p. 363) may simulate infantile cortical hyperostosis in certain respects. In hypervitaminosis A the ulnas and one or more metatarsals, other than the first, have been the bones most frequently involved; the mandibles and other flat bones



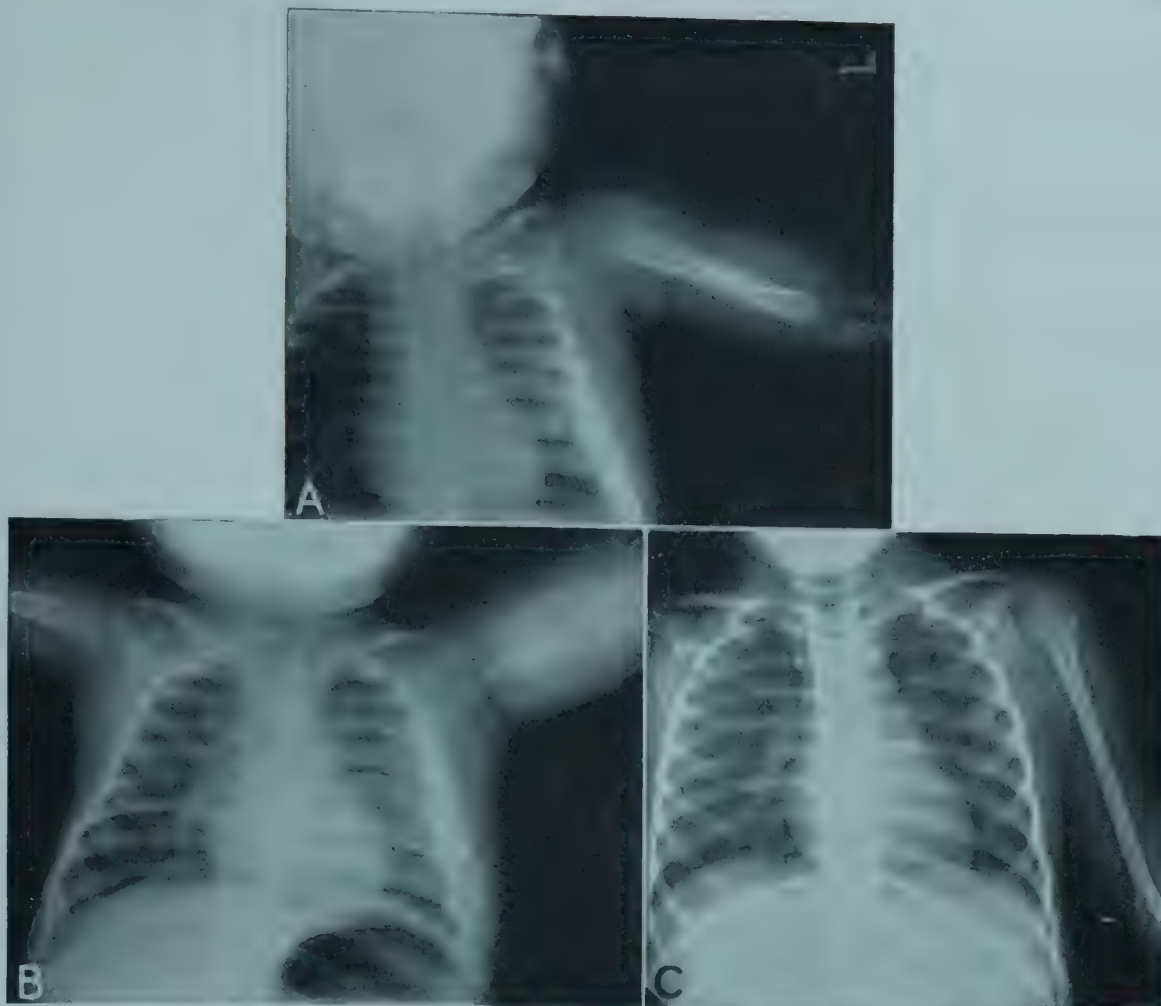


FIG. 388. Infantile cortical hyperostosis. A (3/20/43), Subperiosteal calcification of left lower ribs and left humerus. No evidence of bone destruction. The infant was moderately ill with an upper respiratory tract infection and was somewhat listless. The only localized finding was a disinclination to use the left arm, but there was no paralysis of it. B (4/19/43). Increase in subperiosteal calcification of ribs of left side and left humerus within 1 month. There is similar involvement of lower right ribs and of facial bones. Evidences of illness had mostly disappeared at the time this roentgenogram was made. C, One and a half years later there is no evidence of the cortical disturbance.

are apparently not affected. This distribution plus a history of excessive ingestion of vitamin A serves to distinguish this entity.

## TUBERCULOSIS

### TUBERCULOUS LESIONS OF THE BONES AND JOINTS

These lesions are hematogenous in origin, usually stemming from a pulmonary focus, which may not be demonstrable. There is usually only a single lesion. The bones most frequently involved are the head of the femur (hip), the vertebrae, the fingers and toes.

### TUBERCULOUS DACTYLITIS

Dactylitis occurs most frequently in early childhood and involves one or more of the phalanges, the metacarpal bones or the corre-

sponding bones of the feet. The medullary canal of the involved bone becomes caseous; the cortex, thinned and expanded; the periosteum, thickened. The entire digit develops a spindle-shaped, hard and red swelling as



FIG. 389. Tuberculous dactylitis in an infant 11 months of age.

the soft tissues are affected (Fig. 389). The process is comparatively painless, but it lasts many months and may leave a permanent deformity. The *differential diagnosis* is chiefly from the dactylitis of congenital syphilis, which is more often multiple and symmetric. Dactylitis may also occur in sickle cell anemia and in coccidioidomycosis.

*Treatment* consists in measures for tuberculosis in general. The involved region should be put at rest with a splint or cast, and operation is indicated if an abscess develops. Antibacterial therapy is discussed on page 464.

### TUBERCULOUS SPONDYLITIS

#### (POTT'S DISEASE)

This tuberculous osteitis originates in the body of one or more vertebrae, destroys the bone and spreads to all the tissues of the articulation. The spinous process and arches are unaffected. Kyphosis is most common in mid-dorsal lesions. Some scoliosis may accompany the kyphosis if the lesion is disproportionately unilateral.

The lower dorsal part of the spine is most likely to be involved, with the lumbar and the cervical segments next in order of frequency. Paraplegia occurs in about half of the cases of caries of the upper dorsal or cervical region, but is rarely associated with involvement below the mid-dorsal region. The average duration of tuberculous spondylitis before paralysis appears is about three years, but paralysis may develop even within a few months. Psoas abscess is a complication of caries in the lumbar vertebrae. A cold abscess in the cervical vertebrae may open into the pharynx (retropharyngeal abscess) or above the clavicle; one originating opposite the lower cervical or upper dorsal vertebrae may rupture into the pleura or penetrate to the scapula, but often it gravitates, like abscesses originating in the lower dorsal and lumbar regions, and points above Poupart's ligament.

**Clinical Manifestations.** Symptoms are insidious in onset, the earliest being fretfulness and disturbed sleep. Persistent or intermittent pain may occur over the distribution of the spinal nerves arising adjacent to the affected vertebrae. This pain is increased by pressure on the head, but not by pressure over the lesions. Muscular rigidity splints the back, and the child assumes a position which will best take the weight from the diseased spine and prevent jarring. He may avoid bending to reach an object on the floor, may walk stiffly or carefully on his toes, or may prefer to lie

on his abdomen and to rest frequently across a chair or over his mother's lap. With cervical involvement the child may hold his head stiffly or support it with his hand.

**Differential Diagnosis.** Rickets produces kyphosis of greater length and uniformity, which is unaccompanied by rigidity and disappears when the patient is prone. *Nontuberculous scoliosis* is seldom accompanied by rigidity or pain. *Hip joint disease* may be suspected when lameness is the result of lumbar caries, but in the latter there is no limitation of movement of the hip except in the presence of psoas abscess, when extension will be limited. *Acute nontuberculous osteomyelitis of the vertebrae* can be distinguished by its greater toxicity, leukocytosis and fever. In addition, the roentgenographic findings are usually well established in a tuberculous lesion of the vertebrae when symptoms first become manifest, whereas they are not likely to be demonstrable during the first few days of an acute pyogenic osteomyelitis. The *Klippel-Feil syndrome* may be confused with tuberculosis of the cervical spine, but is readily distinguishable by roentgenogram.

**Prognosis.** The reparative process may not begin for one to three years, but in carefully treated cases recovery with ankylosis and little or no deformity can be expected. Paraplegia often disappears completely. There is danger of relapse from trauma or other causes. Though a large number of children eventually recover with varying degrees of deformity, the prognosis is serious.

**Treatment.** Traditionally, therapy consists in continuous extension on a Bradford frame until evidences of infection are no longer present, and then spinal fusion. Some experience with early surgical eradication of the tuberculous abscess in conjunction with specific antimicrobial therapy has been encouraging.

### TUBERCULOSIS OF THE HIP

#### (TUBERCULOUS COXITIS)

This is the most common tuberculous involvement of the joints. The disease may begin in the synovial membrane, but usually starts as an osteitis of the femoral epiphysis, followed later by a tuberculous arthritis and finally by an abscess resulting in destruction of the femoral head, with displacement and deformity. Recovery may begin at any time.

**Clinical Manifestations.** Usually the first symptom is a slight lameness which is likely to be intermittent, occurring when the pa-



tient first gets out of bed and after exercise. It may disappear for days or weeks at a time. Pain may be present at this stage or may develop later and is usually referred to the knee or the inner side of the thigh. As destruction of the joint proceeds, the thigh is flexed and adducted, and the rotation which initially was outward becomes inward. Swelling about the hip increases, and an abscess may form from which pus may discharge anteriorly to the joint or burrow in other directions. Absorption of the head and neck of the femur may take place without visible evidence of suppuration.

**Differential Diagnosis.** Distinction must be made from *osteochondrosis of the femoral head* (Legg-Calvé-Perthes disease) which occurs in the same age group, but limits abduction to a greater extent than it does extension and whose roentgenographic changes do not extend beyond the femoral capitular epiphysis. In tuberculous coxitis the acetabulum may also be affected. Frequently the two

conditions may be indistinguishable on early films, and the clinical course must be relied upon to differentiate them. A negative tuberculin reaction is of great value. The insidious onset of tuberculous coxitis serves to distinguish it from *rheumatic fever* and *acute arthritis*. *Chronic arthritis* usually begins in the fingers and involves the hips only late in the disease.

**Prognosis.** After abscess formation the disease may last two to four years or longer. When treatment is begun in the first few weeks of the disease, the inflammation may cease entirely before the joint itself is attacked, but in the majority of cases the joint is finally ankylosed. After apparent recovery, recurrences may take place from slight trauma or overuse of the limb.

**Treatment.** See treatment of tuberculosis of the hip.

CHARLES C. CHAPPLE  
JOHN ROYAL MOORE

# The Muscles

Various diseases may be accompanied by secondary changes in striated muscle and must be differentiated from primary diseases of muscle. Muscular atrophy may accompany states of malnutrition, rickets, hyperthyroidism, malignancy or chronic debilitating diseases of many types. Hypertrophy of muscles may occur in hypothyroidism, in diseases of the adrenal and pineal glands or with devel-

opmental defects of the brain in the region of the corpus striatum. Myasthenia and periodic paralysis have been described in hyperthyroidism. These secondary manifestations in muscle may be differentiated from primary diseases of muscle by consideration of pertinent facts in the history and physical examination as well as by the response to therapeutic agents.

## CONGENITAL DEFECTS OF MUSCLE

Developmental abnormalities in the fetus may lead to defects or absence of various skeletal muscles. Apparently any of the skeletal muscles may be congenitally absent in whole or in part, but certain muscle groups are more likely than others to be affected. The muscles most frequently involved are the pectoralis major, pectoralis minor, trapezius, quadriceps femoris, serratus magnus, semimembranosus, abdominalis, gemelli, deltoid, latissimus dorsi and levator palpebrae. Usually the defect is unilateral and involves only a single muscle group. Frequently the absence of a muscle group occurs in association with congenital abnormalities of other organs.

Developmental anomalies producing shortening of various muscles may cause contractural defects. Congenital torticollis results when neck muscles are thus involved. If muscles of the calf are affected, contractural defects of the feet and clubfoot are found. Elevation of the shoulder (Sprengel's deformity) may be caused by anomalous development of either the trapezius or serratus magnus muscles. *Amyoplasia congenita* or *arthrogryposis multiplex congenita* is a syndrome accompanied by immobility of one or more joints of the extremities associated with developmental defects of muscles about these joints. The affected joints are usually fixed in positions of extension.

### TORTICOLLIS

(WRYNECK)

Torticollis is accompanied by shortening or spasm of the cervical muscles and malposition of the head and neck. When the defect is evident at birth or within the first few weeks of life, it is designated as congenital torticollis. If the onset is at a later age, the condition is regarded as acquired.

### CONGENITAL TORTICOLLIS

Congenital fusion of the atlas and occipital bone or of the atlas and the axis, malformations of cervical vertebrae and cervical ribs may be responsible for the production of this defect. If a bony abnormality is not demonstrable, the defect may be considered to be of muscular origin. Congenital muscular torticollis usually results from trauma of a difficult delivery or from an abnormality in fetal position. In some instances a firm fusiform mass may be palpated in the body of the sternocleidomastoid muscle at birth or shortly thereafter. The size of the tumor may increase slowly for several weeks and then decrease, so that the mass may no longer be palpable by the sixth to eighth month. Recovery may occur without residual deformity. In other instances the muscle becomes small, short, fibrous and noncontractile.





FIG. 390. Acquired torticollis, demonstrating tilting of the head and facial asymmetry. (Courtesy of Dr. Herbert R. Kobes.)

Some observers believe that congenital muscular torticollis results from a hematoma in the damaged muscle, with later replacement by a fibrous mass; others, that the lesion has a fibrous structure from the onset.

**Clinical Manifestations.** Manifestations are dependent on the muscle groups affected and the causative factors involved. Character-

istically, the head is drawn downward, the neck shortened on the side of the lesion, and the chin tilted (Fig. 390). Facial asymmetry develops. If the trapezius muscle is involved, the head is drawn backward. A tumor mass may often be palpated in the sternocleidomastoid muscle. Roentgenographic search for skeletal anomalies of the cervical area should also be made.

**Treatment.** The management of congenital torticollis is described on page 320.

#### ACQUIRED TORTICOLLIS

Inflammation of the cervical muscles secondary to cervical adenitis, mastoiditis or arthritis may produce torticollis. Manifestations have followed exposure to cold or efforts to make postural adaptations in compensation for defects of vision or hearing. Rarely torticollis is a manifestation of hysteria.

**Clinical Manifestations.** The symptoms and signs are those of congenital torticollis.

**Treatment.** Treatment for acquired torticollis must be adapted to the cause. Acute inflammatory myositis is best treated with rest, heat and salicylates and with appropriate treatment of any infection in other sites. Treatment of visual and auditory defects is indicated when torticollis represents a postural adaptation to either of such defects. Habit spasm and hysteria require correction of the underlying emotional factors responsible for them.

## INFLAMMATORY DISEASES OF MUSCLE

Skeletal muscle may be the site of local inflammation. Bacterial infection is rare except in association with traumatic lesions or infection in adjacent structures. The *Streptococcus* and *Staphylococcus* are the most common causative organisms of suppurative myositis, but other organisms, including that of clostridial infection producing gas gangrene, may affect the muscles of children. Rarely myositis occurs by direct spread from a localized tuberculous process in adjoining tissues, and tuberculous myositis produced by hematogenous dissemination has been described. Trichinosis is discussed on page 587. Inflammatory changes may occur in association with various infectious diseases, including those of the upper respiratory tract.

#### DERMATOMYOSITIS

See page 922.

#### MYOSITIS FIBROSA

##### (CHRONIC POLYMYOSITIS)

This rare syndrome is a poorly defined subacute or chronic disease of muscle characterized by loss of muscular power and by atrophy and contractures. The etiology is unknown. The pathologic changes are those of muscular degeneration with gradual replacement of muscle by fibrous connective tissue.

**Clinical Manifestations.** The onset is insidious, and constitutional symptoms are lacking. Any or all of the skeletal muscles may be

involved. Frequently the muscles of the thighs and calves are first affected with extension of the process to those of the hips, abdomen, spine, thorax and neck. The muscles are shortened and inelastic, but not painful. As the disease progresses they become firm and woody in consistency. Contractures develop, which are usually of the flexion variety and result in deformities.

**Diagnosis.** The disease is differentiated from *dermatomyositis* by the absence of skin lesions and lack of constitutional symptoms. It is not always readily possible to distinguish this disorder from progressive muscular dystrophy. A diagnosis of *myositis fibrosa* is sometimes applied to localized lesions which tend to regress, but it would seem preferable to include the localized and more or less self-limited processes under such diagnoses as *fibrositis* or *intramuscular fibrositis*.

**Treatment.** Treatment is limited to measures designed to alleviate and correct resultant contractures. The outcome may be fatal, but in some instances remissions occur or the disease becomes arrested.

### PROGRESSIVE MYOSITIS OSSIFICANS

This disease is rare and results in deposition of masses of bone or areas of calcification in muscles, tendons, ligaments and fascial sheaths. It is usually first observed in children and progresses through phases of exacerbation and regression until complete invalidism occurs. Males are more often affected than females. Various congenital anomalies are observed in about 75 per cent of patients afflicted with the disease, microdactylia of the great toes or thumbs being the most frequent one.

**Etiology.** No causative factor is known. Infections and trauma often precede the onset or exacerbations of the disease. There are some indications that the disorder may be associated with a congenital metabolic aberration of osteoblastic tissue.

**Pathology.** Discrete masses of bone are formed in the skeletal muscles. Late in the disease it is sometimes possible to demonstrate a nearly continuous band of bone from the occiput to the pelvis. The joint capsules may be affected, resulting in complete ankylosis. Microscopic changes include replacement of

the connective tissue network of the skeletal muscle by an embryonic type of connective tissue which later forms firm, thick fibrous bands containing cartilage cells and osteoid trabeculae. Calcified intramuscular lesions are structurally and chemically indistinguishable from bone. Muscle fibers caught within the fibrous and calcified network atrophy and undergo degeneration.

**Clinical Manifestations.** The onset may be noted after an acute infection or injury, or without any preceding incident, and is characterized by low grade fever, pain and the appearance of small soft tumors in the involved musculature. The muscles first affected are usually those of the neck and back. There is gradual spread to other muscles, and in advanced cases most of the skeletal muscles may be involved. Those of the hands, feet, tongue, heart, diaphragm, larynx and sphincters escape, as do smooth muscles. The soft muscular tumors may break down and extrude a white or gray material. Erythema of the overlying skin occurs before this extrusion. After a relatively short interval the muscular swelling recedes and is replaced by areas which are firm to palpation, the firmness and density of these lesions increasing as ossification proceeds.

Low grade anemia may accompany the disease. No abnormalities in the chemical constituents of the blood have been demonstrated, but phosphatase activity of the muscles prior to ossification may be increased. Roentgenograms demonstrate calcium deposits with true bone formation.

The disease must be distinguished from *myositis ossificans circumscripta*, in which localized calcium deposits occur in muscles as a result of trauma. It must also be differentiated from multiple exostoses, *myositis fibrosa* and *dermatomyositis*.

**Prognosis and Treatment.** There may be prolonged remissions of the disease, but exacerbations follow and death eventually occurs. When the onset is in infancy or early childhood, patients seldom live longer than the age of puberty. Many types of therapy have been attempted, but all have been without effect, except that remissions have been reported with corticosteroid therapy in the early stage of the lesions.



# METABOLIC AND DEGENERATIVE DISEASES OF MUSCLE

## AMYOTONIA CONGENITA SYNDROME

(OPPENHEIM'S DISEASE)

There is much confusion concerning the various conditions responsible for hypotonia in infants and children. Part of this confusion is related to the varied terminology, but lack of adequate knowledge is the larger factor. The term "Werdnig-Hoffman disease" is now rather widely used for the preferable one of progressive muscular atrophy of spinal origin, a genetic disturbance which is entitled to designation as a clinical entity. There does not seem to be any reason to continue the use of the term "Oppenheim's disease." The conditions responsible for generalized hypotonia in infancy are discussed on pages 1095 and 1099 as the amyotonia congenita syndrome.

## MYOTONIA CONGENITA

(THOMSEN'S DISEASE)

Myotonia congenita is a hereditary muscular affection in which muscles stimulated by voluntary, mechanical or electrical means remain in the contracted state for an abnormally long time. The disease was first described in 1876 by Thomsen, whose observations were derived from members of his own family, in which the disease had existed for seven generations.

**Etiology.** The primary defect in this disorder has not been clearly elucidated. Myotonia occurs with mechanical and electrical stimulation applied to the muscle after blocking the motor nerve. One concept is based on a primary defect resulting in hyperexcitability of muscle fibers so that a single excitation leads to a repetitive series of discharges with progressively diminishing action potential rather than a single muscular twitch. The fact that drugs with cholinergic effects, such as neostigmine, enhance the degree and period of myotonia lends support to this concept. Denny-Brown and Foley, however, do not believe that neuromuscular transmission is disordered, but that the responsible mechanisms is an accumulation of a by-product of contraction, a chemical mediator of intracellular origin.

The physiologic defect is accompanied by

few morphologic changes. However, all fibers of involved muscles are hypertrophic. There are no evidences of degeneration.

**Clinical Manifestations.** The onset is usually noted in early childhood, but manifestations of the disease may not be observed until young adulthood. The characteristic sign is occurrence of sustained contraction of muscles when the patient attempts to use them after a period of rest. Voluntary relaxation may be delayed for five to thirty seconds after contraction. Movements become easier with repetition, and contractions less prolonged. The muscles of the legs are most frequently involved. The patient starts to walk haltingly and slowly, but after a few steps the imperfection of gait disappears, and walking becomes normal. After grasping an object the sustained contraction of muscles of the hand and forearm may make it impossible to release it for several seconds. Most of the striated muscle may be involved. The affection may be severe in some muscle groups and slight in others, and involvement may be greater on one side than on the other. The condition is aggravated by cold, rest, apprehension, fear, excitement, febrile illnesses and forced effort. Seldom are the muscles of respiration or of the pharynx affected.

The muscles of patients with myotonia congenita are usually well developed or even enlarged. Atrophy and contractures do not occur. In the presence of muscular atrophy associated with myotonia, a diagnosis of myotonic dystrophy is indicated.

After mechanical stimulation of the muscles of patients with myotonia, contraction of the fasciculi persists for many seconds with a concavity at the site of mechanical impact. Electrical stimulation, either faradic or galvanic, of moderate intensity produces the "myotonic reaction," in which contraction persists as long as current is applied, and then relaxes slowly.

**Prognosis.** The condition may persist relatively unchanged throughout life, the only hazard being that of accidents contributed to by the myotonia.

**Treatment.** Quinine is effective in reducing the myotonia. For adults a dose of 0.3 to 0.6 gm. (5 to 10 grains) of quinine hydrochloride or sulfate two or three times daily

is usually adequate. Proportionately smaller doses should be administered to children. Patients may learn to adapt to their handicap by engaging in a brief period of "warming up" before undertaking certain movements.

### MYOTONIC DYSTROPHY

This is a rare familial disease accompanied by muscular atrophy and the phenomenon of myotonia. Frequently associated with it are alopecia, cataract, and atrophy of the sex glands. Males are affected about five times as frequently as females. The onset is usually in young adult life, although symptoms may appear in childhood.

**Etiology and Pathology.** Myotonic dystrophy is transmitted as either a dominant or a simple recessive factor. It may appear in one or several generations of a family, and there may have been cataracts and other congenital defects in previous generations. Gonadal atrophy accompanying the disease prevents propagation of the disease through affected persons.

Pathologic manifestations in muscle differ with the degree of atrophy. Early in the disease, muscle fibers vary in size and are rounded in cross sections. In swollen fibers rows of nuclei may accumulate beneath the sarcolemma or in the center of the fiber. With more extensive atrophy there are evidences of widespread degeneration and replacement of muscle by fat and connective tissue. Lesions do not occur with constancy in the nervous system, and those observed are usually considered secondary to primary involvement of the muscle. Morphologic changes have been infrequently observed in the pituitary, adrenal and thyroid glands. The testes may be atrophic.

**Clinical Manifestations.** Muscular weakness and atrophy develop initially in the muscles of mastication and of the face and neck. Delayed relaxation following initial contraction of muscles may appear before, concurrently or after the development of atrophy. This myotonia is analogous to that of myotonia congenita, except that atrophy does not accompany the latter disorder. The myotonia of myotonic dystrophy is frequently limited to muscles of the forearms and legs. Other abnormalities such as baldness, cataracts or testicular atrophy may also be present, and mental deficiency is common.

**Prognosis.** The disease is slowly progressive; contractures develop and disability in-

creases. Death usually occurs before the age of forty-five years, pneumonia being the most common cause.

**Treatment.** Myotonia sometimes is controlled by administration of quinine, but such therapy in no way affects the progress of muscular atrophy. Other therapy includes procedures which will moderate the discomforts attendant upon the deformities.

### PROGRESSIVE MUSCULAR DYSTROPHY

This is one of the more common primary diseases of muscle. It is characterized by weakness and atrophy of the skeletal muscles with increasing disability and deformity as the disease progresses. Several clinical types are recognized, but muscular atrophy occurs in all forms; pseudohypertrophy appears as an early and prominent sign in one form. Genetic patterns are varied and may be of a sex-linked, simple recessive or dominant type. Muscular dystrophy accompanied by pseudohypertrophy is usually transmitted by a sex-linked factor, and most cases of facioscapulo-humeral dystrophy appear through a dominant genetic pattern. Manifestations of the disease are likely to occur early in life when it has been transmitted through sex-linked or simple recessive factors. In contrast, when a dominant mode of inheritance is involved, the onset occurs later in life. The disease occurs about three times as often in males as in females. Moreover, muscular dystrophy occurring in females is likely to be less severe and less rapidly progressive.

**Pathology.** There are no essential differences in the pathology of the various clinical types of the disease. On gross examination the muscles are pale and fibrous. In pseudohypertrophic muscles, fatty infiltration is responsible for producing a characteristic yellow color on gross section. True muscular hypertrophy is seldom if ever observed at necropsy. Microscopically, there are evidences of cellular degeneration. Muscle fibers vary in diameter, some appearing small and shrunken, others large and swollen. Accumulations of nuclei are found along the sarcolemmal sheath. There is fragmentation of fibrils and evidence of hyaline and granular degeneration. On cross section, muscle fibers will be seen to have lost their polygonal shape and are rounded or oval, individual fibers being widely separated from each other by fat, fibrous connective tissue and areolar tissue. Late in the disease connective tissue



replaces most of the muscle mass, and only occasional, small, degenerative muscle fibers will be observed.

The myocardium may show similar changes, but usually the process affecting the cardiac muscle is less marked. Smooth muscle is unaffected. Changes in the anterior horn cells have been described, but these are irregular in occurrence and cannot be considered responsible for the profound muscular atrophy. Decalcification and osseous atrophy are found in late stages. Thick, soft accumulations of subcutaneous fat often appear about the pelvic girdle and shoulders.

The disease is accompanied by creatinuria in adults and excessive urinary excretion of creatine in children. Creatinine excretion, however, is decreased. There is, in addition, increased urinary excretion of glycoxyamine, an intermediary compound in the biologic synthesis of creatine. When the precursors of creatine, the amino acids glycine, arginine and methionine, are provided in adequate amounts, glycoxyamine and creatine are excreted in the urine, indicating that there is no defect in the synthesis of these materials. Urinary excretion of creatinine correlates in some measure with the amount of residual functional muscle. As the disease progresses, creatinine excretion decreases.

**Clinical Forms.** All clinical forms of muscular dystrophy may be considered variations in manifestations of a single disease, differing only in the muscle groups affected, the age at onset and rate of progression. A single case may have characteristics of several forms. In deference to classic nomenclature, and since clinical manifestations greatly depend on the particular groups of muscles affected, the more important clinical forms of muscular dystrophy are described.

**Pseudohypertrophic form.** This is the most common form in childhood. The onset is usually before the fifth year of life. Certain muscle groups are enlarged, representing characteristic pseudohypertrophy. Atrophic changes are noted in other muscles and follow in muscles initially enlarged. Sex-linked or simple recessive genetic factors are effective in its transmission. The disease is progressive, few patients living past the age of puberty.

The first signs are noted in rare instances in infancy or early childhood, the child finding it difficult to stand or learn to walk. More often the child is observed to have gradually increasing weakness of the lower extremities. A waddling gait results from weakness of the gluteal muscles, and he walks with his feet

thrown widely apart. He may fall frequently. Riding a tricycle or ascending stairs may become impossible. The child may be unable to comb his hair or raise his hands above his head because of involvement of the muscles of the shoulder girdle. Weakness of the shoulder muscles is manifested by the manner in which the arms slip upwards and through the examiner's hands when they are placed in the axillas in an attempt to lift the child.

A characteristic feature is the patient's inability to arise readily to an upright position from a sitting position on the floor (Fig. 391). The patient turns on his side, flexes his knees and hips, and with arms extended raises his trunk to assume a position of kneeling. The feet are brought forward and the legs extended at the knees. Then by bringing the hands successively to the shins, knees and thighs, he pushes his body to the upright position. This succession of movements is generally considered pathognomonic of progressive muscular dystrophy.

In the upright position there is marked lordosis, and the abdomen is thrust forward prominently. The pelvis and sacrum tilt anteriorly, and there is forward inclination of the lumbar vertebrae. Winging of the scapulas may be noted.

Muscles are usually involved symmetrically. Pseudohypertrophy is observed most frequently in the infraspinatus, supraspinatus, deltoids and triceps, and in the muscles of the calves. Macroglossia sometimes occurs. Usually the muscles of the face and of the forearms are unaffected. Atrophy is usually first observed in the sternal portion of the pectoralis major. As the disease progresses there is also atrophy of the deltoid, triceps, biceps, gluteus and the anterior thigh muscles. Atrophy begins near tendinous ends, so that on contraction the muscle stands out in bold relief. Late in the disease all muscles of the lower extremities, spine, pelvis and shoulder girdle are atrophic. In some instances there are large subcutaneous depositions of fat, which tend to preserve body contours; in others the extreme muscular atrophy results in an appearance of inanition. Contractures and skeletal deformities result.

Tendon reflexes may be normally active early in the disease, but become hypoactive and later disappear as the muscles become too weak to respond to stimuli. Superficial reflexes are unchanged. Fasciculation does not occur. Response to electrical stimulation is decreased, but the reaction of degeneration is not observed. Cramping pains in the ab-



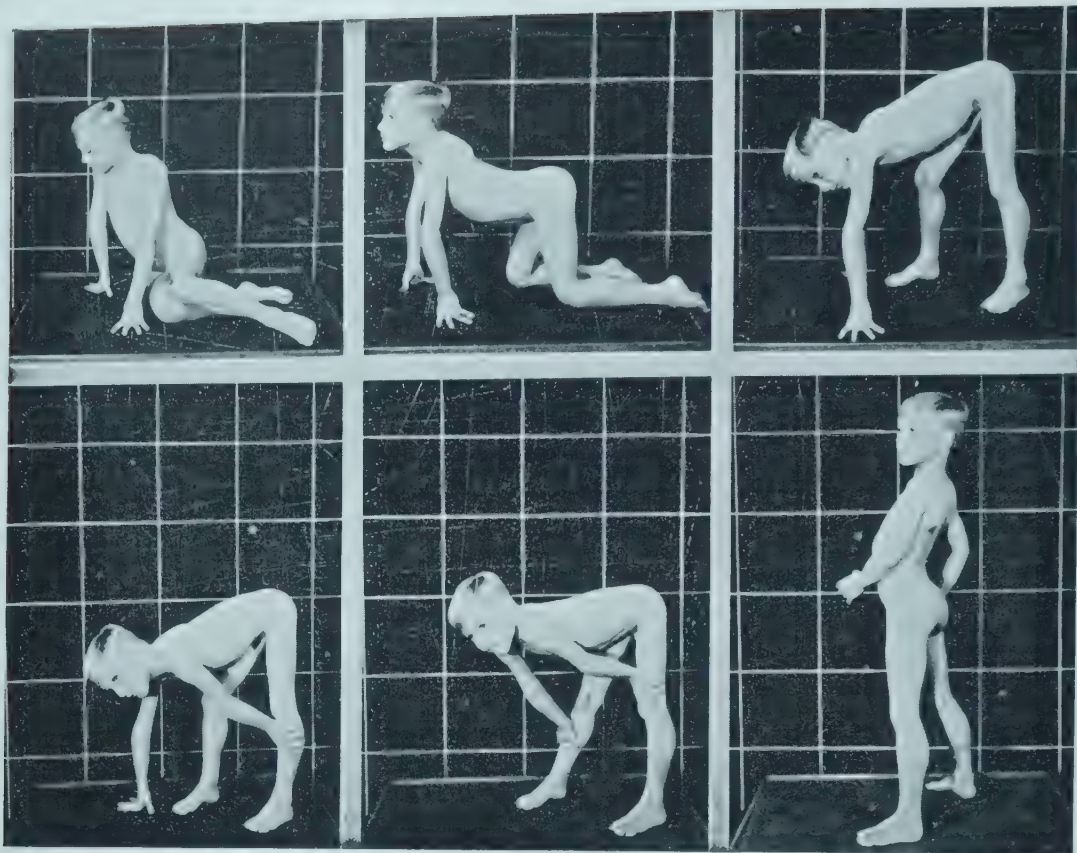


FIG. 391. A child 7 years of age with pseudohypertrophic muscular dystrophy, showing characteristic manner of rising from the floor. The last picture shows the standing position with the marked lordosis.

domen and in the muscles of the lower extremities are common. There may be mottling and cyanosis of the skin of the legs resulting from inadequate venous return, secondary to loss of muscle tone. In late stages of the disease tachycardia may be noted.

These children are usually cheerful, bright and hopeful despite the disabilities and long periods of invalidism consequent to the disease. Learning capacities are usually unimpaired, though mental deficiency is an occasional accompaniment.

A variant of the pseudohypertrophic form is the simple hereditary *atrophic form of Leyden-Moebius*, which is not associated with pseudohypertrophy and is stated to progress more slowly.

**Facioscapulohumeral form (type of Landouzy and Déjerine).** In this type the onset usually occurs between the ages of six and twenty years. Hereditary transmission follows a mendelian dominant pattern. The muscles first affected are those of the face and the shoulder girdle. The first defect often noted is inability to raise the arms above the head. The face becomes expressionless and mask-like, the patient being unable to close his eyelids, lift his eyebrows or wrinkle his forehead.

The process progresses slowly and over a period of years spreads to muscles of the pelvis and lower extremities.

**Juvenile muscular atrophy (type of Erb).** The onset of this type of the disease usually occurs in adolescence or early adult life. The muscles of the shoulder girdle are first affected, winging of the scapulas resulting because of atrophy of the serrati magni and the trapezii. There is difficulty in elevating the arms above the head. The muscles of the face are not involved. The disease is slowly progressive, the patient's condition often remaining unchanged for years.

**Diagnosis.** The clinical signs and characteristics of progressive muscular dystrophy which are important in differential diagnosis are the symmetrical and proximal distribution of muscular weakness, pseudohypertrophy, slow progression of the disorder, absence of sensory changes and the occurrence of the disease in other members of the family. In contrast, polyneuritis is associated with muscular weakness and atrophy of the extremities accompanied by pain, tenderness and sensory changes. Muscular weakness in spinal muscular atrophy is present at birth or appears early in infancy. Progressive neural



muscular atrophy involves the distal muscles of the extremities and of the hands. It is also associated with fibrillary tremors and electrical changes of degeneration.

**Prognosis.** The disease is progressive, death usually occurring within five to ten years of the onset in the pseudohypertrophic form. Few patients survive adolescence. Intercurrent infection is the most common cause of death. In rare instances myocardial insufficiency may be the terminal event.

**Treatment.** There is no specific therapy. Various amino acids, vitamins and hormones have been used in the treatment of this disease. Although encouraging therapeutic results have been reported, no therapy has proved to be beneficial. Efforts at supportive treatment are also of little avail. Orthopedic appliances and surgical procedures have been used in attempts to correct the contractures which develop late in the disease, but any benefit derived is temporary. Since inactivity seems to be accompanied by increased disability and deformity, it is important to utilize and exercise the muscles in which any degree of function remains. If other illnesses intervene which require periods of bed rest, massage and electrical stimulation may be used as a substitute for exercise.

A tendency to obesity in these children is common, and, unless dietary control is practiced, overweight may inflict an unnecessary disadvantage on the muscularly handicapped child.

## MYASTHENIA GRAVIS

**Etiology.** Myasthenia gravis is characterized by abnormal fatigability of skeletal muscle. The etiology is unknown. The defect seems to be manifest in the myoneural junction; there is either an insufficiency of acetylcholine at this site or an elevation of the threshold of the motor end plates with consequent partial block to incoming nerve stimuli. Neostigmine decreases the fatigability of affected muscles, as do other inhibitors of cholinesterase.

**Pathology.** There are no consistent gross or microscopic morphologic changes in the affected muscle. However, aggregates of small round cells, lymphorrhages, are often found in the skeletal muscles. Hyperplasia of the thymus or thymoma is present in some instances.

**Clinical Manifestations.** The disease is uncommon in infants and children. The first

manifestations may be ptosis or difficulties in mastication, speech and swallowing. Later the defect may extend to muscles of the neck, trunk and extremities. The affected muscles may be capable of contraction only for brief intervals or respond in limited extent to attempts to utilize them. Muscular response also tends to be weaker as the day progresses. Relaxation of facial musculature results in an appearance of apathy or lack of expression, often referred to as the "myasthenic facies." Involvement of muscles of mastication and deglutition may cause regurgitation of food through the nares or lead to episodes of choking. It may be impossible for the patient to climb stairs, walk, sit up or arise from bed when the muscles of the trunk or extremities are affected. Death may result when there is involvement of the muscles of respiration.

There is no muscular atrophy, and fibrillary contractions are absent. The deep reflexes are depressed or absent, and superficial reflexes are unimpaired. Electrical excitability shows no qualitative changes, but on repeated stimuli the muscles soon fail to respond (myasthenic reaction), although response may again be elicited after an interval of rest.

*Myasthenia gravis in the newborn infant* may be a transitory manifestation in an infant of a mother with the disease, or it may represent the onset of myasthenia in infants of nonmyasthenic mothers.

The clinical manifestations in the transitory disturbance in infants of myasthenic mothers tend to be severe, and death may occur. These infants respond promptly to neostigmine, but within a matter of weeks recover spontaneously, and no further treatment is necessary.

Much less frequently myasthenia gravis may be congenital in origin with manifestations present at birth or shortly thereafter, but usually of a much less serious order than is the case in the transitory disturbances. The course is progressive, however, and continuous therapy is needed.

Ptosis, a weak cry, hypotonia and easy fatigability, especially manifest in nursing, are common signs. It is likely that many instances of myasthenia of each of the foregoing types are mistakenly diagnosed as birth injury or narcotization.

Whenever an infant has hypotonia, with or without associated respiratory disturbances at or shortly after birth, which is not readily explainable by other cause, a therapeutic trial

with neostigmine would seem to be indicated. It is mandatory in infants of myasthenic mothers.

**Diagnosis.** The diagnosis is indicated when there is rapidly developed fatigue of skeletal muscle without atrophy, which is corrected in whole or in part by neostigmine. Bulbar paralysis, encephalitis and muscular dystrophy may need to be considered in the differential diagnosis.

**Prognosis.** The disease is chronic and is accompanied by remissions in which symptoms are alleviated or entirely absent for intervals of several weeks to years. Death may result from respiratory obstruction due to food particles lodged in respiratory passages or from respiratory failure when the muscles of respiration are affected. Infections are a hazard for these patients, since muscular weakness is exaggerated at such times. Malnutrition may result from difficulties in deglutition.

**Treatment.** Partial or complete relief from symptoms may be afforded by treatment with neostigmine. The drug may be administered orally as the bromide in doses of 5 to 15 mg. two to four times daily. It may also be given parenterally as the methyl sulfate; 0.5 to 1.5 mg. represents usually effective dosage. The drug, when administered subcutaneously or intramuscularly, will be effective within a few minutes, whereas effects are noted following oral administration after an interval of thirty to forty-five minutes. Tolerance to neostigmine may develop after prolonged treatment and it may become necessary to increase the dose. The amount of the drug administered should be carefully regulated to provide maximal comfort for the patient without excessive dosage. Undesirable side effects of neostigmine may be relieved with atropine. A number of other effective drugs are also available. Pyridostigmine bromide is said to have less undesirable effects on the gastrointestinal tract than neostigmine, and ambenonium chloride a more prolonged action. The anticholinesterase compounds, tetraethylpyrophosphate (TEPP) and octamethyl pyrophosphoramidate (OMPA) are said to provide more evenly sustained strength.

The occasional association of thymoma or thymic hyperplasia with myasthenia gravis has led to treatment by thymectomy or irradiation of the thymus. Such treatment should be reserved for patients not readily controlled by medical therapy or for those having a very large gland, when there is reason to believe it might be a thymoma.

The use of the respirator or tracheotomy may be lifesaving when the muscles of respiration and of swallowing are severely affected.

## FAMILIAL PERIODIC PARALYSIS

This syndrome is characterized by recurring attacks of flaccid paralysis of variable extent associated with a defect in potassium metabolism. The muscles are not trophic, and there is no muscular weakness in the intervals between attacks.

The disorder is relatively uncommon. It is a genetic disorder, occurring with equal frequency in both sexes. Many persons within a family may suffer from the disorder with manifestations of varying severity in different members. The trait may be transmitted through either parent as a dominant or a simple recessive character.

**Clinical Manifestations.** The disorder is usually manifest in childhood. Initial episodes of paralysis rarely occur after puberty. Attacks are most likely to develop during the night or after periods of inactivity. The patient may awaken to find himself paralyzed. The proximal muscles of the extremities are first affected, often followed by involvement of most of the voluntary musculature.

Paralysis may involve only a few muscle groups or may be total. Sphincter muscles and muscles of the face, eyes and tongue are not affected. During episodes of paralysis, tendon reflexes are depressed, and there is failure to respond to galvanic or faradic stimulation. Between attacks tendon reflexes and electrical excitability are normal.

Paralytic episodes are likely to follow excessive intake of liquids or carbohydrate foods, exposure to cold or injection of epinephrine or insulin. Patients may recognize symptoms which herald an attack and predict its occurrence hours in advance. Headache, somnolence, excessive thirst, fatigue or vague pains may occur as prodromes. A single paralytic episode may last from a few hours to two or three days. The intervals between attacks vary from a day or two to many years. The level of serum potassium at the onset of attacks varies, but decreases of 10 to 30 per cent are usual. The decrease is apparently the result of a shift of potassium from blood to the extravascular compartments. There is no increase in urinary potassium preceding an attack, but it is regularly observed as the paralysis recedes.

**Prognosis.** Death may occur during an initial or subsequent paralytic episode, either



from respiratory or cardiac failure. There is a tendency to reduction in the number and severity of attacks after middle life.

**Treatment.** Administration of potassium salts will control or abort a paralytic episode and will prevent occurrence of attacks. For terminating paralysis, 5 gm. of potassium chloride should be given orally, and this dose may be repeated in fifteen to thirty minutes if necessary. In severe paralytic seizures 50 cc. of a 2 per cent potassium chloride solution may be given intravenously. Recovery occurs usually before there is any perceptible increase in the potassium level. Recurrences are prevented in most patients by the daily ingestion of 2 to 4 gm. of potassium chloride. It is advisable to administer the drug at the time of retiring.

ROBERT E. SHANK

REVISED BY EDITOR

## REFERENCES

### General

- Adams, R. D., Denny-Brown, D., and Pearson, C. M.: *Diseases of Muscle; A Study in Pathology*. New York, Paul B. Hoeber, Inc., 1953.
- Szent-Györgyi, A.: *Chemistry of Muscular Contraction*. 2d ed. New York, Academic Press, Inc., 1951.

### Congenital Defects of Muscle

- Bing, R.: Ueber angeborene Muskeldefecte. *Arch. f. path. Anat. u. Physiol.*, 170:175, 1902.
- Eagle, J. F., Jr., and Barrett, G. S.: Congenital Deficiency of Abdominal Musculature with Associated Genitourinary Abnormalities: A Syndrome; Report of 9 Cases. *Pediatrics*, 6:721, 1950.
- Sheldon, W.: Amyoplasia Congenita. *Arch. Dis. Childhood*, 7:117, 1932.

### Torticollis

- Hulbert, K. F.: Congenital Torticollis. *J. Bone & Joint Surg.*, 32-B:50, 1950.

### Myositis Fibrosa

- Blau, A.: Primary Generalized Myositis Fibrosa: Report of Two Cases with Histopathology. *J. Mt. Sinai Hosp.*, 5:432, 1938.
- Stewart, A. M., and MacGregor, A. R.: Myositis Fibrosa Generalisata. *Arch. Dis. Childhood*, 26:215, 1951.

### Progressive Myositis Ossificans

- Eaton, W. L., Conkling, W. S., and Daeschner, C. W.: Early Myositis Ossificans Progressiva Occur-

ring in Homozygotic Twins. *J. Pediat.*, 50:591, 1957.

- Lockhart, J. D., and Burke, F. G.: Myositis Ossificans Progressiva. *Am. Dis. Child.*, 87:626, 1954.
- Riley, H. D., Jr., and Christie, A.: Myositis Ossificans Progressiva. *Pediatrics*, 8:753, 1951.

### Myotonia Congenita

- Denny-Brown, D., and Foley, J. M.: Evidence of a Chemical Mediator in Myotonia. *Tr. A. Am. Physicians*, 62:187, 1949.
- Hirsch, D. R., Dancis, J., and Ward, R. S.: Myotonia Congenita. *J. Pediat.*, 35:760, 1949.
- Maas, O., and Paterson, A. S.: Myotonia Congenita, Dystrophia Myotonica and Paramyotonia; Reaffirmation of Their Identity. *Brain*, 73:318, 1950.

### Myotonic Dystrophy

- Wohlfart, G.: Dystrophia Myotonica and Myotonia Congenita. *Histopathologic Studies with Special Reference to Changes in the Muscles*. *J. Neuro-path. & Exper. Neurol.*, 10:109, 1951.

### Progressive Muscular Dystrophy

- Danowski, T. S., and others: Muscular Dystrophy. *A.M.A. Am. J. Dis. Child.*, 91:, 326, 339, 346, 356, 429, 436, 442, 449, 1956.
- Moore, W. F., Jr.: Cardiac Involvement in Progressive Muscular Dystrophy. *J. Pediat.*, 44:683, 1954.

### Myasthenia Gravis

- Green, R. A., and Booth, C. B.: The Development of Myasthenia Gravis after Removal of Thymoma. *Am. J. Med.*, 25:293, 1958.
- Kibrick, S.: Myasthenia Gravis in the Newborn. *Pediatrics*, 14:365, 1954.
- McCrae, D.: Myasthenia Gravis in Early Childhood. *Pediatrics*, 13:511, 1954.
- Wilson, A., Maw, G. A., and Geoghegan, H.: Cholinesterase Inhibition and Signs and Symptoms in Myasthenia Gravis. *Quart. J. Med.*, 20:21, 1951.

### Familial Periodic Paralysis

- Gass, H., Cherkasky, M., and Savitsky, N.: Potassium and Periodic Paralysis: A Metabolic Study and Physiological Considerations. *Medicine*, 27:105, 1948.
- Grob, D., Johns, R. J., and Liljestrand, A.: Potassium Movement in Patients with Familial Periodic Paralysis. *Am. J. Med.*, 23:356, 1957.
- Tyler, F. H., Stephens, F. E., Gunn, F. D., and Perloff, G. T.: Studies in Disorders of Muscle. VII. Clinical Manifestations and Inheritance of a Type of Periodic Paralysis without Hypokalemia. *J. Clin. Investigation*, 30:492, 1951.

# The Skin

It is often possible to arrive at the diagnosis of a dermatosis and prescribe therapy with little help from the history. This situation is particularly advantageous in dealing with infants or young children who cannot transmit subjective complaints. The importance of the history from the mother or attendant or from an older child himself is not to be underestimated, however. The family history is particularly important when dealing with an allergic disease of the skin such as atopic eczema or a parasitic infestation such as scabies.

The cooperative activity of the dermatologist and the pediatrician and, on occasion,

the allergist is often necessary for accurate diagnostic appraisal and for satisfactory therapeutic results.

The child's skin is more sensitive to topical applications than is an adult's skin, so that drugs incorporated in a prescription for topical use must be correspondingly diluted. Roentgen therapy, valuable in the management of many dermatoses in adults, must be used sparingly and with caution on the skin of a growing child, not only because of local dermal effects, but also because of the potential dangers to underlying tissues, such as the epiphyses of bones and glandular structures.

## CONGENITAL AND HEREDITARY ANOMALIES AND DEFECTS\*

### NEVI

Two groups of nevi are recognized: (1) the vascular group, due to hyperplasia of the blood or lymph vessels; and (2) the nonvascular group, in which there is an overgrowth of epidermal or connective tissues.

#### NEVUS VASCULOSUS (see also p. 1358)

Vascular nevi are congenital formations composed chiefly of blood vessels and are often referred to as "birthmarks," although they may not appear until some time after birth. It is best not to interfere with the simple, flat type, commonly seen at birth, particularly in the occipital region; the majority disappear spontaneously.

The *nevus flammeus*, or *port-wine mark*, which is always flat, does not respond well to any known method of treatment. The slightly elevated so-called *strawberry mark* or *nevus* (Fig. 392) responds well to carbon dioxide snow or dry ice, which is used in the form of a pencil of the exact size to fit the

lesion and is held upon it with moderately firm pressure for five to forty seconds. Additional treatments may be given at intervals of three to four weeks. After each treatment a daily dressing of zinc oxide ointment or other bland emollient such as hydrophylic petrolatum, U.S.P., is advisable. Radium therapy is effective, but, unless it is given with great care, pigmentation or telangiectasia may appear years later.

There are distinct differences of opinion as to the advisability of treating strawberry nevi during infancy and early childhood, inasmuch as many disappear spontaneously. Some progress, however, and, since best results are obtained early, treatment can be considered by the experienced therapist.

*Angioma cavernosum* is treated most effectively with irradiation, by injection of sclerosing solutions, a combination of the two, or by surgery.

The earlier treatment is applied after the appearance of any type of elevated vascular nevus, the better the result, since the lesions tend to grow with the child. Death has been

\* See also page 338.





FIG. 392.

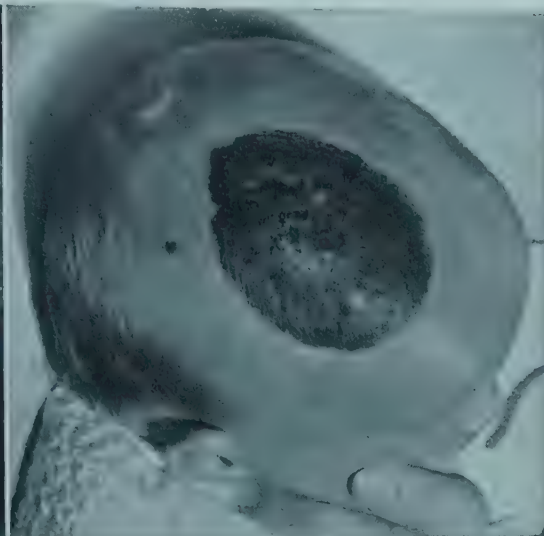


FIG. 393.

FIG. 392. Vascular nevus (strawberry mark).

FIG. 393. Nevus pigmentosus.

reported from hemorrhage following the rupture of neglected cavernous nevi, although occasionally trauma may result in spontaneous involution.

#### NEVUS PIGMENTOSUS

(MOLE) (See p. 1361)

LYMPHANGIOMA (See p. 1359)

#### ICHTHYOSIS

Ichthyosis is a congenital, hypertrophic disease characterized by dryness and scaling of the skin. In the winter the condition becomes more marked, the skin exhibiting scales which may be small and thin or large and thick, producing a "fish-skin appearance." Though cures cannot be expected, proper therapy will partially control the manifestations and make the patient more comfortable. Treatment consists in infrequent bathing using a superfatted soap and inunction of the skin with a greasy ointment such as one composed of 2 to 5 per cent salicylic acid in hydrous wool fat, hydrophilic petrolatum or goose grease. Relatively large doses of vitamin A may be given during the winter months, but toxic doses should be avoided.

#### KERATOSIS PALMARIS ET PLANTARIS

These lesions occur, usually symmetrically, as warty thickenings in the palms and soles. They may be hereditary or acquired. The condition is intractable, but improvement will result from the constant use of an ointment containing 5 to 25 per cent of salicylic acid in a lanolin base.

#### EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is a rare hereditary disease of the skin in which vesicles and bullae develop from slight trauma. In its most severe form, designated as epidermolysis bullosa dystrophica, the mucous membranes are involved, nails are absent or deformed, and

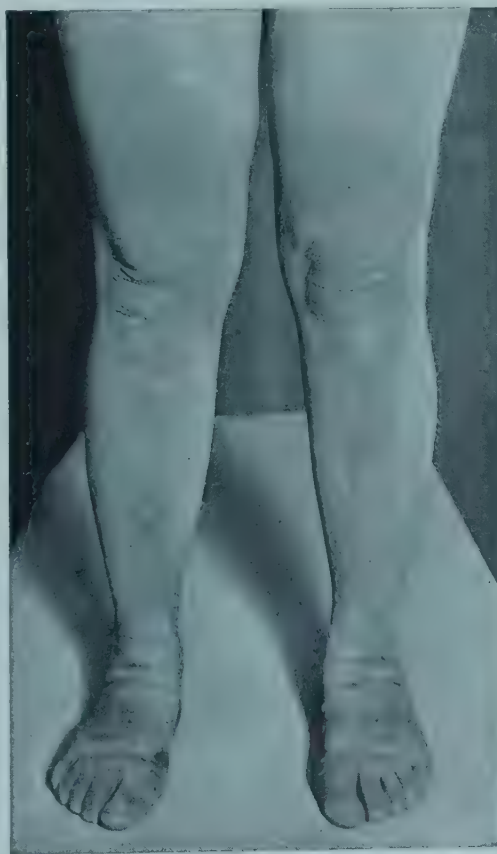


FIG. 394. Ichthyosis.

the teeth may be abnormal and some may be absent. The fatality rate is high in such cases. When the mucous membrane of the oral cavity is involved, management of the child is exceptionally difficult. Lesions may be produced by eating coarse foods and then interfere with eating. The lesions usually appear during infancy, and in some instances mild defects disappear during adolescence. Occasionally a case has not become manifest until adulthood. Nothing will prevent the development of the lesions except avoidance of trauma. When a vesicle or bulla forms, it should be punctured and a sterile dressing applied. Antibiotic therapy is indicated when secondary infection occurs.

### CONGENITAL ECTODERMAL DYSPLASIA

This disease is characterized by incomplete development of the epidermis or its appendages or its absence in certain areas (Fig. 395). There may be several or all of the following: dental aplasia; congenital absence of the sweat glands (anhidrotic type); partial absence of the pilosebaceous apparatus; a dry, white, smooth, glossy skin; sparseness of the hair; alteration of the nails; and a characteristic facies, including prominent supraorbital ridges, a depressed nasal bridge, and eyes that slant upwards. The condition is familial, more commonly affecting males.



FIG. 395. Congenital ectodermal dysplasia. Dysplasia of single tooth erupted, with paucity of eyebrows and eyelashes. (Courtesy of Dr. Reuben Friedman.)

The first manifestation in early infancy may be an otherwise unexplained high fever secondary to high environmental temperature. Children with the anhidrotic type suffer severely during hot weather, and heat strokes may result from prolonged exposure to high temperature. Relief may be obtained by keeping the skin wet by sponging, spraying the clothing or by immersion in water.

### PACHYONYCHIA CONGENITA

Pachyonychia congenita is a rare congenital anomaly characterized by dystrophy of the nails, anomalies of the hair, hyperkeratosis of the palms and soles, and bullous lesions occurring most commonly on the feet (Fig. 396). The nails appear to grow straight out



FIG. 396. Pachyonychia congenita with secondary infection.

from the nail bed and often must be removed surgically so that the fingers can be used effectively.

### XERODERMA PIGMENTOSUM

This is a rare disease which becomes manifest in childhood or rarely in later life, and is characterized by hyperpigmentation, atrophic areas, telangiectases and malignant growths. It is transmitted as a recessive character. Fatal termination from malignancy is the invariable result. Affected persons should avoid strong sunlight. Malignancies are readily apparent and should be removed as rapidly as they appear.



**CUTIS HYPERELASTICA**

(CUTIS LAXA, EHLERS-DANLOS SYNDROME, DERMATORRHEXIS)

This unusual condition is characterized by hyperelasticity of the skin, hyperflexibility of the joints, fragility of the skin capillaries, and

at times by multiple, freely movable, subcutaneous fatty nodules. Bleeding into and beneath the skin is, as a rule, easily incited by trivial trauma and may be extensive. As a result, the arms and legs are frequently covered with ecchymotic scars.

**PIGMENTARY CHANGES IN THE SKIN****ALBINISM**

In complete albinism the epidermal tissues, the hair and iris are devoid of pigment, the skin is preternaturally white, and the entire hair of the body is fine, silky and whitish. Photophobia and nystagmus occur as a result of absence of the protective pigment in the choroid, and are a considerable annoyance to the patient. The pupils appear red in reflected light.

**FRECKLES**

(LENTIGO)

Freckles are pinhead-sized to pea-sized, brownish or blackish pigmented macules. Some children have a special predisposition to freckling, which may at times be hereditary. There is rarely any indication for treatment, and it should usually be discouraged.

It consists in attempting to produce exfoliation of the epidermal cells containing the pigment, since permanent removal will usually result in scarring. Desquamation may be accomplished by the use of keratolytic agents in ointments or lotions.

**VITILIGO**

This is an acquired pigmentary affection characterized by variously sized and shaped whitish patches with hyperpigmented borders. The disease progresses slowly, becoming conspicuous only after a number of years, and usually persists through life. In children it sometimes disappears spontaneously. There is no specific treatment. Strong sunlight should be avoided, since it increases the pigment in borders, while the patches remain white.

**HYPERTROPHIES AND ATROPHIES****CICATRIX**

Depressed or raised scars result from deep injury or disease of the skin involving the papillary body of the corium. Depressed scars such as follow smallpox, chickenpox or pustular acne vulgaris cannot be entirely obliterated, although desquamation of the skin by various techniques, including dermabrasion, may bring about slight improvement. The appearance can be improved by cauterizing elevated scars to the level of the skin.

**KELOID**

A new growth of the connective tissue, which appears as a small pea-sized nodule and in subsequent years slowly increases in size,

may arise spontaneously, particularly in the Negro race, or may develop at the site of traumatic or infectious wounds. The lesion may be painful or pruritic. Good therapeutic results are possible with roentgen ray or radium therapy. Excision or electrofulguration is nearly always followed by recurrence and at times by an even larger growth.

**KERATOSIS FOLLICULARIS**

(DARIER'S DISEASE)

Keratosis follicularis is a rare disease in which pinhead- to pea-sized dark-colored, acuminate or rounded papules mark the sites of horny plugs embedded in funnel-shaped dilations of the pilosebaceous follicles. The le-

sions may be numerous and closely grouped. Treatment with large doses of vitamin A in a water-miscible preparation may be con-

sidered. The possibility of toxic effects from continued administration of large doses of vitamin A must be recognized (p. 363).

## DISTURBANCES IN THE SUBCUTANEOUS FAT

### SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

(ADIPONECROSIS SUBCUTANEA NEONATORUM, PSEUDOSCLEREMA)

This is a self-limited disease characterized by a patchy distribution of circumscribed areas of fat sclerosis, which involves especially the buttocks, the scapular region and the cheeks. Lesions do not occur on the abdomen, the palms or soles, the axilla or the inner aspects of the thighs. The involved areas are firm, usually movable and well demarcated. During resolution there may be central softening, and the lesion misinterpreted as an abscess. It has been believed that trauma is an important causative factor and that the low olein content of the subcutaneous fat of the newborn predisposes to the condition. Microscopic sections of the skin reveal necrosis of fat cells, an infiltration of epithelioid or giant cells, edema and thickening of the vascularized septums, absence of elastic tissue, and thickened, protoplasmic, needle-like crystals in forms of rosettes or sheaths in the spaces surrounding the fat cells.

No treatment is indicated, and under no circumstances should the lesions be incised. They recede spontaneously within three to four months, usually without causing significant atrophy.

### SCLEREMA NEONATORUM

(SCLEREMA ADIPOSUM)

Sclerema is a diffuse hardening of the subcutaneous tissues occurring in debilitated, especially premature, infants. It may appear at any time during the first weeks of life, and is especially prone to be associated with diarrheal disturbances and dehydration. The hardening of the subcutaneous tissues is usually first noted in the lower extremities, often in the calves, from which it rapidly extends upward. Ultimately it may involve the entire body surface with the exception of the palms, soles and scrotum. The skin is shrunken, smooth and cold. The areas of induration are extremely hard and do not pit on pressure,

resembling the tissues of a frozen cadaver. Though sclerema is often a terminal manifestation, recovery is possible.

Pathologically, the changes consist in a stearin-like hardness of the fatty tissue combined with dehydration; on cutting the tissue there is practically no escape of fluid. Histologically, fat crystals may be present, but sections often differ little from normal.

There is no specific therapy. Variable results have been experienced with the use of corticotropin (ACTH) and cortisone; though a clinical trial with one of them is justified, other aspects of therapy must not be neglected. Oxygen therapy is often necessary. In view of the possibility of an existing or acquired infection, broad-spectrum antibacterial therapy is indicated at least during administration of the adrenal steroid. Correction of any water and electrolyte imbalance is essential.

### SCLEREDEMA

(SCLEREMA EDEMATOSUM)

Scleredema is seen chiefly in weak and premature infants, and often in association with diarrheal disturbances. It usually begins on the second to fourth day of life as an edematous swelling of the dorsal surface of the feet, calves, thighs, mons pubis and also of the upper extremities and eyelids. The characteristic pitting which occurs on pressure disappears slowly. In contrast to sclerema neonatorum, there is an obvious increase of volume of the affected parts, and, in contrast to subcutaneous fat necrosis, there are never any sharply circumscribed lesions. The edema may be extensive or may involve only selected sites, particularly the feet. Death usually occurs in four to five days, though recovery is possible.

Pathologically, there are no characteristic changes other than intense edema, which may involve the skin, subcutaneous tissue and underlying muscles; nonspecific inflammatory changes may also be present.

There is no specific therapy (see under Sclerema Neonatorum).



## LIPODYSTROPHY

Lipodystrophy is characterized by progressive loss of subcutaneous fat from the face, neck, thorax and upper extremities, and occasionally by an increase in fat in the lower part of the body. The cause is obscure. The disease is insidious in onset, beginning usually between the ages of eight and ten years. It has followed acute infections, and occurs twice as often in females as in males. The increase of fat in the lower half of the body is apparently limited to the female. Both hypothyroidism and hyperthyroidism have been reported in patients with lipodystrophy. Harris and Reiser observed a patient whose serum fat increased after a meal with a high fat content and who also had creatinuria and a lowered dextrose tolerance.

Biopsy of atrophied areas reveals almost complete absence of subcutaneous fat tissue; that which remains has no unusual staining properties.

The onset and course of the disease are asymptomatic. There is no pain in the areas of fat atrophy as there is in Dercum's disease (adiposis dolorosa). The active phase of

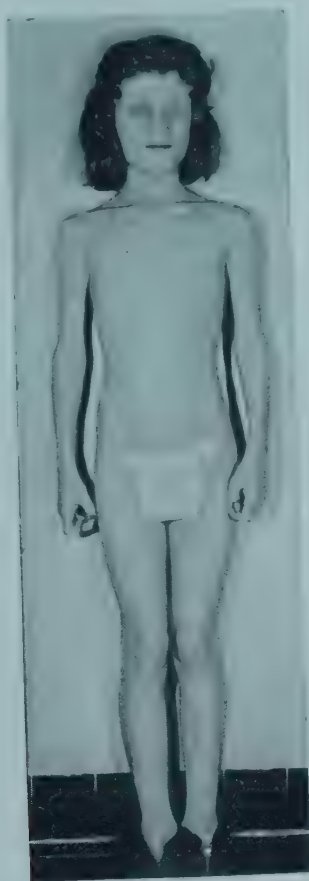


FIG. 397. Lipodystrophy in a girl aged 9 years. Note emaciation of face and neck in contrast to fair nutrition of the remaining portion of the body.

atrophy extends over a period of weeks or months, but the effects persist. The skin and muscles of the diseased areas are normal. The appearance of the patient is typical: the face is gaunt and the cheeks are sunken, with numerous lines and wrinkles about the mouth (Fig. 397). The arms or thorax may likewise appear emaciated, but the lower extremities are normal or may appear to have an increased amount of subcutaneous fat. This increase may be due to an increased food intake in a fruitless attempt to overcome the wasting of the face.

There is no specific *therapy*. The disease has no effect on life expectancy.

## REFERENCE

Harris, J. S., and Reiser, R.: Lipodystrophy. *Am. J. Dis. Child.*, 59:143, 1940.

## RELAPSING NODULAR NONSUPPURATIVE PANNICULITIS

### (WEBER-CHRISTIAN SYNDROME)

The Weber-Christian syndrome is characterized by recurrent febrile episodes during which nonsuppurative nodules develop in the subcutaneous tissue. The condition is infrequent at any age and rare in children; nothing is known of its etiology. The lesions appear to be limited to the panniculus. Microscopically, the more or less circumscribed lesions reveal infiltration of the fatty tissue by large numbers of leukocytes and phagocytosis of fat cells by macrophages, which have a foamy, vacuolated appearance.

Relapses or "attacks" occur in completely irregular fashion. There may be single or multiple lesions, which develop rapidly and vary in size from less than a centimeter to several centimeters. The nodule may be painless or only slightly tender, is movable and usually distends the overlying skin, which is red or violaceous. The nodules may occur on any part of the body. During the active phase there may be a low grade fever, or the temperature may be as high as 104° F. The nodules may regress within a few days or may persist for several weeks; they usually do not leave any visible evidence, but there may be dimpling of the skin. The white blood cell count may be within normal limits, or there may be a leukopenia.

The *prognosis* must be guarded, since several fatalities apparently attributable to the disease have been reported. Recurrence is the rule, although recoveries or complete remissions are observed. No therapeutic agents, in-

cluding corticosteroids, have been effective. The *treatment* is entirely symptomatic, but must include guidance for the child and his family in their adjustment to the situation.

#### REFERENCE

Sanford, H. N., Eubank, D. F., Stenn, F.: Chronic Panniculitis with Leukopenia (Weber-Christian Syndrome). *Am. J. Dis. Child.*, 83:156, 1952.

## DISEASES OF THE SEBACEOUS GLANDS

### MILIUM

The lesions appear as small, round, yellow or pearly-white sebaceous concretions just beneath the epidermis and are most common upon the forehead and cheeks. They occur commonly in infants and children and may be present at birth, but the cause of their formation is unknown. The lesions in infants or very young children disappear spontaneously, but in adolescents they must be incised with a fine scalpel and the contents liberated.

### ADENOMA SEBACEUM

Adenomas of the sebaceous glands may be present at birth or may appear shortly afterward. The lesions are pinhead- to pea-sized, rounded, elevated papules or nodules, situated particularly upon the nose, cheeks and chin. The color may be that of normal skin, waxy or reddish, and there may be an associated telangiectasia. Adenoma sebaceum frequently occurs in association with tuberous sclerosis (q.v.), in which mental deficiency is a prominent feature. Carbon dioxide snow applied over the affected areas for ten to twenty seconds with light pressure will often cause their disappearance. Larger lesions may require electrodesiccation.

### ACNE VULGARIS

Acne is an inflammatory disease occurring in and around sebaceous glands, characterized initially by comedones (blackheads) and later by superficial and deep papules and, if neglected, by pustules. The forehead, cheeks and chin are the regions usually affected, although the chest, shoulders and back may be involved. The disease is essentially one of adolescence and represents an overactivity of the sebaceous glands; more sebaceous material is formed than can be eliminated. It dilates the gland and pore, which becomes darkened from chemical changes and ingrained dirt, providing an ex-

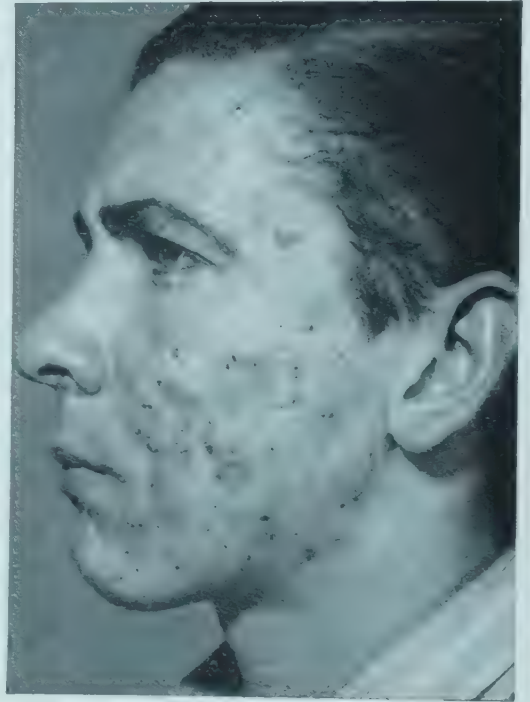


FIG. 398. Acne vulgaris.

cellent culture medium for bacteria. Resulting abscesses may be deep and lead to eventual pitting and scarring.

The etiology is unknown. The most important consideration in management is early treatment. In cooperative patients this will prevent the lesions from producing disfiguring scars, thus avoiding social and personality disturbances.

. Constitutional *treatment* consists in improvement in general health through attention to diet (p. 151), sleep and other hygienic factors. Menstrual disorders (p. 155) may provide additional evidence of the need for such guidance. Avoidance of chocolate is generally recommended.

Local therapy is of great importance. The skin must be kept scrupulously clean by frequent use of soap and water to remove dirt and bacteria, and at bedtime this should be followed by the free application of a lotion such as lotio alba or the following modification of it:



	Gm. or Cc.
Zinc sulfate .....	4.0-6.0
Sulfurated potash .....	2.0-4.0
Rose water .....	120

Numerous flesh-colored proprietary lotions and creams containing sulfur compounds are also readily available.

If the skin is oily, 70 per cent alcohol or acetone may be applied before the lotion. Vitamin A may be given orally during the winter months in generous doses, but avoiding potentially toxic ones. These measures, rigorously adhered to, will control the lesions in many cases. Permanent cure cannot be expected during adolescence, but the treatment

should never be left entirely to time and nature, or scarring will inevitably result.

When these measures do not control the sebaceous overactivity, roentgen therapy is used at times. It should be reserved for extreme situations, and treatment must be provided by an experienced physician who is thoroughly aware of the potential dangers. Natural sunlight is often beneficial if not overdone, as is ultraviolet light if given in sufficient amount to produce mild erythema and desquamation. If scarring results from deep-seated postular lesions, the depth of the scars can often be lessened by dermabrasion.

## DISTURBANCES OF THE HAIR

### ALOPECIA

A physiologic or pathologic deficiency of hair, either partial or complete, is termed alopecia. *Congenital alopecia* commonly manifests itself either as scanty growth, a lack of development only in certain areas, or as a retarded appearance of the hair. Rarely is there complete absence of the hair due to arrested development of the follicles. Such cases are usually hereditary, and there may be delayed or defective dentition as well as other evidence of ectodermal dysplasia.

### ALOPECIA AREATA

This disease is characterized by loss of hair from round or oval patches; in rare instances these areas coalesce and produce total baldness. The scalp, eyebrows, eyelashes and, at times, the entire cutaneous surface may be affected (*alopecia totalis*). The patches are rounded; the skin is smooth and soft with a dead white or faintly pink color and is totally devoid of hair. Alopecia areata may develop suddenly or gradually and spread by peripheral extension until it reaches a certain size, when it tends to remain stationary. The disease usually persists for several months, during which time the hair tends to return gradually. The hair almost always grows back in children except in the totalis type, which is often persistent. When regrowth occurs, the



FIG. 399. Alopecia areata.

patch is first covered by fine downy, whitish hairs, which later change into coarser pigmented ones. The etiology is unknown. Many of these children are emotionally disturbed prior to the alopecia. It has been suggested that there may be a causal relationship.

*Treatment* consists in improving physical and emotional health. Dried brewers' yeast or vitamin B complex has been thought to be beneficial. Local measures such as daily massage of the patches with a 0.1 to 0.25 per cent anthralin ointment and erythema doses of ultraviolet rays from a mercury quartz lamp are believed to hasten regrowth of hair.

# DRUG ERUPTIONS

## (DERMATITIS MEDICAMENTOSA)

Skin eruptions may be produced by a number of drugs and serums. Table 116 shows the skin reactions to some of the common drugs.

Table 116. Drug Eruptions

<i>Drug</i>	<i>Type of Eruption</i>	<i>Drug</i>	<i>Type of Eruption</i>
Acetanilid.....	Erythematous	Iodides.....	Acneiform, bullous, erythematous, urticarial, papular, purpuric; may resemble erythema nodosum
Aminopyrine.....	Urticarial	Penicillin.....	Morbilloform and urticarial; angioedema
Arsenic.....	A wide variety of eruptions; at times much pigmentation or exfoliation	Phenolphthalein..	Erythematous, urticarial, bullous, macular; resembling erythema multiforme
Barbiturates.....	Maculopapular to morbilliform; urticaria; purpura; erythema multiforme; exfoliative dermatitis	Quinine.....	Scarlatiniform, urticarial, purpuric, bullous, ulcerative; sometimes with desquamation
Belladonna (atropine).....	Scarlatiniform, urticarial	Salicylates.....	Erythematous, scarlatiniform, purpuric; resembling erythema multiforme; sometimes with desquamation
Bismuth.....	Scarlatiniform or urticarial, with pruritus	Streptomycin....	Urticaria
Bromides.....	Acneiform, vesicular, pemphigoid, ulcerative, large papules, pustular, ecthymatous (Fig. 400). Mucous membranes may be involved. There may be excretion of bromides through breast milk	Sulfonamide....	Morbilloform, exfoliating dermatitis, urticaria
Chloral.....	Scarlatiniform, papular, urticarial, purpuric, lichenoid	Tetracyclines....	Urticaria; angio-edema chiefly from chlortetracycline
Digitalis.....	Scarlatiniform, papular		
Ephedrine.....	Erythematous, purpuric		



FIG. 400. Bromide eruption. Ecchymatous eruption following administration of potassium bromide.

## DERMATITIS AND ECZEMATOID LESIONS\*

Dermatitis, or inflammation of the skin, a term restricted to acute inflammations which result from known irritants, is characterized by heat, redness, pain and swelling. The term "eczema" is used interchangeably with derma-

titis, but is generally limited to cases which tend to be persistent or recurrent, irrespective of whether the cause is an external or internal one. Eczema may be considered a syndrome with numerous etiologic possibilities.

\* For infantile eczema, see page 1312.



**DERMATITIS VENENATA****(ALLERGIC CONTACT DERMATITIS)**

Dermatitis venenata includes the group of inflammatory conditions caused by vegetable and mineral irritants. Most common in children is the dermatitis produced by poisonous plants, chiefly poison ivy (*Rhus toxicodendron*) and poison oak (*Rhus diversiloba*). Poison sumac, dogwood, ash and the primrose may also cause a contact dermatitis, and there are many other rarer plants and shrubs which irritate the skin. From a few hours to several days after exposure the hands, face and other exposed areas of the skin become the seat of innumerable vesicles and blebs, accompanied by redness, swelling, burning and intense itching. The vesicles may appear in linear streaks, and the eruption may be carried to other parts of the body, particularly the genitals, by auto-inoculation. Some persons are so highly susceptible that direct contact is not required, the poison apparently affecting them if they are in the proximity of the plants. At times the poison may be brought into the house on the fur of a cat or dog and communicated to the child who fondles his pet. Some persons enjoy comparative immunity, although it may disappear any time during life.

Immunization against the dermatitis of poison ivy is a controversial issue. If desensitizing injections of ivy extract are given, they should be administered in early spring in a

single dose or in multiple doses according to the manufacturer's instructions. They are protective, if at all, for only one season.

*Treatment* of the acute rash with ivy extract is contraindicated.

In the active case of dermatitis venenata, no matter what the cause, relief of itching is the paramount consideration, since, unless it is relieved, more damage will be done by scratching than by the disease. Corticosteroids, if used early either locally or systemically, seem to be beneficial. If they are used systemically for more than a day or so, an antibiotic should be prescribed to combat infection. Quick relief is usually obtained by hot compresses of liquor aluminum acetate (Burow's solution) in a strength of 4 tablespoonfuls of the concentrated solution to 1 quart of hot water, followed by the free application of the following lotion:

	Gm. or Cc.
Sodium thiosulfate.....	8.0
Resorcin and boric acid, of each.....	4.0
Glycerin.....	4 to 8
Zinc oxide powder.....	30.0
Witch hazel.....	60.0
Distilled water, to make.....	180.0

Potassium permanganate compresses (1:4000 or approximately one 5-grain tablet in a quart of water) and numerous other types of solutions have been recommended. When edema is present, continuous hot compresses should be used during waking hours until the edema completely subsides, which may be several days.

**SEBORRHEIC DERMATITIS**

In infants the so-called cradle cap is believed to be a type of seborrhea; it occurs on the scalp either as a thick, greasy crust or as thin, dry scales. In older children seborrhea in its simplest form is manifest as ordinary dandruff, representing a normal though excessive exfoliation of the epidermis, which may be dry or oily, according to the type of skin. When this scale, for reasons not well understood, becomes marked, it is frequently infected by bacteria. In this stage seborrheic dermatitis may involve the scalp, ears, eyebrows and lashes, angles of the nose, or the cheeks and even the trunk.

*Treatment* must be directed primarily to the scalp. A simple ointment of sulfur precipitate, 1 gm., and salicylic acid, 0.6 gm., in 30 gm. of petrolatum or Aquaphor applied nightly and accompanied by a scalp shampoo

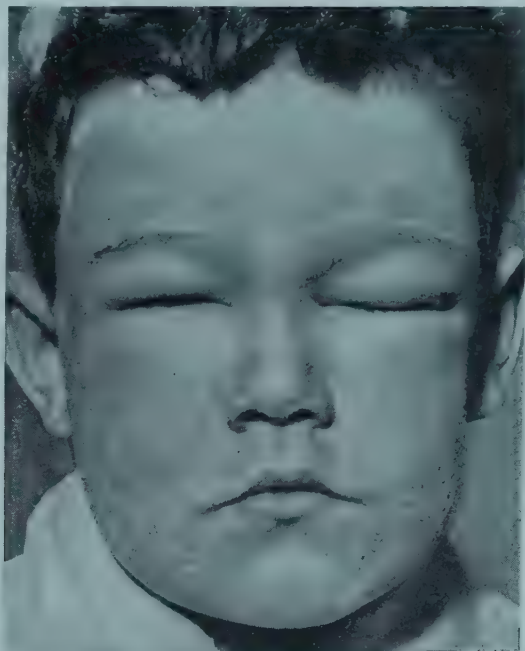


FIG. 401. Dermatitis venenata (*Rhus toxicodendron*).

which includes selenium sulfide (Selsun) for a dry scalp or tellurium dioxide (Teles) for an oily scalp, once or twice a week often suffices to free the scalp of scale. A mixture of equal parts of crude oil and olive oil with a daily shampoo may also be used. On non-hairy areas an ointment of sulfur precipitate, 0.3 gm., and salicylic acid, 0.2 gm., in 30 gm. of petrolatum often brings about rapid improvement. Ointments combining an antibiotic and a corticosteroid are effective for seborrheic dermatitis involving nonhairy areas.

### INFECTIOUS ECZEMATOID DERMATITIS

Ecematoid conditions are occasionally produced by the irritation from purulent secretions from abscesses, discharging sinuses, eyes or ears. The lesions may be dry and scaling, vesicular or pustular, and crusted. The application of bacitracin or tetracycline ointment

may bring about rapid improvement, provided the purulent discharge is no longer permitted to irritate the area. If extensive crusting is present, a starch poultice (see Formulary, p. 1301) will be useful in removing the crusts, after which one of the above-mentioned ointments may be used. Any simple ointment, such as petrolatum, may be applied to prevent irritation from purulent discharges.

### LEINER'S DISEASE

(ERYTHRODERMA DESQUAMATIVUM)

Leiner's disease is usually associated with an exudative diathesis, especially a seborrhea of the scalp. The onset is usually in the second or third month of life. The lesions appear first about the buttocks and the gluteal folds and extend over the remainder of the body. The skin is red and covered with grayish-white scales, which at first are opaque, but later become somewhat lustrous (Fig. 402).



FIG. 402. Leiner's disease. Note plaquelike scales on chest. (Hill, in *Practice of Pediatrics*, edited by McQuarrie. W. F. Prior Co., Inc.)



FIG. 403. Ritter's disease.



There is often an eosinophilia. Vomiting and diarrhea, cyanosis, hypertonia and eventually cachexia are prominent symptoms. The prognosis in general is favorable. The treatment is symptomatic.

### ITTER'S DISEASE

(DERMATITIS EXFOLIATIVA NEONATORUM)

Ritter's disease usually develops in the first few weeks of life as a local hyperemia of the cheeks and around the corners of the mouth, from where it spreads to involve all the body. Quickly there is wrinkling of the skin and desquamation of it in sheets, leaving large, denuded, reddened, dry areas. *Nikolsky's sign*

(easy removal by friction of undenuded skin) is characteristic, but not pathognomonic. There is usually no fever. There may be a leukocytosis with a mononucleosis. Sections of the skin are characterized by desquamation, cellular infiltration and edema. The case fatality rate was about 50 per cent before the advent of antibacterial therapy. The prognosis is now much more favorable.

It has been questioned whether Ritter's disease and Leiner's disease are separate entities, since there is some overlapping in both the clinical and the pathologic manifestations. The clinical patterns are distinct, however; Ritter's disease appears to be infectious in origin, whereas Leiner's disease has elements suggestive of an allergic etiology.

## ERYTHEMATOPAPULAR AND SQUAMOUS ERUPTIONS

### PSORIASIS

It has been estimated that about half of the cases of psoriasis begin in childhood. The disease is uncommon before the age of ten, and extremely rare under three years of age. Heredity seems to be a factor in a small percentage of cases. Psoriasis almost invariably begins as small, reddish, pinpoint- to pinhead-sized papules, surmounted by minute scales. The patches increase by peripheral extension, becoming a centimeter or more in diameter. The individual patches in the well developed case are dry, round, sharply defined, more or less infiltrated and elevated, and covered with profuse, shining, gray or whitish mica-like scales. When the scales are removed, a reddish base is exposed, on which there may be one or more punctate hemorrhages. The sites of predilection are the scalp and the extensor surfaces of the elbows and knees, although the eruption may occur in patches over the trunk and extremities. The nails may show pitting. Constitutional symptoms are lacking, but there may be a variable degree of itching.

Psoriasis pursues, as a rule, a chronic course, although at times the eruption may disappear spontaneously. Recurrence, however, may be expected throughout life. The cause is not known; psoriasis is not contagious.

*Treatment* is at times successful in clear-

ing an individual attack, but permanent cure is not obtained. If the patient can be hospitalized, the Goeckerman method of treatment is best.

On the first day all the patches of psoriasis are covered thickly with an ointment consisting of 2 to 4 per cent crude coal tar, 2 per cent zinc oxide and 50 per cent corn starch in petrolatum, which is left on overnight. The following morning it is removed with light mineral oil, a thin layer of oil being left on the skin. Ultraviolet light is then applied for one minute at 30 inches after dividing the skin surface of the body into six areas, each of which is treated as a unit. The time of exposure is increased and the distance of the lamp from the skin is decreased daily to maintain the skin in a state of mild erythema. After each light treatment the patient spends one-half to two hours in an oatmeal bath, which loosens the scales. After the bath another thick coating of ointment is applied to the skin, particularly over the patches; another coat is applied before retiring. This program is continued daily until no psoriatic scales remain and there is little or no induration in the patches. Autohemotherapy, consisting in withdrawing 10 ml. of blood from a vein and immediately injecting it into the gluteal muscles, is also given five times at intervals of two days, but one may doubt its value.

The most important point in the ambulatory treatment of psoriasis is the recognition that the eruption has a cyclic course, a stage of activity or evolution followed by quiescence. In general the disease is more active during the winter months.

Best results from local therapy are achieved



FIG. 404. Psoriasis.

during the quiescent phase. The scales must first be removed by a thorough scrubbing with soap and water or by application of a soft ointment containing 2 per cent each of ammoniated mercury and salicylic acid. Chrysarobin is then applied in a strength varying from 1 to 10 per cent, or a chrysarobin derivative such as anthrarobin, which may be purchased as Anthralin ointment. It should not be used for children in concentrations greater than 0.1 to 0.25 per cent. Ointments must be thoroughly rubbed into the patches. If a dermatitis results from the application, a bland ointment may be substituted temporarily. Roentgen therapy is used for obstinate patches, but probably has no place in the therapy of children. Ultraviolet light therapy is of value only after a crude coal tar ointment has been applied the previous evening and partially removed with warm oil before the exposure. Natural sunlight is beneficial, but overexposure must be avoided. Recently beneficial results have been observed with the use of Kenacort or Aristocort.

### PITYRIASIS ROSEA

Pityriasis rosea is a self-limited inflammatory disease of the skin characterized by pink or

reddish erythematous patches appearing chiefly on the trunk, upper arms, and thighs, and at times accompanied by a mild constitutional disturbance. A primary or herald patch may precede the eruption by a few days to a week. The eruption appears fairly rapidly as minute lesions which enlarge peripherally to a centimeter or so in diameter. Often the patches are oval, their long axes

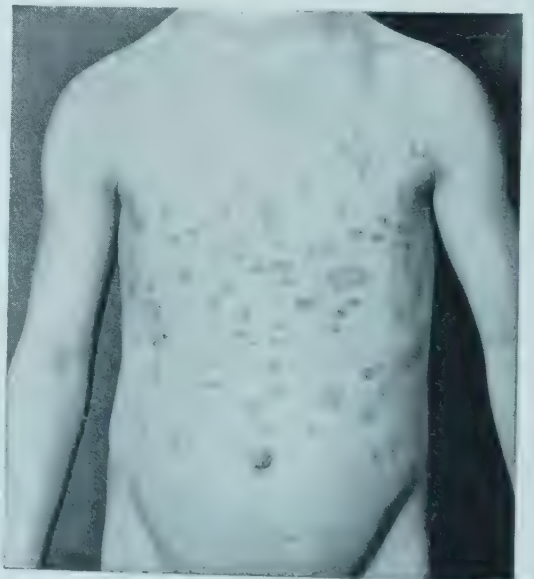


FIG. 405. Pityriasis rosea (showing herald patch).



following the lines of cleavage of the skin. Slight, branny scaling is usually present. Itching is absent or moderate, although, particularly at night, it may be severe. The cause of pityriasis rosea is unknown.

The disease is noncontagious. For the relief of itching a lotion consisting of liquor carbonis detergens, 15 cc., and calamine lotion (see p. 1301) sufficient to make 180 cc. (6 ounces) is useful. The patches of pityriasis rosea rarely appear in areas of suntanned skin, and ultraviolet light therapy at times seems to shorten the course of the disease. Untreated, the average case clears up spontaneously in about six weeks. With treatment, however, the eruption may disappear within two or three weeks.

## KERATOSIS PILARIS

The extensor surfaces of the arms and thighs are the usual sites of this disorder, which is characterized by closely aggregated, pinhead-sized, conical elevations corresponding to the orifices of the hair follicles. The skin is dry and rough and has the feeling of a fine nutmeg grater when the finger is passed over it. Some cases appear to be due to a vitamin A deficiency, and treatment should include vitamin A in doses of 25,000 to 50,000 units daily. A simple ointment consisting of 10 parts of cocoa butter and 90 parts of cold cream massaged thoroughly into the skin will soften the dry patches.

# INFECTIONS OF THE SKIN

## BACTERIAL INFECTIONS

### IMPETIGO CONTAGIOSA

For Impetigo Neonatorum, see page 339.

Impetigo contagiosa is a localized, superficial infection of the skin, caused most often by the *Staphylococcus*, less often by the *Streptococcus*, and characterized by vesicles which quickly become purulent, rupture and form crusts. Usually by the time the physician sees the child the crusts, which have the appearance of being lightly "stuck on" the skin, predominate; but close examination may reveal unruptured lesions, particularly if no treatment has been applied (Fig. 406). The disease spreads rapidly among contacts. The sites of predilection are the face, ears and nares, but any part of the skin, including the scalp, may be involved. Mild itching is the only symptom. At times several lesions may become confluent with central healing, or a large bulla may rupture and heal centrally, but show continued activity at the border. This type of lesion is known as *impetigo circinata*. When the lesions spread peripherally with irregular contours, they are termed *impetigo gyrata*. So-called *Bockhart's impetigo* is usually limited to the scalp, where the lesions are discrete follicular pustules, but it may also occur on the upper and lower extremities. When lesions of impetigo border the scalp, a search should be made for pediculi.

The differential diagnosis of impetigo is

rarely difficult. The circinate and gyrate types may be mistaken for *tinea circinata*, but the lesions of the latter are more uniformly circular, consisting of scaling patches with tiny peripheral vesicles, and they do not have the exudative, crusted appearance of impetigo. In

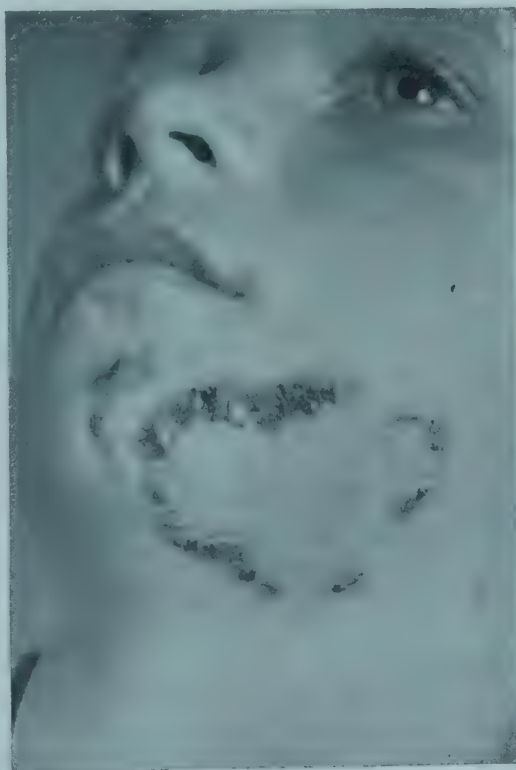


FIG. 406. Impetigo contagiosa gyrata.

*pustular eczema* the patches are deeper, larger and more diffuse and are accompanied by itching. The lesions of *ecthyma* are considerably deeper and are covered with a thick, hard crust.

The *treatment* of *impetigo contagiosa* is not difficult, but must be carried out carefully and conscientiously to achieve quick results. When there are only a few lesions, local treatment is sufficient, but when there is extensive involvement, as, for example, of most of the face or scalp, or when lesions are widely distributed over the body or when local lesions do not respond to surface therapy, systemic antibiotic therapy is indicated. In such instances penicillin administered orally or intramuscularly, or one of the tetracyclines or erythromycin by the oral route is apt to be effective.

Local treatment consists in removing the crusts in such a manner that bleeding is avoided, the opening of unruptured pustules with a sterile needle, and the application of bacteriocidal ointment. The use of hot compresses or starch poultices will frequently facilitate the removal of crusts. The ointment should be applied immediately and repeated sufficiently often to keep the lesions completely covered. For local therapy it is preferable to select antibiotics, such as bacitracin or neomycin, which are infrequently used systematically.

## ECTHYMA

Differing from *impetigo* only in that the lesions are more deep-seated and therefore likely to leave pigmentation and slight scarring, *ecthyma* is characterized by discrete, flat, deep pustules which dry with heavy crust formation. It is believed that either streptococci or staphylococci may produce *ecthyma* when introduced into such lesions as scabies, pediculosis, insect bites or deep scratches, particularly when the hygiene is poor.

*Treatment* consists in both general and local measures. The general hygiene should be corrected, and an adequate diet, including essential vitamins, should be provided. Otherwise the treatment is that described for *impetigo*.

## FURUNCULOSIS

A furuncle begins as a painful, deep-seated infection of a sebaceous gland or hair follicle

and gradually approaches the surface, appearing as a rounded or acuminate, reddish prominence. In a few days softening takes place, with formation of a central slough or core. Slight, usually temporary, scarring follows. The invading bacteria are almost invariably staphylococci. When the lesions are multiple and occur in crops, they are termed "furunculosis."

*Treatment* of a single furuncle should be conservative, consisting of dressings of 10 to 25 per cent Ichthammol ointment or any other mildly antiseptic ointment until softening is complete, when it will usually rupture spontaneously; if necessary, the furuncle may be incised. When a series of furuncles appears, the urine should be examined to determine whether diabetes is present, though there is no close relationship.

Emphasis should be placed on a diet containing generous amounts of fresh fruits and vegetables, eggs, milk and meat. In severe cases staphylococcal toxoid or an autogenous vaccine may be used. Frequent application of 70 per cent alcohol to the skin surrounding the lesions may help in preventing spread of bacteria to neighboring follicles. Preparations containing hexachlorophene are also useful in this respect and for cleansing the skin. Lesions of the face, particularly of the nose and upper lip, should never be incised or traumatized. Hot, wet compresses of a saturated magnesium sulfate solution applied for fifteen to sixty minutes three or four times in twenty-four hours or continuously during the daytime will ultimately cause the lesions to open and drain. If the compresses are applied intermittently, the lesion may be dressed during the interim periods with a 10 or 20 per cent Ichthammol ointment. Systemic administration of an appropriate antibiotic is indicated for severe and generalized furunculosis.

## FURUNCULOSIS IN INFANTS

Debilitated infants as a rule have a low resistance to infection and frequently acquire infections of the skin. Extensive furunculosis involving the scalp, back and posterior portions of the extremities occurs occasionally in such infants. There are usually systemic disturbances, such as fever, anorexia and toxemia. In the more severe instances response to treatment is poor and relapses are frequent. *Treatment* consists in attention to fluid, electrolyte and other nutritional re-



quirements and in systemic antibiotic therapy. The case fatality rate has been ma-

terially reduced in recent years by such therapy.

## *Tuberculosis of the Skin*

For Erythema Nodosum, see page 1300.

Cutaneous tuberculosis is rare in the United States. The tubercle bacillus may invade the skin directly through an abrasion (primary infection), by continuity from an underlying tuberculous lesion such as that of a lymph node, or by hematogenous distribution. Cutaneous lesions such as tuberculides and erythema nodosum may also be produced by circulating toxins of the tubercle bacillus.

### **LUPUS VULGARIS**

Lupus vulgaris frequently begins in childhood as numerous pinpoint- to pinhead-sized, grouped or disseminated, reddish, yellowish or brownish, flat papules. When compressed by a glass slide, the papules are reddish-brown. Gradually they enlarge to form tubercles or nodules which in turn coalesce into variously shaped and sized pustules. Although extension continues slowly, the older lesions may disappear by absorption, leaving a scaly, atrophic scar, or they may ulcerate, form crusts and eventually heal with a residual scar. The disease is chronic and may persist into adult life with considerable disfigurement. A type occurring in children, known as *multiple disseminated lupus vulgaris*, consists of multiple, small, discrete nodules or patches which appear suddenly and are scattered over the cutaneous surface. Lupus vulgaris may be associated with other types of skin tuberculosis such as tuberculosis verrucosa cutis, scrofuloderma or tuberculous ulcers, and with visceral, bone, joint and pulmonary tuberculosis.

*Treatment* of lupus vulgaris should be both constitutional and local. A high vitamin diet, fresh air and controlled exercise are recommended. Specific antituberculous therapy with isoniazid in conjunction with para-aminosalicylic acid is the treatment of choice at this time (see p. 465 for dosage). Local treatment has for its object the extirpation of the lupus tissue with as little resultant scarring as possible. Individual nodules or small patches may be thoroughly destroyed by electrofulguration under local or general anesthesia. Larger patches are best treated with

the Finsen lamp, but this is not obtainable in the United States.

### **TUBERCULOSIS VERRUCOSA CUTIS**

Inoculation of the tubercle bacillus into the skin from without may produce one or more warty vegetations which occur most commonly on the hands. The lesion begins as an inflammatory vesicopustule or papule and slowly increases in size, and the surface becomes encrusted. When the inflammation is marked, pus may be expressed from the crypts. When healing occurs, a smooth, scaly scar remains.

The lesions are easily destroyed by electrofulguration under local anesthesia. Carbon dioxide snow, pyrogallol acid ointment and roentgen therapy have also been used.

### **SCROFULODERMA**

This lesion begins in one or more lymph nodes or in bone and extends to the surface to involve the skin in a true tuberculous process. When lymph nodes are involved, they are initially swollen and painful, but later undergo caseation and suppuration and form sinuses which discharge a caseous, sanious pus. The resultant skin involvement appears as an oval or linear ulceration with violaceous, undermined edges and an uneven base with pale, flabby granulations. The surface may be crusted. (See p. 467 for treatment.)

### **PRIMARY TUBERCULOUS LESIONS**

#### (TUBERCULOUS CHANCER)

Tubercle bacilli may invade the skin or mucous membrane through abrasions; the intact skin is not vulnerable. The resemblance of the primary lesion to a syphilitic chancre is at times striking. The common sites are the lip (Fig. 407), nose, chin, extremities and genital region; there is an accompanying involvement of the regional lymph nodes to complete the primary complex. The initial lesion may occur as a dark red papule, a small crusted ulcer with an elevated border or as a small plaque. Tubercle bacilli may be found in the skin lesion and in the lymph nodes; the histologic findings are those of



FIG. 407. Primary tuberculous lesion.

tuberculosis. Excision of the primary lesion and of the lymph nodes is indicated if they are in appropriate sites. Antibacterial therapy should be used if excision is performed and in other instances if the lesion appears to be progressive (see p. 467).

### LICHEN SCROFULOSORUM

These lesions are pinhead-sized, firm, yellowish-brown or reddish nodules. The nodules

coalesce into coin-sized patches and are situated chiefly on the trunk. They may be accompanied by slight itching. The course is chronic, although the prognosis is favorable. Treatment consists in specific therapy for any systemic tuberculous infection and in measures to improve the general health, which include a diet with a high vitamin content, especially of vitamin D.

### TUBERCULIDES

Tuberculides are thought to be caused by the toxins of the tubercle bacillus, the most common type in children being the papulonecrotic tuberculide. The lesions, which appear in crops, are pea-sized or smaller, firm, bluish-red papules, crusted at the summit. When the crust is removed, there is a crater-like depression. Search should be made for the primary tuberculous focus, which is usually in the lungs.

*Treatment* consists in improving the general health by means of fresh air, sunshine, vitamin D and an adequate diet. Antimicrobial therapy is indicated for the systemic tuberculous infection (see p. 464).

## Lupus Erythematosus

The two principal varieties of lupus erythematosus are *chronic discoid lupus erythematosus* and *systemic lupus erythematosus* (see p. 925).

In the chronic discoid variety the early lesions are rounded or oval pinhead- to pea-sized erythematous, slightly raised areas which increase in size either by peripheral extension or by coalescence of neighboring lesions. Fully developed, the disease appears as one or several sharply margined, reddish or violaceous patches, varying from a half-inch to several inches in diameter. The surface is covered with thin, white or gray scales, which are usually adherent and extend deeply into the sebaceous glands. The border of the patch is slightly elevated, and the center tends to atrophy. There is some infiltration and thickening of the patch. Occasionally, especially in children, the disease spreads symmetrically over the nose and cheeks, creating the outline of a butterfly with wings spread. Subjective symptoms of moderate itching and burning may be present. The sites of predilection are the face, particularly the

nose, cheeks and ears, and less often the scalp, lips and buccal mucous membranes. When inflammation is marked and there is no atrophy, the term "subacute" may be applied.

In children the *treatment* of lupus erythematosus of the discoid type is important, since healing may be obtained, although the scars usually persist. Among the drugs used are chloroquine diphosphate, quinidine hydrochloride (Atabrine), quinine, potassium, para-aminobenzoate (PABA), bismuth and gold. In general it is preferable to try the least toxic drugs first, such as chloroquine, PABA or Atabrine. The yellow discoloration of the skin resulting from treatment with Atabrine is a deterrent against its use. Dosages of these drugs are as follows: chloroquine, 0.25 to 0.5 gm. twice a day; Atabrine, 50 to 100 mg. three times a day; and PABA, 0.1 to 0.2 gm. per pound of body weight per day in six divided doses during the waking hours.

Gold therapy is now rarely used and is definitely contraindicated in the more inflammatory (subacute) types.



In all types of lupus erythematosus, exposure to strong sunlight must be strictly avoided, and a protective (sun screen) lotion

or cream should be applied even for minimal exposure.

## FUNGUS INFECTIONS

Fungi are responsible for a number of different skin diseases which include the various types of ringworm, favus, pityriasis versicolor and moniliasis.

### RINGWORM

(TINEA)

A number of the subvarieties of both the small-spored and the large-spored groups of fungi are of etiologic significance in ringworm. The most important of the small-spored group is *Microsporum audouini*, which causes about 90 per cent of the cases of ringworm of the scalp in children and apparently affects only human beings. *Microsporum felinum* and *Microsporum lanosum* produce ringworm of the human scalp and skin. Microsporiasis occurs in cats, dogs, horses and other mammals and may be contracted by children from any of these animals. The large-spore fungus or trichophyton is responsible for most of the varieties of ringworm of the hairless skin.

### RINGWORM OF THE SMOOTH SKIN

Customarily, ringworm of the skin other than the scalp is known as (1) tinea circinata, (2) tinea cruris or (3) ringworm of the hands and feet. In tinea circinata the lesions are situated most often upon the face, neck, hands and forearms. In children with the microsporon type of scalp involvement, patches may extend just beyond the hair margin on the neck or forehead, but should not be confused with tinea circinata. Tinea circinata begins as one or several rounded or slightly irregular pea-sized, reddish-pink, slightly raised, scaly patches. Peripheral spreading and central clearing progress simultaneously; a well developed patch may be 1 or more cm. in diameter, and the outline is that of a ring, from which it receives its common name, ringworm (Fig. 408). Itching may be present, but is usually mild.

*Tinea cruris* is a variety of tinea circinata, but the clinical appearance may be modified by perspiration and by bacterial contamination. The lesions appear upon the upper and

inner surfaces of the thighs, and may also involve the scrotum, the anal fold and the buttocks. Initially, the appearance of the lesions is identical with that of circinata, spreading peripherally with a tendency to central clearing. Local warmth usually causes an exaggeration of the inflammation and itching, and secondary bacterial infection may cause the patches to be studded with pinhead-sized pustules. In the treatment of the inflammatory stage the following formula, applied freely three times in twenty-four hours, is recommended:

	Cc. or Gm.
Bichloride of mercury.....	0.060
Witch hazel water.....	30
Calamine lotion (U.S.P.) (with or without phenol), to make.....	180

After the inflammation has subsided Whitfield's ointment (U.S.P.XV) or the following formula may be applied twice daily.

Salicylic acid.....	2.0
Benzoic acid.....	4.0
Castor oil.....	30 cc.
Isopropyl alcohol (50%) to make.....	120 cc.

### RINGWORM OF THE HANDS AND FEET

Ringworm of the foot, popularly termed "athlete's foot," is the most common of all types of fungus diseases. A similar eruption may occur on the hands. There are also eruptions (dermatophytids) of the hands, legs and trunk associated with ringworm infection of the feet, which are probably caused by absorption of toxins from the local lesions.

Three types of eruptions appear on the feet: (1) intertriginous, involving the inter-spaces of the toes and having a dry or sodden, scaly and fissured appearance; (2) acute vesiculobullous, which more commonly occurs on the soles and sides of the feet; and (3) chronic thickened and hypertrophic, in which the skin is thickened and covered with scale formation. Secondary bacterial invasion of fissures may result in lymphangitis, cellulitis, phlebitis or erysipelas.

Treatment of ringworm of the hands and feet depends upon the type of eruption. In the intertriginous type one of the following



FIG. 408. Tinea capitis and tinea circinata.

methods may be used: (1) soaking the feet in a 1:4000 hot solution of potassium permanganate, (2) painting daily with Castellani's paint, (3) the daily application of Whitfield's ointment (U.S.P.XV), or (4) an ointment containing zinc undecylenate and undecylenic acid in a vanishing cream base applied morning and night. Strong applications should never be used initially. After the scales have been removed and the fissures have healed a dusting powder may be used for several weeks to guard against recurrence and to keep the interspaces dry. Several proprietary powders have found favor, such as Desenex, Timofax, Korium and Epto, or the following may be used:

	Gm.
Salicylic acid.....	1.0
Benzoic acid.....	2.0
Starch.....	10.0
Talc.....	16.0

In the *acute vesicular* and *bullous types* the patient or parent should be taught to open the lesions aseptically, after which the feet should be soaked in a 1:4000 hot solution of potassium permanganate for twenty minutes, twice daily. A 1:15 dilution of Burow's solution (made by adding 4 tablespoonfuls of Burow's solution to 1 quart of hot water) may be used instead of the permanganate. Only after the acute phase has subsided are stronger parasitocidal remedies to be prescribed, but, to prevent recurrence, it is advisable to apply Whitfield's ointment

(U.S.P.XV) until the dead skin is entirely removed. Socks must be boiled, and shoes and slippers may be sterilized by placing a piece of blotting paper soaked in 4 per cent formalin on the inner soles for twenty-four hours, followed by exposing them to the open air and sun for another twenty-four hours.

In the dry, *squamous, noninflammatory* or *hypertrophic type*, Whitfield's ointment (U.S.P.XV) may be used from the beginning. If the thickening of the skin is marked and the scale heavy, ointments containing 10 to 25 per cent salicylic acid may be required for exfoliation. The hypertrophic form is rare in children. Roentgen therapy should never be used during the acute stage, and, although helpful in subacute or chronic stages, its use should probably be restricted to the most severe cases in older children and adults. Dermatophytids will usually disappear after effective treatment of the primary focus. Relief of itching may be obtained by the frequent application of Schamberg's calamine lotion (see p. 1301).

#### RINGWORM OF THE SCALP

(TINEA TONSURANS, TINEA CAPITIS)

This type of ringworm, which is practically limited to children, begins as small rounded, reddened, scaly patches. Typical lesions consist of practically bald, discrete, rounded, coin-sized, slightly reddened patches covered with grayish scales and broken hairs (Fig. 408). The hairs in a patch are lusterless and



consist of broken stumps. They lie loosely in the follicles and are easily extracted. Rarely, the scalp may be diffusely involved without production of circumscribed patches.

In *tinea kerion* (pustular tinea) there are raised, boggy or edematous patches, honey-combed with distended openings of hair follicles, through which a yellowish pus exudes. The suppuration hastens the cure, but may lead to scarring and to permanent baldness.

Mild itching is the only common symptom of ringworm of the scalp, but when kerion is present, there may be tenderness and pain. Most cases are caused by *Microsporum audouini* or *Microsporum lanosum*.

Clinical recognition is not difficult. A positive diagnosis is made by examination under a beam of ultraviolet light passed through a Wood's filter (glass containing nickel oxide) or by microscopic examination of extracted hairs. For the latter the hair is prepared by immersion in a 20 per cent solution of potassium hydroxide and examined without staining. Abundant spores which have a fish roe appearance are seen on the hair. Diagnosis of the exact type of fungus is made by culture on maltose agar.

Infections caused by *Microsporum lanosum* are cured by local remedies, such as petrolatum, containing 1 per cent each of iodine crystals, thymol and oil of cinnamon, a 10 per cent ammoniated mercury ointment or a salicylanilide ointment.

When infection is due to *Microsporum audouini*, local applications alone are rarely adequate. Though the infection tends to disappear spontaneously at puberty, epilation is usually necessary to obtain a cure in the more resistant cases during childhood. If this is done manually, the scalp is washed thoroughly with soap and water, as many hairs as possible are removed with depilating forceps, and a parasitocidal ointment is rubbed in for ten minutes. An ointment containing 5 per cent of salicylanilide and 95 per cent Carbowax is efficacious in some cases, but usually fails to cure completely. Better results can be expected if daily extraction of infected hairs is performed under a Wood light at home in conjunction with continued local application of the ointment. A skull cap made of a material that may be boiled is worn continuously to prevent spread of the infection to others. Roentgen epilation is effective, but the possibilities of affecting the pituitary gland or osseous growth centers and of causing permanent baldness are serious

deterrents. During the bald period parasitocidal ointments must be continuously applied. Epilation by means of thallium acetate is to be condemned.

## FAVUS

(TINEA FAVOSA)

Caused by *Trichophyton schoenleini*, tinea favosa is rare in the United States and is seen chiefly in immigrants. In children the lesions are chiefly on the scalp and consist of one or several small, yellowish patches which enlarge and may form sulfur-yellow cups, or scutulae, from each of which a hair projects from the depressed center. Scarring is associated with permanent alopecia. The treatment is the same as for the more resistant types of ringworm of the scalp.

## PITYRIASIS VERSICOLOR

(TINEA VERSICOLOR)

Pityriasis versicolor is an uncommon disease in children, but when untreated may last for months or years. Caused by *Malassezia furfur*, it is characterized by pinhead- to pea-sized, yellowish-brown macules which slowly increase in size and coalesce with the formation of large brownish patches whose surfaces are covered with a fine, furfuraceous, mealy scaling. Mild itching is usually present.

Treatment consists in washing thoroughly with soap and water, followed by the application of an ointment composed of 1.0 to 1.5 gm. of precipitated sulfur and 0.6 gm. of salicylic acid in 30 gm. of an emulsion base. The applications should be made daily and continued for two weeks after the eruption has disappeared from the surface of the skin. Solutions of sodium hyposulfite (4 cc. in 30 cc.) or of bichloride of mercury (0.6 cc. in 30 cc.) are easily applied, and either one is effective.

## MONILIASIS

(CANDIDIASIS)

Many eruptions of the skin formerly diagnosed as eczema are monilia infections. Monilia are frequently found in the vaginal secretions of pregnant women, and in this way infants may be infected. Oral lesions are not infrequent, but lesions of the skin are rare. Finnerud cultured scrapings from the angles of the mouth of 100 children with perlèche and found organisms believed to be cryptococci or Monilia in 77 per cent. Whether these

organisms were primary or secondary invaders was not established.

The skin in moniliasis may show a disseminated, papulovesicular, scaling eruption or localized intertriginous lesions.

A weak iodine solution (1 per cent tincture) or an ointment containing 1 per cent of salicylic acid and 2 per cent precipitated

sulfur in an emulsion base may be used on the skin. Gentian violet in a 1 per cent aqueous solution is effective but unsightly. It may be removed from clothing with spirits of ammonia. Among the newer agents, Nystatin may be used systemically and locally, and amphotericin B locally for cutaneous moniliasis.

## PARASITIC INFESTATIONS

For Bites and Stings of Other Insects or Parasites, see page 598.

### SCABIES

See also page 599.

Scabies results from infestation of the skin by *Acarus* or *Sarcoptes scabiei*, commonly called the itch mite, which is barely visible to the naked eye. The female parasite burrows in the epidermis, deposits her eggs and, in doing so, produces a burrow or cuniculus which appears as a tiny, straight or tor-

tuous, grayish or blackish, linear elevation. At the point of entrance a small vesicle or pustule is often seen. The most common sites for burrows are the webs of the fingers and flexor surfaces of the wrists. The lesions can often be identified only with a magnifying glass. In well developed scabies there may be seen, in addition to the burrows, a multi-form eruption consisting of papules, vesicles, crusts, excoriations and thickening. The sites of predilection for the more advanced cases are the interdigital spaces, the flexor surfaces of the wrist and arm, the axillary folds, the nipples of the female breast, the umbilicus, the buttocks, the penis and the toes (particularly in infants). In young infants the eruption may be so severe as to resemble eczema. Facial lesions are rarely observed except in nursing infants whose mothers have scabietic lesions on the breasts.

Itching is intense, particularly at night, and secondary inflammation results from the unavoidable scratching. Secondary infection is common and may be manifested as impetigo, ecthyma or furunculosis. Pyodermia of the hands should always cause the examiner to search for evidence of scabies (Fig.

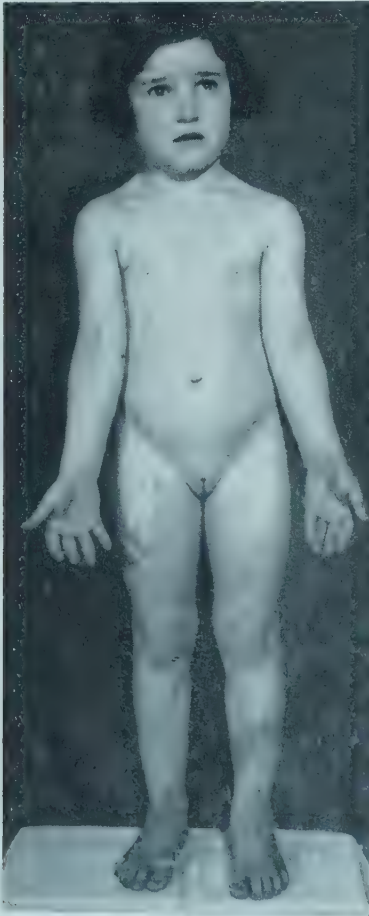


FIG. 409. Scabies. (Courtesy of Dr. Reuben Friedman.)



FIG. 410. Scabies. Note linear pattern of individual lesions.





FIG. 411. Scabies involving genitals. This is a common site of infection, and one that is often missed. (Courtesy of Dr. Alex Steigman.)

FIG. 412. Scabies with secondary infection.

FIG. 411. Scabies involving genitals. This is a common site of infection, and one that is often missed. (Courtesy of Dr. Alex Steigman.)

409). Untreated scabies may last indefinitely with no tendency to spontaneous healing. Though the clinical *diagnosis* is usually not difficult and may often be substantiated by the history of other cases in the family, it can be made at times only by finding the parasite. By using a sharp razor blade it is not difficult to remove an entire burrow, which is then placed in saline solution or tap water on a glass slide and examined microscopically with a low power objective. Diagnosis may be made upon recognition of a whole or any part of an *Acarus*, of an ovum or fecal matter. Diagnosis may be simplified by examination of the infant's mother or attendant.

The objects of *treatment* are destruction of the parasite and alleviation of the accompanying dermatitis. The *Acarus* is easily destroyed by such remedies as sulfur, beta-naphthol, balsam of Peru, styrax, oil of cade, pyrethrum, rotenone and benzyl benzoate.

Benzyl benzoate in concentrations of 10 to 30 per cent is available in proprietary formulas as an emulsion and an ointment. It has the advantages of being rapidly effective and of clean application. The usual method of application is to cover all affected areas with the preparation immediately after a bath while the skin is still moist. As soon as this application has dried, a second one is made. Twenty-four hours later a second bath is taken with soap and water. Dermatitis may occasionally occur. If itching continues and there is no evidence of dermatitis, another

application of benzyl benzoate should be made five to seven days later.

Carpenter has used an emulsion consisting of:

	Gm. or Cc.	Concentrated Preparation Gm. or Cc.
Benzyl benzoate.....	10.0	68.0
DDT.....	1.0	6.0
Benzocaine.....	2.0	12.0
"Tween 80".....	2.0	14.0
Water, to make.....	100.0	—

The concentrated preparation is diluted with 5 parts of water before use. The emulsion is applied by spraying. A single spraying is usually sufficient, but three or four may be necessary. This emulsion is both scabicial and ovacidal. Among the newer effective preparations are creams of benzene hexachloride (Kwell) and of crotomyl-N-ethyl-o-toluide (Eurax). The body is covered with either one twice daily for three days and then again for three days one week later. Clean clothes and bed clothing should be used after each three-day course and the soiled clothing thoroughly cleansed.

All members of the family should be treated simultaneously.

If itching persists after the disease has been eradicated, Benadryl or Pyribenzamine may afford considerable relief.

PEDICULOSIS

There are three varieties of *Pediculus*: *P. capitis*, head louse; *P. corporis*, body louse; and *P. pubis*, crab louse.

PEDICULOSIS CAPITIS

This disease, caused by *P. capitis*, is characterized by severe itching of the scalp. The

resulting scratching leads to the formation of excoriations with serous, purulent or sanguineous exudation, which dries and forms crusts and mats the hair together. A foul odor is usually present. From the secondary infection in the scalp the postcervical nodes may become involved and in some cases suppurate. Scattered papules, impetiginous crusted lesions, pustules and excoriations are frequent about the face and neck. Pediculi are present on the scalp in varying numbers, and the ova or nits are in abundance. The ova are grayish, translucent, oval bodies attached to the hair by a membranous sheath. They hatch out in three or four days.

To be effective, *treatment* must destroy the pediculi, devitalize the ova and allay the inflammation. Crude petroleum oil, either pure or mixed with an equal quantity of olive oil, is effective; it should be thoroughly applied to the scalp for one or two nights followed each morning by a shampoo with plain soap and water or tincture of green soap and water. Frazer recommends an emulsion containing DDT, 2 per cent; naphtha, 15 per cent; emulsifying agent, 5 per cent; and water, 78 per cent, worked thoroughly into the scalp with a paint brush. This is left on overnight and combed out the following morning. A simple measure for removal of the ova is to comb the scalp daily with a fine comb dipped in hot vinegar (dilute acetic acid). Recovery of the more heavily infested cases may be hastened if the hair is cut short. Creams of benzene hexachloride (Kwell) and of crotonyl-N-ethyl-o-toluide (Eurax) are effective against both the parasite and the ova. When

there is pustulation around the margins of the scalp, bacitracin ointment may be applied.

### PEDICULOSIS CORPORIS

Pediculosis corporis, rare in children, is produced by a parasite larger than the head louse. It resides in seams of underclothing where ova are deposited. The louse is present on the skin only when foraging. Ova hatch in about six days. The itching in pediculosis corporis is intense; as a result, examination of the person shows chiefly excoriations or long scratch marks. Close examination will reveal hemorrhagic points where the pediculi have extracted blood. Transitory wheals, small papules and localized infections may also be present.

*Treatment* consists primarily in disinfection of the clothes and bed linens. Cleaning the clothes and pressing them with a hot iron will destroy ova and parasites. Bed linen should be boiled. For the relief of itching a lotion of 2 to 5 per cent carbolic acid in olive oil may be prescribed.

### PEDICULOSIS PUBIS

This disease is almost exclusively observed in adults. The author has seen only one case in a child, and, as commonly happens, the parasites and ova were found on all hairy areas except the scalp. In children the eyebrows are particularly likely to be involved. One application of Cuprex usually suffices for a cure. Five per cent DDT powder in talc dusted over the infested area is also an excellent and clean remedy.

## VIRAL INFECTIONS

### VERRUCAE

#### (WARTS)

Commonly known as a wart, a verruca is a pinhead- to bean-sized circumscribed elevation of the skin due to epidermal and papillary hypertrophy. Various types are distinguished: (1) *verruca vulgaris*, the common wart, which occurs as single or multiple lesions, most often upon the hands of children (Fig. 413); (2) *verruca plana juvenilis*, smooth, flat, slightly elevated, light brown lesions occurring chiefly on the face, neck and dorsum of the hands; (3) *verruca filiformis*, slender threadlike outgrowths occurring chiefly upon the face, eyelids and neck; and (4) *verrucae plantaris*, or plantar warts,

which somewhat resemble a callus and occur upon the sole of the foot. Plantar warts may occur singly or in groups and may be extremely painful. They have a characteristic appearance when the horny plate which covers them is removed. Warts are auto-inoculable and slightly contagious.

The *treatment* of warts is often unsatisfactory. Internal treatment is of doubtful value, but is occasionally attempted when a number of warts are present. In evaluating therapy it must be remembered that warts frequently disappear spontaneously, undoubtedly accounting for the multiplicity of medicinal treatments as well as those based upon superstitions and psychotherapy.

The best method of treatment for all types



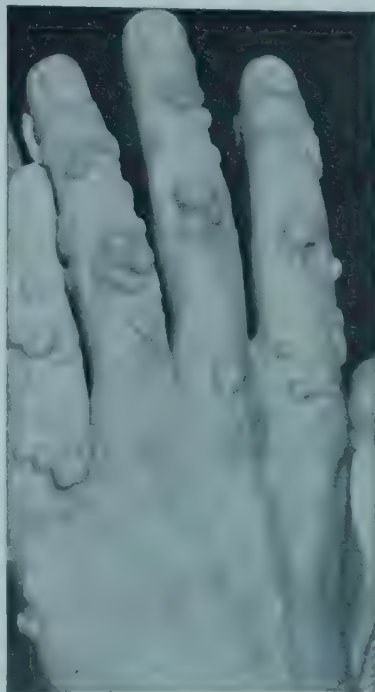


FIG. 413. Verruca vulgaris.

of warts except possibly those on the sole, especially if there are only a few, is removal under local anesthetic. One per cent Novocain is injected beneath the growth, which is then thoroughly curetted and the base cauterized with 50 per cent trichloroacetic acid, actual cautery or electrofulguration. Care must be taken to trim off any overhanging edges that might promote secondary infection. Monochloroacetic acid and dichloroacetic acid are occasionally used to destroy warts, but must be applied with great care. Cauterization of a large number of flat warts may lead to disfiguring scars. Exfoliation by erythema doses of ultraviolet light should be tried before resorting to more radical therapy. Podophyllin (10 per cent) in tincture of benzoin painted carefully on the warts at weekly intervals occasionally is also effective, or the following prescription, which is applied to the wart once daily on a cotton applicator, may be tried:

Salicylic acid (5 per cent) . . . . .	1.5 gm.
Podophyllin (5 per cent) . . . . .	1.5 gm.
Tincture benzoin, q.s. ad . . . . .	30.0 cc.

Plantar warts are the most resistant to therapy. Successful results are usually obtained by removing as much of the growth as possible by means of 40 per cent salicylic acid plasters and then using roentgen or radium therapy on the remainder of the growth. Rarely, however, is radioactive therapy justi-

fied in children. Surgical removal is possible by using Eufocaine anesthesia, which usually prevents pain. The wart is scooped out with a curet, and a pressure bandage is applied after packing the wound with Terramycin powder and Gelfoam. There may be recurrence after any type of therapy.

### MOLLUSCUM CONTAGIOSUM

This is a slightly contagious, auto-inoculable disease characterized by pinhead- to pea-sized, elevated, smooth, waxy, semiglobular, white or pinkish lesions. First appearing as pinhead-sized, discrete, slightly elevated papules, the lesions gradually enlarge and develop a central depression or umbilication (Fig. 414). Pressure on the growth causes expulsion through this central area of a white, cheesy material. The number of lesions slowly increases until a hundred or more may be present.

*Treatment* consists in destroying the growth by incision followed by expression of contents and then by cauterization of the cavity with a stick of silver nitrate, with trichloroacetic acid or an electrocautery point. Boring each lesion with a pointed applicator stick dipped in pure phenol is a simple and often efficacious mode of treatment. New lesions should be destroyed as soon as they appear. They will often disappear without operation with the daily application of 10 per cent lactic acid and 10 per cent salicylic acid in a vehicle of flexible collodion.

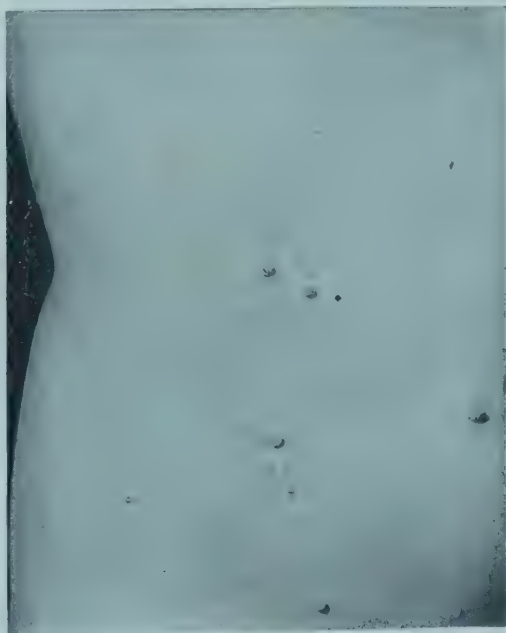


FIG. 414. Molluscum contagiosum.

## THE ERYTHEMAS

The term "erythema" is commonly used to signify a hyperemia of the skin which may be localized or widespread and may be caused by external or internal factors. Pressure with the finger on an erythematous area will blanch the area momentarily. A number of clinical types of erythema are relatively common. The external types are (1) *erythema caloricum*, which results from exposure to extremely high or low temperatures; (2) *erythema solare* (sunburn), caused by exposure to the actinic rays of the sun; and (3) *erythema traumaticum*, due to cutaneous injury. The internal or toxic erythema, sometimes ineptly termed "stomach rash," may be associated with diseases which do not naturally have an exanthem and with certain drugs.

Severe sunburn may be treated with hot saline solution compresses followed by application of a bland ointment. Children who are to be exposed to the sun for prolonged periods of time should be thoroughly covered with a tannic acid and salol, or a quinine lotion or cream, of which there are a number of satisfactory proprietary preparations.

### MILIARIA RUBRA

(PRICKLY HEAT)

This is a common disturbance of infants and occasionally of older children and is perhaps best considered a sweat retention syndrome. It is characterized by small pinpoint- to pinhead-sized erythematous papules and at times vesicles. They appear after excessive heat from climatic or other external conditions such as excessive clothing. There is evidence of slight inflammatory changes surrounding the ducts of the sweat glands. This condition is closely related to sudamina. Any area of the body may be affected, but the face, neck, shoulders and chest are especially susceptible. Prophylaxis consists in avoidance of overheating by removal of clothes during periods of extreme heat, frequent bathing and the judicious use of an electric fan or air-conditioning unit.

*Treatment* is not particularly satisfactory. A bath with starch added (1 pound of lump laundry starch in a half-tub of lukewarm water) or Aveno powder, a proprietary made from oatmeal, followed by dusting the skin thoroughly with borated talcum powder or

other so-called prickly heat powder gives considerable relief. Calamine lotion containing 1 or 2 per cent phenol and 0.25 to 0.5 per cent menthol is often effective in allaying the itching.

### INTERTRIGO AND DIAPER RASH

Commonly known as chafing, this condition is common in children and occurs where two moist skin surfaces are in apposition, such as the groin and inner thighs, buttocks, flexures of joints, and neck. Moist and fecal-soiled diapers allowed to remain on the infant for relatively long periods are one of the common causes. Untreated, a dermatitis or eczema may be superimposed on the erythema, producing local heat and soreness.

*Treatment* consists in keeping the affected areas clean and dry. During the day infants with diaper rashes should be placed on their abdomens and an incandescent light placed over the exposed buttocks. At night the buttocks should be covered with zinc oxide or some other bland ointment. Simple talc or frequent dabbing with calamine lotion (p. 1301) usually suffices for the milder cases and for intertrigo in regions other than the diaper area. Strongly alkaline soap should be avoided in the washing of diapers, which should be thoroughly rinsed and dried.

The so-called *ammoniacal diaper rash* is characterized by erythema on the convex surfaces of the buttocks, without involvement of the opposed surfaces, and by papulovesicular



FIG. 415. Papulovesicular lesions of ammoniacal dermatitis.



lesions which, when broken, become umbilicated or crater-like (Fig. 415). In circumcised male infants there is often an associated ulceration about the external urethral meatus. The causative factor is the production of ammonia in the urine by urea-splitting bacteria which originate in the intestine and infest the skin about the buttocks. The ammonia is formed after the urine has been voided, and the odor is greatest after the wet diaper has been allowed to remain on the infant for several hours. Ammoniacal dermatitis is treated in the same manner as other diaper rashes, but its prevention is of the greatest importance.

The incorporation of an antiseptic in the diapers has proved an effective method to inhibit the growth of ammonia-producing organisms. A number of antiseptics have been used. They are added to the final rinse water; the diapers should then be wrung out lightly and allowed to dry. The commonly used antiseptics for home laundry have been bichloride of mercury and boric acid. Both are dangerous as poisons, and it is doubtful whether such a weak antiseptic as boric acid is effective. There are a number of commercial preparations, most of which have as their active ingredient a quaternary ammonium compound known as Hyamine 10X. This compound may also be bought in solutions of several strengths. The recommended dilution for a diaper rinse is 1 ounce of a 10 per cent solution in 4 gallons of water for 10 pounds of fabric; one dozen diapers weighs approximately 2 pounds. This compound is also toxic and should be kept out of the reach of children. At present the majority of commercial diaper laundries use phenylmercuric acetate in a concentration of about 1:150,000 as the antiseptic in their final rinsing solution.

## ERYTHEMA MULTIFORME

The skin manifestations of erythema multiforme may at times be preceded or accompanied by fever, malaise, rheumatoid pains and other constitutional disturbances. The eruption, which usually appears abruptly, may consist of macules, maculopapules or vesicles and blebs, although one type of lesion tends to predominate in an individual case (Fig. 416). There may be mild itching and burning. Sites of predilection are the dorsal surfaces of the hands, the forearms, the tibial regions, the face, and the back of the neck, but at times the eruption may be widespread.

The mucous membranes, as, for example, of the mouth, eye or genital region, may be involved. When the patches are circular with peripheral spreading and central clearing, the affection is called *erythema circinata*. Concentric rings of vesicles, particularly on the palms, are termed *herpes iris*. A form of erythema multiforme bullosum characterized by widespread lesions which also involve the mucous membranes and are associated with a severe form of conjunctivitis and constitutional symptoms with high fever, has been termed the *Stevens-Johnson syndrome*. Loss of sight is an occasional sequel.

The lesions of erythema multiforme tend to occur in crops and may persist for one to four weeks. In some instances there is a distinct tendency to recurrence, with frequent attacks over a period of years, but in general it is a self-limited disease. The *diagnosis* is based upon the acute onset of the individual attack, the multiforme quality of the eruption, the absence of severe itching, and the tendency to recurrence.

*Treatment* is symptomatic and should be directed at maintenance of fluid and electrolyte balance and of the general nutrition. The disease is self-limited. Antibacterial therapy is indicated only when there is a reasonable possibility of an associated bacterial infection. Corticosteroids are not curative, but

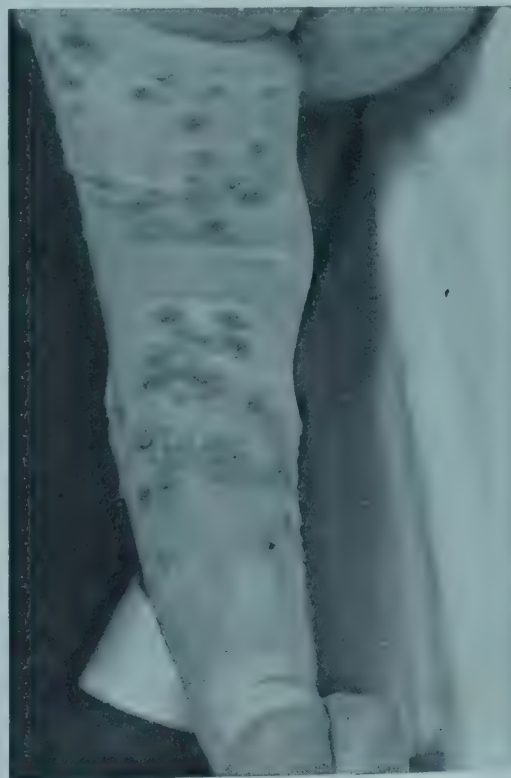


FIG. 416. Erythema multiforme bullosum.



FIG. 417. Erythema multiforme. Herpes iris type of eruption.

may suppress the manifestations and on such a basis are justified in acutely ill children.

### ERYTHEMA NODOSUM

This variety of erythema is rare in infants, but is relatively common in older children and adolescents. It may occur in the course of a number of different conditions, but is generally associated with primary tuberculosis, coccidioidomycosis and hemolytic streptococcal infections, including rheumatic fever. There are, of course, distinct geographic variations in the incidence of the basic diseases. The disease is usually ushered in with fever, localized pains, and malaise. Round or oval nodelike swellings, varying in size from a hazelnut to an egg, develop rapidly over the region of the tibia and less often on the forearms and thighs. The nodes are red, tense and shining, and exquisitely tender to the touch. At first hard, they gradually soften, but never ulcerate. They persist for a week to ten days, when the color and swelling gradually disappear.

The prognosis is favorable so far as the skin lesions are concerned, but the ultimate outcome depends on the underlying disease. Differentiation is chiefly from *erythema induratum*, in which the lesions are more commonly on the backs of the lower legs, are less acute in their evolution, and may ulcerate.

*Treatment* of an attack consists chiefly in rest in bed with the legs elevated. If the pain is severe, salicylates or other analgesics may be administered.

### URTICARIA PAPULOSA

(LICHEN URTICATUS)

For Urticaria, see page 1318.

This type of urticaria occurs exclusively in children and is distinguished by an eruption of papules which appear chiefly in the summer months. It has been suggested that insect bites act as a "trigger mechanism" to bring out the lesions of urticaria papulosa. These papules are about the size of a pinhead, or slightly larger, and are pale red; they are irregularly disseminated, most of them occurring on the trunk and extremities. They are preceded by a wheal which causes itching, particularly at night, often leading to the erroneous diagnosis of scabies. Unlike the lesions of scabies, they occur on the face and are rarely seen on the hands. The following lotion is recommended to relieve itching:

	cc.
Coal tar solution .....	15
Calamine lotion (p. 1301), to make .....	180

### URTICARIA PIGMENTOSA

Wheals develop which last for several weeks and then disappear, to be followed by brown-



ish macules. Sometimes the macules appear without any preceding wheals, and it has been suggested that some such cases probably belong in the category of nevi. Infants may occasionally present vesicles and bullae. The eruption is persistent, often beginning in infancy and lasting until puberty or throughout life. In rare cases the bones, the liver, the bone marrow and lymph nodes may be involved. Antipruritic lotions may be used for relief of itching.

PRURIGO

This is an inflammatory disease of the skin, characterized by pinhead- to pea-sized, pale red papules, occurring chiefly upon the extensor surfaces of the extremities, beginning in infancy or early childhood, lasting for years or throughout life, and accompanied by intense itching. As a result of the intense itching the affected areas are covered with excoriations and bloody crusts. After a time the skin becomes harsh, dry, thickened and, at times, pigmented. The neighboring lymph nodes, particularly those in the inguinal re-

gion, are often enlarged sufficiently to be visible. The disease is difficult to control, but fortunately is rare in the United States. *Treatment* consists in relieving the intense itching by means of Aveno baths and the application of an ointment containing tar or sulfur, and in improving the general health of the child.

HYDROA AESTIVALE (See also p. 280)  
(RECURRENT SUMMER ERUPTION)

This disease is vesicular and tends to recur each summer on the exposed areas of skin. Beginning usually in the second or third year of life, the disease tends to disappear after puberty. The eruption first appears as red macules upon which vesicles quickly develop singly or in groups. As the vesicles rupture, the lesions become crusted, and subsequently there is slight scarring. Symptoms of burning and itching are usually mild. The patient should avoid exposure to sun, wind and excessive heat. If crusting is marked, a bland ointment may be applied.

FORMULARY FOR DISEASES OF THE SKIN

Calamine lotion (Schamberg formula):

	GM.	OR	CC.
Resorcin and boric acid,			
of each .....	4.0		
Glycerin .....	4.0		
Calamine powder .....	30.0		
Witch hazel .....	30.0		
Distilled water, to make .....	180.0		

(Neocalamine powder may be used in place of calamine to approximate skin color.)

Starch poultice (for removing crusts):

Mix 1 tablespoonful of laundry starch, 1 table-  
spoonful of boric acid powder and 2 tablespoonfuls  
of cold water. Add 1/2 cup of boiling water, stirring  
constantly. Spread between thin layers of gauze and  
apply to area to be treated.

	GM.	OR	CC.
Coal tar paste:			
Coal tar and zinc oxide powder, of			
each .....	2.0		
Mix and add starch and petrolatum,			
of each .....	15.0		
Whitfield's ointment (for ringworm, noninflamma- tory):			
Benzoic and Salicylic acid ointment, U.S.P. XV			
Salicylic acid .....	1.0		
Benzoic acid .....	2.0		
Polyethylene glycol ointment .....	30.0		
Dusting powder:			
Zinc oxide powder .....	4.0		
Boric acid powder .....	4.0		
Starch .....	12.0		
Talc .....	12.0		

CARROLL S. WRIGHT

# Burns

Burns are among the most frequent accidental injuries of infants and children. Morbidity and mortality rates from these injuries exceed those from poisoning. Burns of infants and young children are incurred mostly in the home, whereas older children receive burns in their home, school and play activities. Thermal or chemical agents, electricity and exposure to ultraviolet rays, roentgen rays or radioactive substances are other factors responsible for burns.

Permanent disfigurement and disability and immediate and delayed mortality depend upon the extent of the surface area involved and upon the depth to which the burn penetrates. Even small burns involving the skin over joints may produce contractures which seriously limit motion. Death during the acute phase results chiefly from alterations in blood volume and from changes in the composition of the circulating blood. Plasma loss begins quickly after the burn and persists at least one or two days. In third-degree burns considerable destruction of the red blood cells occurs immediately in addition to plasma loss. Moreover, during the first week after the burn, renal damage of the lower nephron type may exaggerate these changes. Death after the first few days results from local or intercurrent infection and from debilitation.

The *treatment* of burns involving small and superficial areas of the skin is simple. The involved area is cleansed, and a sterile ointment is applied. White petrolatum (U.S.P.) or an ointment with a local anesthetic may be used. The local application of sulfonamides or boric acid ointment is not recommended. Sedatives and analgesics may be necessary.

Since second- or third-degree burns involving 12 per cent or more of the body area usually require hospital treatment, it is important to have an approximate estimate of the area of the body surface involved. The extent of the burn may be estimated according to directions on page 196.

Because shock always occurs with extensive burns, measures to prevent it should be in-

stituted promptly. The patient should be given morphine parenterally and placed on a sterile sheet; the burned areas should be covered with sterile towels until surgical care of the area can be undertaken. Blood from the patient should be obtained for hematocrit and hemoglobin determinations as well as for typing and crossmatching for transfusion. Plasma should then be administered intravenously until the results of these determinations are available.

Although there are no completely satisfactory formulas for calculation of the amounts of plasma, blood and electrolyte solutions to be administered, the method stated on page 195 is suggested. The amount of fluid calculated to be administered initially must be altered later in relation to subsequent laboratory determinations, urinary output and clinical appraisal of the patient. For extensive burns the amount of colloid solutions, especially blood, may be greater than calculated, whereas the amounts of physiologic saline solution may be less. In all instances of shock whole blood is preferred over all other solutions. Plasma is preferred over colloidal solutions such as dextran. If plasma which has not been irradiated to kill the virus of infectious hepatitis must be used, gamma globulin should be administered as a prophylactic.

The foot of the patient's bed should be elevated. No attempt to raise or reduce the patient's temperature is necessary. Oxygen may be given to combat restlessness and cyanosis. Tetanus toxoid or antitoxin and gas gangrene antitoxin may be given, and therapy with antibacterial agents may be instituted while preparations for surgical care are being completed.

There is considerable difference of opinion as to the advantages of the various types of local treatment. The production of an eschar by rapid coagulation with tannic acid has been discarded. Various substances containing antiseptic dyes or antibacterial agents which establish a film over the burned area have been used. These preparations would



seem to have their greatest usefulness when a burn has been untreated for thirty-six to forty-eight hours.

The pressure bandage method of Koch has gained considerable favor when early treatment is possible. The burned area should be carefully débrided and cleansed surgically. The entire burned surface is then covered with fine mesh gauze, such as rayon. This is covered with several layers of dry, coarse mesh gauze, and absorbent cotton or fluffed mechanic's waste is placed on top. Compression is then secured by tightly bandaging the entire dressing. Under ordinary circumstances this type of dressing is allowed to remain in place for two or three weeks. If there is an elevation of temperature or a foul odor from the dressing, however, it should be removed and treatment of the infected wound instituted. Some advocate the application of a light plaster of Paris cast instead of pressure bandages. Others perform no initial débridement, but administer antibacterial agents as prophylaxis against infection.

Wallace has treated burns by the open method, i.e., exposure to air, elevation of the burned area, immobilization and prophylactic antibacterial agents. No local irritants are applied, and dry heat, such as that pro-

vided by a cradle with an electric light, is avoided. Such a method of handling burns has considerable merit in the event of a civilian disaster.

Early grafting of skin is recommended when possible for deep or extensive burns. Other types of reconstructive plastic surgery may be necessary.

The importance of teaching children the hazards of fire cannot be overemphasized. Parents must exercise great care to keep hot objects beyond the reach of toddlers.

ROBERT H. HIGH

#### REFERENCES

- Allen, H. S., and Koch, S. L.: The Treatment of Patients with Severe Burns. *Surg., Gynec. & Obst.*, 74:914, 1942.
- Artz, C. P., and MacMillan, B. G.: Treatment of Burns of Difficult Areas. *Am. J. Surg.*, 91:517, 1956.
- Blocker, T. G., Jr.: Local and General Treatment of Acute Extensive Burns. The Open-Air Regime. *Lancet*, 1:498, 1951.
- Cope, O., and Moore, F. D.: The Redistribution of Body Water and the Fluid Therapy of the Burned Patient. *Ann. Surg.*, 126:1010, 1947.
- Wallace, A. B.: The Exposure Treatment of Burns. *Lancet*, 1:501, 1951.

# Allergic Diseases

## GENERAL DISCUSSION

The term "allergy" was first used by von Pirquet to denote altered tissue reactivity. It is now generally used to describe those reactions resulting from antigen-antibody union within the living animal. The present concept of the allergic mechanism is that histamine or some similarly acting substance, produced when antigen and antibody unite within or on the surface of the cell, reacts in turn on the neuromuscular apparatus of the shock organ (skin, lung or other tissue) to produce the allergic reaction. The fundamental and characteristic allergic lesion is the urticarial wheal, which is the result of capillary dilatation, increased capillary permeability, and edema. There is a diapedesis of leukocytes, composed early of polymorphonuclear cells and later mostly of monocytes.

Much confusion surrounds the various conceptions of how human allergy is related to human and animal anaphylaxis (nonallergic sensitization). Both normal man and animals can be sensitized by the administration of foreign proteins; the nonallergic person absorbs antigen from his gastrointestinal tract in the same manner as does the allergic person. In addition, equal capacities for the production of antibodies from such specific antigenic stimulation as from typhoid vaccine have been observed in nonallergic and in allergic children by Rubin and Rapoport. Passive sensitization of the skin of normal persons by means of the passive transfer of antibody indicates that their cells have the capacity to become sensitized and, when antigen is injected into the passively sensitized site, to react to the union of antigen and antibody. The allergic reaction depends on the presence of antibodies produced by previous sensitization with an antigen (*active sensitization*). The anaphylactic response may be similarly brought about by the injection of preformed antibodies which sensitize the recipient to subsequent exposure to antigen (*passive sensitization*).

How, then, does the sensitized allergic

person differ from the sensitized nonallergic (normal) person? In an attempt to distinguish human allergy from anaphylaxis, Coca coined the word "atopy" to designate a constitutional response of certain persons to foreign substances, chiefly protein in nature. The constitutional factor in the allergic person appears to be inherited.

The chief distinguishing feature of the allergic person is the ease with which he produces, after antigenic stimulation, specific antibodies which can be demonstrated by passive transfer.

This type of antibody, known as the *atopic reagin* or *skin-sensitizing antibody*, is different from other antibodies which both normal and allergic persons develop in response to antigenic stimulation. The skin-sensitizing antibodies are more heat-labile, have a molecular weight higher than that of human gamma globulin, and do not readily traverse the placental barrier from mother to infant. In contrast, other immune antibodies developed in both normal and allergic persons in response to antigenic stimulation are heat-stable, are associated with the gamma globulins, are not firmly fixed in skin as are atopic reagins and are easily transmitted through the placenta.

The anaphylactic response may occur in animals and in man without the inherited constitutional factor, and is characterized in most instances by absence of passive transfer antibody.

The usual sensitizing component in antigen is protein. Carbohydrates, lipids and various chemicals may, however, by protein linkage (haptens), act as antigens to produce antibodies specific for themselves. It is also possible that certain of these substances in their *pure* forms may act as antigens.

Whether bacterial and viral hypersensitivity, which differs in many ways from the ordinary hypersensitivity to such antigens as egg white, is related to the peculiar structure of the bacterial and viral antigens is not clear. Some believe that the differences depend on an altered inflammatory tissue reaction in the



host which results in an unusual response to the antigen.

True allergic sensitivity must be differentiated from idiosyncrasy, in which the antigen-antibody mechanism is not involved. Idiosyncrasy simply represents a peculiarity in tolerance for a certain substance. In such cases one is unable to demonstrate circulating antibodies or skin reactivity.

Contact dermatitis, which plays an important role in allergic eczema, more so in adults than in infants, must also be differentiated from true allergy. It is an idiosyncrasy of the skin to contact with an irritating agent. Some agents produce dermatitis when they come into contact with any skin; others produce dermatitis only in peculiarly sensitive persons. The child with allergic eczema often acquires contact dermatitis from chemicals which would not otherwise irritate his skin.

#### *PATHOGENESIS OF THE ALLERGIC STATE*

Probably the most important factor in the development of clinical allergy is the inherited capacity to be sensitized allergically to foreign substances. It is estimated that about 75 per cent of allergic persons have a family history of allergy; about 35 per cent have a bilateral family history. In the latter instance the tendency in the offspring to allergy is greater, and the manifestations usually occur earlier in life and are more severe. The inherited quality in allergy is not a specific form of sensitivity to a specific substance, but simply the ability to develop an allergic type of sensitization. The mother may be sensitive to one food, the child to another. The types of reaction may also be dissimilar; for example, the mother may have hay fever and the child eczema.

Both allergic and nonallergic persons may become sensitized (develop specific antibodies after ingestion of a particular food) and yet not have clinically manifest disease. Not infrequently persons with a positive family history of allergy will react on skin testing to pollen of ragweed or other plants, yet show no symptoms when these pollens abound in the atmosphere. Many known and probably many unknown factors may help to explain such phenomena. Factors related to age limit the allergic response; the frequency of eczema in infancy and the rarity of asthma in the very young infant illustrate an age difference. Often the occurrence of an acute infection in the allergic person is the trigger for an asthmatic attack. Peshkin found that asthma frequently had its onset shortly after pertussis

and sometimes after measles. The part played by such infections is not clear. Some have felt that they are related to bacterial sensitization, others that the alteration of the immune state by the infection is more important; for example, the response to an injected antigen increased during tuberculous infection in animals.

Reactions to specific foods which occur only during the pollen season suggest synergistic actions of antigens. There is evidence that combined administration of a strong antigen with a weak antigen increases the antibody response to the weak antigen.

Alterations in hormonal balance influence clinical allergy as evidenced by changes in allergic reactivity during pregnancy and the profound effects of corticosteroids in depressing both antibody production and the allergic response itself.

Dehydration depresses the allergic response, which varies also with changes in the salt composition of the body. Little is known of the mechanism by which the allergic response is thus altered. The reaction of the dehydrated animal to intravenous histamine is depressed, suggesting an altered neuromuscular response.

Sensitization in the fetus may occur by the passage of preformed antibodies across the placenta, but permanent sensitization does not develop in this manner.

Active sensitization can be induced by placental transfer or by ingestion of antigens in breast milk, as evidenced by the fact that many infants with atopic eczema are sensitive to egg white before eggs have been eaten. The removal of a particular food from the mother's diet has relieved eczema in a nursing infant. Whether cows excrete foreign antigens (such as those of grass, weeds or grains) into their milk is not known. Since overindulgence in certain foods, especially uncommon ones, floods the circulation with antigen (in nonallergic as well as in allergic persons), it might be wise for the pregnant or nursing woman in families known to be allergic to refrain from overindulgence in an effort to spare the child this specific sensitization.

The normal adult may absorb unsplit proteins from his gastrointestinal tract, and there is evidence that this tendency is even greater in the young infant. Schloss showed that when a new food is introduced into an infant's diet, antibodies against it are produced which indicate absorption of whole protein; subsequent administration of the food is not

followed by further antibody responses. With each new food this process is repeated. With the rapidly expanding diet during infancy many occasions arise which induce new antibodies, and which in the allergic child might well induce clinical allergy. Consequently it would seem good practice to continue breast feeding for several months in infants of allergic families. The feeding of cow's milk while awaiting the arrival of breast milk in the early days of life may be a dangerous practice for such babies.

Food mixtures are not advisable for the allergic child, since they create confusion in planning elimination diets. Owing to the possibility of sensitization induced in utero or through breast milk and because the intensity of the allergic reaction varies directly with the amount of antigen consumed (after original sensitization), it would seem prudent to begin each new food cautiously. When sensitization to a particular food is not great, cooking may change the antigenic constitution of the food sufficiently to allow its ingestion without inducing an allergic response, as in the case of milk or egg.

Sensitization also occurs by inhalation, absorption through the skin and by parenteral injections of foreign substances.

#### **METHODS OF TESTING FOR HYPERSENSITIVENESS**

**History.** An adequate and detailed history is the most reliable tool for detection of the antigen producing an allergic manifestation. It must be remembered that three to four weeks may elapse between the ingestion of a new food and the clinical manifestation of allergy to it. This interval may be greatly shortened in persons who may be more active antibody producers or are more alert reactors. In a child sensitized in utero or through breast milk an allergic response may occur within a few moments after the ingestion of a new food.

**Elimination Procedures.** Elimination of potential allergens is an effective method for detecting the etiologic agent in the young infant whose diet is composed of few foods and whose environmental contacts are relatively limited. The mother who undertakes such elimination must understand the completeness with which selected foods must be eliminated as well as the need for accurate observation. Early and minor changes in the child's disposition, which can usually be detected only by the mother, may provide the clue to the causative agent.

Foods are the main cause of allergic reactions in children under two years of age. Inhalant allergens play a relatively minor role in infants, although allergic rhinitis during the second year of life is not uncommon, and eczema due to the inhalation of house dust is thought to occur after infancy. About four to five years of age the incidence of allergic reactions to foods and inhalants is about equal. After this age inhalants become the more common etiologic factor, although foods remain an important consideration throughout life.

The foods most commonly allergenic for the young child are cow's milk, egg, wheat and orange. Hill found that many infants who had positive skin reactions to lactalbumin also reacted to casein. Since casein is antigenically similar in all species, in these instances there would be no therapeutic value in changing from one milk to another. Cross reactions may also occur with lactalbumin.

The elimination diet in the infant may be limited to milk and crystalline vitamins. If it is advisable, the antigenicity of whole cow's milk may be decreased by boiling for fifteen to twenty minutes or by acidification with lactic acid, or evaporated milk may be substituted. Since milk with additional vitamins is almost a complete diet, the child may be maintained on it for some time without fear of nutritional deficiency. If the offending substance is absent in this diet, improvement should be noted within five to seven days in the case of eczema or other persistent allergic phenomena. New foods can be added one by one at weekly intervals, starting with small quantities if the child is closely observed for changes in the clinical disease.

If no improvement is noted when cow's milk is the sole food, some other milk, human or goat, or, better still, some nonmilk product such as soybean "milk," amino acid "milk" or meat "milk" may be given.

In older children, who have a more complicated diet, the elimination diets of Rowe (p. 1412) may be used to advantage.

Rowe suggests four diets: one of them consists of milk alone; another excludes the three most common offenders, milk, egg and wheat; the other two are composed of foods that rarely cause sensitization. A diet should be given for ten days before changing or making additions to it. In the case of eczema, all possible contact irritants should be removed while the diet is being investigated. In the case of asthma, inhalant allergens should be eliminated when possible; the



child's bedroom and playroom must be cleared of such common inhalants as feathers, wool particles, house dust and animal danders. An air conditioner in the room may help in eliminating pollen.

To eliminate all contact and inhalant allergens, it may be necessary to place the child in a clean, bare hospital room where the environment is more readily controlled. Tolerance tests for environmental factors may be begun in the hospital after clinical manifestations have subsided.

The best test for the clinical importance of a potential allergen is administration of it by the route it is normally taken. If the asthmatic episodes are believed to result from contact with a cat, for example, skin testing with cat dander is not so reliable a test as having the child play with a cat. In a highly sensitive child exposure to known excitants may be dangerous, and these tests should, therefore, be done with great care.

**Skin Tests.** When it is impossible to identify all offending allergens by history or elimination regimens, specific testing of the reactivity of skin or mucous membrane can be done. Complete reliance, however, cannot be placed on skin testing for determination of the causative factors in allergic disease. As noted elsewhere, positive skin tests to specific substances may be obtained in the absence of any evident disturbance when the person is exposed to them. On the other hand, a high percentage of foods which produce gastrointestinal symptoms when ingested do not incite positive skin tests. Under certain circumstances, moreover, as during dehydration states or fever or after an acute allergic episode, the skin reactivity to an antigen may be depressed temporarily, as it is, for example, to tuberculin. The skin of the very young infant reacts relatively poorly to skin tests, and, since he is a poor antibody producer, the passive transfer test is of little value.

Before using any testing material it is important that its potency be known. This can be done only by testing persons known to be sensitive to the materials. Reliable antigens for testing are supplied by many commercial firms. Certain extracts are nonspecifically irritating and produce falsely positive reactions.

**Intracutaneous test.** The intracutaneous test is the most reliable of skin testing methods, although falsely positive reactions are more common with it than with the others. It has the advantage of being easily quantitated, so that some estimate of the degree of sensitivity can be had. The initial intracutaneous test

should be made with a weak dilution of the extract. Only 0.01 cc. of solution should be injected, care being taken that it be placed intracutaneously. The height of positive reaction occurs within ten to fifteen minutes, at which time the test should be read. A reaction which develops pseudopodia is of the highest order of magnitude and may be recorded as 4 plus; positive reactions of a less degree can be graded downward to 1 plus. The estimation of the degree of reaction is arbitrary, and each physician must set his own standards. Since constitutional reactions are not uncommon, no test should be performed without epinephrine available for hypodermic administration, and a tourniquet at hand so that the circulation above the test site can be occluded to prevent further absorption in the case of reaction. For safety it is best to perform intracutaneous testing only if the scratch test is negative. In the case of eczematous children an intracutaneous test with egg white probably should not be done even though the scratch test is negative.

**Scratch test.** The scratch test is usually performed on the forearm or back. An aseptic superficial scratch is made about  $\frac{1}{8}$  inch in length with an attempt not to draw blood. Liquid antigens, such as sterile milk or egg white, or solid antigens dissolved in tenth-normal sodium hydroxide or prepared as liquid glycerin extracts, are dropped on the scratch and gently rubbed into it with a fresh wooden or glass applicator for each antigen. The test is read in fifteen to twenty minutes. The sodium hydroxide solution should be used as a control test.

**Patch test.** The patch test is useful for contact antigens, but is often difficult to evaluate. The antigen tested may cause dermatitis only under certain circumstances, as in the presence of moisture or friction or at a certain pH, or the reaction may be limited to the areas of allergic dermatitis. To evaluate the test properly, one or more of these conditions may have to be reliably reproduced, and some knowledge of the nonspecific irritating qualities of the test substance must be had. The testing patches are prepared by placing the antigen in powder or liquid form on a small piece of filter paper, centered on a square of cellophane which in turn is placed on a larger square of adhesive. In the usual case the coverings are removed in forty-eight hours and the test read. If itching develops, the coverings are removed and the test material washed off. In the case of irritating oleoresins the test may be read after one hour.

**Mucous membrane tests.** The ophthalmic test for sensitivity to serums and direct testing of the nasal mucous membrane with inhalants are at times valuable aids. When the skin test is positive to a therapeutic serum, the instillation of 1 drop of a 1:10 dilution of the serum into the conjunctival sac may determine whether or not it is safe to give the serum. A positive conjunctival test is evidenced by chemosis of the eye and tearing. When the skin test is positive and the eye test is negative, the chances of a dangerous reaction following serum administration are remote. If both tests are positive, serum of another species should be sought. Severe chemosis of the eye can be alleviated by instillation of 1 or 2 drops of a 1:1000 solution of epinephrine. By applying the antigens of inhalants to the nasal mucous membrane one can determine whether a positive skin test

is diagnostic. If no reaction occurs when the pollen is directly applied to the nose, it is unlikely that this pollen is the cause of the symptoms. These tests should not be applied during the pollen season.

**Passive transfer test.** The passive transfer antibody found in the blood plasma is the characteristic antibody produced in the allergic person and can be used to sensitize the skin of a nonallergic person to a specific antigen. This is the *Prausnitz-Küstner reaction*. This test is of little or no value when antibody production is low, as in the very young infant. It has its greatest value in testing an eczematous infant whose entire skin area is involved or in infants with dermographism who respond to every trauma with false reactions. It is also of value in checking a positive direct skin test reaction. Since direct testing is usually more informative, it is reasonable to delay testing until the skin is treated and the child can be tested directly.

The skin of a healthy nonallergic person is prepared for the passive transfer test by injection of 0.05 cc. of the patient's serum intracutaneously in each of a series of areas on the volar surface of the forearms. Care should be taken that the serum is sterile, that it is Wassermann negative and does not contain malarial or other parasites. A history of hepatitis in the patient should preclude its use. The areas injected are ringed with gentian violet in a circle about 1½ inches in diameter to denote the area sensitized. Twenty-four to forty-eight hours are allowed to elapse before subsequent testing with the suspected antigens, so that adequate localized cellular sensitization may develop. These areas remain sensitized for four to five weeks.

Tests are performed by intracutaneous injection of the suspected antigens; a control test with each antigen is made on unsensitized skin of the recipient just opposite the test area. An appreciable increase in degree of response of the test area over the control indicates a positive reaction. Sites where positive reactions have occurred should not be used for further tests. Areas having negative responses may be used over again. The recipient should not eat the foods to be tested within twenty-four hours before the tests are performed, for if the testing serum is of high titer, the sites may react to them.

### Selection and Interpretation of Tests.

The choice of reagents for testing will be guided by the probable nature of offending substances as indicated by a carefully taken history, which should explore in detail the relationships of onset or disappearance of allergic symptoms to changes in diet or environment. It is impracticable and inadvisable to test the allergic child with all available antigens when in many cases a dozen or so well chosen tests will detect all major offenders.

In infants with eczema or gastrointestinal allergy particular attention should be given to testing those foods known to be part of the diet. In the case of mixed foods in the diet it will be necessary to appraise each constituent, but it is generally better to eliminate

such foods entirely than to test to all possible allergens therein. Gastrointestinal disturbances have been associated with ingestion of certain canned foods which did not occur with the same food prepared at home. House dust and wool, common offenders in eczema, should also be considered for testing.

In inhalant allergy the detailed composition of articles of furniture (chairs, bed rugs, pillows, mattresses, draperies), toys and clothing should be established and possible offenders tested. House dust, feathers, wool, seasonal allergens (pollens, molds) and animal danders should receive attention as indicated; these allergens may induce atopic dermatitis as well as respiratory manifestations through inhalation. Occasionally dyes and other synthetic materials in garments require careful study.

It is advisable that only two or three tests be done at the initial visit. This allows an estimate of the reactivity of the skin and of the general hypersensitivity of the patient so that severe constitutional reactions can be avoided. One should not include in the first group of tests more than one of the substances which from the history are possible offending agents, since a cumulative effect might result in a constitutional reaction. Furthermore, if all tests are positive, one cannot be certain whether they are true positive reactions or whether they result from nonspecific irritation of a reactive skin. When great numbers of tests are positive, they should be checked by passive transfer testing. The child should be watched for at least a half hour after testing, since constitutional reactions may be delayed.

A positive skin test reliably performed when the antigen itself is not irritating denotes allergic sensitivity to the material tested. It does not indicate that the allergic disease present is necessarily caused by the reacting substance. It may represent a past etiologic factor no longer involved or possibly a future excitant. In order to incriminate the positively reacting substance as a causative factor in the disease, the specific antigen must be demonstrated in the child's diet or environment. It would be reassuring if its withdrawal were always associated with relief from symptoms and its reincorporation would again produce the disturbance. Owing to the frequency of multiple sensitivities, however, the removal of a single offending substance is often not followed by relief.

The highest percentage of positive skin reactions occurs in hay fever and pollen



asthma patients, in more than 90 per cent of whom hypersensitivity can be demonstrated. In children with other forms of asthma and with eczema, positive reactions occur in about 75 per cent. Only about half of the patients with gastrointestinal allergic symptoms and fewer of those with urticaria and angio-neurotic edema react positively.

Before an essential food substance is eliminated from a child's diet because of a positive reaction, the skin test with the specific antigen should be repeated so that the presence of a positive reaction is verified. *Good clinical judgment rather than blind reliance on skin testing will benefit the patient most.*

#### TREATMENT OF THE ALLERGIC STATE

Since there is no means to eliminate the inherited quality which makes the patient atopically hypersensitive, treatment of an allergic condition is limited to (1) removal of offending allergens, (2) hyposensitization against specific allergens, and (3) decreasing the responsiveness of the child toward offending allergens.

**Removal of Offending Allergens.** At times, when a single or only a few allergens cause symptoms, excellent results are obtained by their avoidance. Too often poor results are due to the mother's lack of understanding of the thoroughness with which elimination must be effected. Bread or crackers may contain enough milk to continue a "milk disturbance," and other prepared foods may contain such common allergens as egg and wheat. Lanolin may be thoughtlessly used in wool sensitivity. Time must be taken to explain all possible sources of trouble.

Sensitivity to specific foods is often not permanent. Sensitivity to milk in the infant, for instance, may disappear after a few months. Even hypersensitivity itself may be completely lost. For this reason, after a period of elimination of several months, one may cautiously reinsert the allergen into the diet or environment. This should be done only if continued avoidance imposes unusual hardship or if the former allergen is felt to be essential. Such a test should be made with great care, since reintroduction of the allergen may be followed by an explosive allergic episode.

At times the clinical expression of allergy is mild; if the causative agent is an important food, as, for instance, milk, one must weigh harm against good in determining whether to remove the offending substance. Thus in mild eczema it may be elected not to alter the diet,

but to use local treatment only. The diet of the child must remain nutritionally adequate. The Rowe elimination diets (p. 1412) are especially useful for older children.

The removal of offending pollen allergens can be accomplished by sending the patient to a pollen-free locality or by air-conditioning his room. Freedom from pollen inhalations for the long night period often results in day-long relief.

The antigenicity of certain foods can be decreased by various procedures, for example, that of milk by prolonged cooking, acidification, evaporation and drying.

**Hyposensitization against Known Specific Antigens (Desensitization).** In the case of multiple sensitivities or when the exciting antigen or antigens cannot be determined or the allergen cannot be avoided (house dust, pollens, molds), measures aimed at decreasing the responsiveness of the child to the allergen may prove helpful. Specific hyposensitization is used mainly in the treatment of pollen sensitization. When such essential infant foods as milk or egg are found to be the cause of an allergic disturbance, they can be given orally in minute and gradually increasing amounts to bring about hyposensitization. In eczema it is best to remove all egg from the diet. Hyposensitization with vaccines (antigen) made from bacteria isolated from the patient's upper respiratory tract occasionally proves helpful.

Treatment by hyposensitization is based on the assumption that the injection of small quantities of antigen in gradually increasing doses increases the circulating antibodies. Decrease in symptoms is associated with a reduced dermal and conjunctival response to the antigen, but the existence of a high level of antibodies accounts for persistence of some degree of skin sensitivity.

The rapid return of clinical hypersensitivity when antigen injections are discontinued results from a fall in circulating antibodies. There is a limited capacity for antibody production, which, when attained, cannot be raised by continued injection of antigen. The ceiling of antibody production following the injection of pollen antigens as well as some others is reached more rapidly in subsequent courses of treatment and with smaller doses of antigen than during the first course. However, except in rare instances and in older people, who tend to lose their atopic manifestations, the cessation of specific therapy is followed by return of symptoms.

Temporary insensitivity to antigens follows

sublethal anaphylactic shock in sensitized animals; this is not a safe procedure in man.

Before hyposensitization is undertaken it must be decided whether the severity of symptoms justifies treatment. When the symptoms are mild and infrequent, they may be better tolerated by the child than a series of painful injections. It is possible, however, that later development of asthma and asthmatic bronchitis may be prevented by early treatment of mild respiratory allergy.

Only with certain proteins and in certain persons is complete relief of symptoms possible. Subcutaneous injections of pollen antigens result in complete relief in only about 20 per cent of the cases, although the majority of patients have their symptoms reduced by about 75 per cent; some are made ill by each injection.

In hyposensitization by the subcutaneous method the initial dose is determined by the degree of skin reactivity and should contain the smallest amount of antigen which produces a positive intradermal test. There is wide latitude in choosing the subsequent doses, the interval between doses, and how long to carry on treatment. The largest dose is usually about 500 to 1000 times the initial dose, with each dose one and a half times to twice the preceding doses (somewhat less at high dosage levels), with an interval of three to five days between injections. If severe reactions occur, the preceding dose may be repeated and subsequent doses increased at a slower rate. Patients with a high degree of sensitivity will secure relief with smaller doses of antigen than those less sensitive.

In *preseasonal therapy* for pollen asthma or hay fever it is desired to attain the maximum dose just before the onset of the pollen season. In the usual case this will require about three months when the weaker dilutions are given at three-day intervals or the stronger ones at five-day intervals. Since the injected pollen remains antigenic for forty-eight to seventy-two hours, the interval between doses should not be less than three days. On the other hand, if the interval is too long, loss of hyposensitization may occur. Opinions differ as to whether treatment should be continued after the season has begun. When treatment is continued, the dose should be about half the maximum one and given at seven- to ten-day intervals.

When treatment is discontinued and when the pollen season is over, the degree of protection rapidly falls off. To maintain a high degree of hyposensitization after specific ther-

apy the person must remain more or less constantly in contact with the allergen. This is as true for foods as for pollens.

Many allergists recommend *perennial treatment* for pollen sensitization to avoid repetition of intensive preseasonal treatment. When the maximal dose is achieved in the initial preseasonal treatment, half of this dose is given at weekly intervals throughout the pollen season and then every three or four weeks throughout the year until four to six weeks before the onset of the next season. Then the interval is shortened to five days and the dosage gradually increased so that the original maximal dose is reached as the season commences. Some allergists give the maximal dose for perennial treatment and do not shorten the interval of treatments pre-seasonally.

When a patient with pollinosis has received no preseasonal treatment, *coseasonal therapy* may be tried. The results are not so good as with preseasonal therapy, but there is often some benefit. In coseasonal therapy small doses are given at short intervals with no attempt to attain large doses. The intracutaneous route of injection is preferred. Should relief occur after the first few daily injections of increasing concentrations of pollen, the dose is not increased further. The amount of antigen to be given is the amount necessary to produce a wheal about a centimeter in diameter.

Before any injection the patient or his parent should be asked whether a reaction occurred after the previous injection, so that the dose to be given can be properly adjusted. Severe constitutional reactions may appear immediately after the injection or be delayed for an hour or so. The immediate ones may be fatal. All foreign proteins are more safely given into an extremity than into the trunk, so that a tourniquet can be placed above the site of injection, if necessary, to slow the rate of absorption. Epinephrine (0.3 to 0.5 cc.) should also be given subcutaneously in the other arm for severe constitutional reactions, and an equivalent amount injected at the site of the reaction. When symptoms are delayed for an hour or more, they may be distressing, but are rarely serious; their management is similar to that of manifestations which occur soon after injection. In the milder cases the reaction is local with itching and swelling. Generalized urticaria and sneezing may be associated with moderately severe reactions, and asthma and anaphylactic shock with the serious ones.



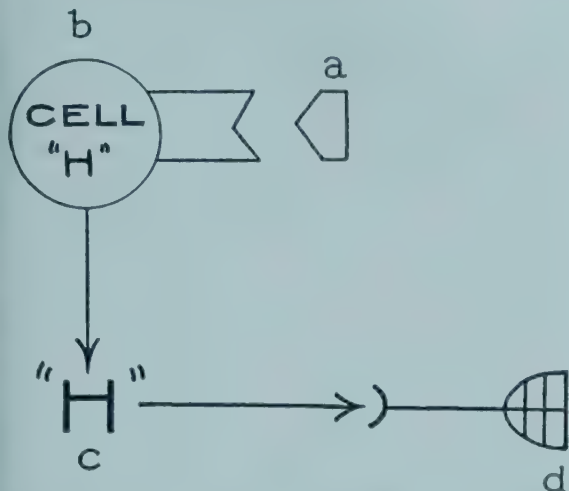


FIG. 418. A summary diagram of the mechanism of the allergic response and the sites of action of the 3 modes of treatment, *a* = Antigen—Its removal from the environment eliminates the antigen-antibody reaction. *b* = Sensitized cell with attached antibody. Hyposensitization is presumably brought about by the production of an immune or blocking antibody which prevents the antigen from attaching itself to the antibody (reagin) on the sensitized cell. *c* = Liberation of histamine, serotonin and possibly other substances, normally within the cell, after cell injury induced by the antigen-antibody union. The action of the so-called antihistaminics (Pyribenzamine, Benadryl and others) in preventing the histamine effect is thought to be accomplished through competitive inhibition for sites affected by histamine. Epinephrine has its beneficial effect in opposing the pharmacologic action of histamine through stimulation of the sympathetics. *d* = The neuromuscular organ which is stimulated to produce the clinical reaction by the "H" substance. Many nonspecific measures reduce its responsiveness; ACTH and cortisone may play their major role in this capacity.

In most instances severe reactions can be prevented by attention to details in treatment. Care should be taken that the antigen is not injected intravenously. Successive doses should be increased cautiously. If a long interval has elapsed since the previous injection, the next dose should be reduced. When a patient has a reaction with each injection, the dose should be reduced or treatment discontinued entirely. The administration of epinephrine with each dose may delay the reaction, but usually does not prevent it; when epinephrine is given with pollen extract, it promotes permanent skin marks. Administration of an antihistaminic drug before injections of antigen may avert untoward reactions.

**Decreasing the Responsiveness toward Offending Allergens (Nonspecific Hyposensitization).** There is suggestive but inconclusive evidence that the allergic response

may be decreased by a variety of nonspecific means. In evaluating any therapy, however, the frequent fluctuations in severity of symptoms which occur in the natural course of allergic states must be kept in mind. Reference has been made to the alterations in allergic responsiveness which depend on age. During hormonal upheavals, such as occur in pregnancy, there may be favorable fluctuations in the allergic response. Estrogenic substances have been helpful during menopausal urticaria; occasionally thyroid medication has been of value in treating eczema in the hypothyroid child. The corticosteroids greatly decrease allergic responsiveness by mechanisms not clearly elucidated. Emotional outbursts are often followed by itching and flare-ups of eczema or bouts of asthma. Psychotherapy may justly be considered a method of inducing nonspecific hyposensitization.

Severe illness and states of dehydration often lead to a decrease not only in allergic symptoms, but also in skin reactivity to specific antigens. It is not uncommon for an eczematous eruption to disappear during a state of acute dehydration, only to reappear when the infant is again hydrated. Anaphylactic shock in the guinea pig can be prevented by dehydration brought about by water restriction, sodium chloride depletion or potassium chloride administration, whereas measures which favor retention of water, such as forced water feeding and sodium chloride administration, exaggerate the anaphylactic response.

Definite improvement has been observed in infants with eczema following use of measures promoting mild dehydration; older children with eczema have not responded as well. Asthma, hay fever and other forms of allergy also are often improved by this form of therapy. Care should be exercised to avoid such a severe state of dehydration as might impair kidney function or produce inspissation of bronchial secretions.

The so-called antihistaminic drugs are discussed with the individual allergic disturbances (see p. 1320).

Sedatives and antispasmodic and anesthetic drugs are sometimes helpful in allergy states. Nonspecific protein and vaccine therapy have been used with indifferent results. Though good results have been attributed to the use of vitamins, especially ascorbic acid, in large doses, clinical experience has not been confirmatory. When multiple factors are responsible for an allergic disturbance, the control of one or more of them often reduces the

allergic response to the others. This is strikingly demonstrated in the relief from allergic disturbances brought about by prevention or cure of respiratory infections. Resistance to allergic manifestations is increased by adequate rest, and the allergic response is minimized when the general health of the child is at its best.

MITCHELL I. RUBIN

## REFERENCES

### *Pathogenesis*

- Ferrebee, J. W.: Allergy. Annual Review of Medicine. Stanford, Annual Reviews, Inc., 1953, Vol. 4.
- Landsteiner, K., and Jacobs, J.: Experiments on Immunization with Haptens. Proc. Soc. Exper. Biol. & Med., 30:1055, 1933.
- Lewis, T.: The Blood Vessels of the Human Skin and Their Responses. London, Shaw & Sons, Ltd., 1927.
- Lippard, V. W., Schloss, O. M., and Johnson, P. A.: Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein. Am. J. Dis. Child., 51:562, 1936.
- Pirquet, C. von: Allergie. Münch. med. Wchnschr., 53:1457, 1906.
- Prausnitz, C., and Küstner, H.: Studien über die Ueberempfindlichkeit. Zentralbl. f. Bakt., 86: 160, 1921.
- Rubin, M. I., and Kellett, C. E.: Influence of Dehydration on Phenomena of Anaphylaxis in Guinea Pigs. Bull. Johns Hopkins Hosp., 49:170, 1931.
- Tullis, J. L., ed.: Blood Cells and Plasma Proteins. New York, Academic Press, Inc., 1953.

### *Treatment*

- Cook, M. M., and Stoesser, A. V.: Influence of Induced Variations in Electrolyte and Water Exchanges with Pitressin in Bronchial Asthma. Proc. Soc. Exper. Biol. & Med., 38:636, 1938.
- Loveless, M. H.: Immunological Studies of Pollinosis; Relationship between Thermostable Antibody in Circulation and Clinical Immunity. J. Immunol., 47:165, 1943.
- : Immunological Studies of Pollinosis; Enhanced Response in Hay Fever. J. Immunol., 47: 283, 1943.

## ECZEMA

The term "eczema" is used for a wide variety of unrelated inflammatory dermatoses. In adults contact dermatitis is commonly regarded as eczema, whereas, in childhood, eczema is considered an atopic manifestation to some specific allergen which is usually ingested, but may be effective by contact. Eczema is the most frequent expression of the allergic state in the first year of life. Few diseases in infancy produce so much annoyance to baby, mother and physician. The clinical manifestations in the infant differ from those in the older child. Frequently

eczema in the infant is complicated by contact dermatitis resulting from an applied medication, or true allergic contact dermatitis, as to silk or wool, which may be the primary entity. Seborrhea is uncommon in the older child, but is frequently associated with infantile eczema and may be mistaken for it.

## INFANTILE ECZEMA

### (ATOPIC DERMATITIS)

Eczema is commonest during the first two years of life, commences often during the first few months and occurs most frequently in bottle-fed babies or in breast-fed babies who receive additional foods. It is occasionally seen in wholly breast-fed infants as a result of passage of food proteins through the breast milk. An infant, of course, can be sensitized by antigens through inhalation or by contact. There is no predisposition according to sex or race. It occurs most frequently in the winter months.

**Etiology.** In spite of general agreement on the allergic quality of infantile eczema, it is not always possible to demonstrate specific hypersensitivity by skin tests or passive transfer. This fact has led to differences in opinion concerning the underlying mechanism, many doubting that an antigen-antibody mechanism is involved. The high incidence in later years, however, of hay fever and asthma in children who had eczema in infancy favors an allergic basis. It is presumed that about 75 per cent of the cases of eczema in infants and children is atopic dermatitis.

The importance of local skin factors in infantile eczema is uncertain. The skin of the infant differs from that of the adult anatomically and chemically and shows greater inflammatory response to scratch (dermatographia) and to other irritants. Changes in skin reactivity with age may account for the different character of eczema in the older child (neurodermatitis) and for the loss of the tendency to exhibit eczema as a manifestation of allergy. Such normal characteristics of the infantile skin as increased irritability and high water and sodium chloride content are said to be exaggerated in the skin of eczematous infants. Moreover, improvement may result from protection of the skin from irritation and from measures designed to reduce the water and the sodium content of the body.

Possible sources of irritation include rubbing or scratching and irritation from clothes, foam soaps, hard water, cold, wind and strong



sunlight, or skin infection. These may be important factors in the continued activity of infantile eczema.

Infection in the skin is of great importance in determining the degree of activity of some cases of infantile eczema. Even without pustulation large numbers of bacteria, chiefly streptococci and staphylococci, may be found. Rapid improvement may occur at times with antimicrobial therapy. Flare-ups of eczema often occur with infection of the respiratory tract.

The significance of unsaturated fatty acids in eczema is not clear. The level of them in serum may be low in infantile eczema, but in our experience the feeding of unsaturated fatty acids in linseed oil has not resulted in striking benefit (p. 102).

Overfeeding may have an adverse effect in eczema. Fat infants tend to have a moist, weeping eczema; thin ones a dry, scaling eczema. Feeding of large amounts of carbohydrate tends to increase water retention. Reduction in the carbohydrate intake often leads to improvement in the skin. Reduction in the fat of the diet has also been said to improve the condition of some patients (see above). Hill postulates that sensitivity to egg white, commonly found in the eczematous child, is in some unknown way important in the etiology of the disease.

**Clinical Manifestations.** The lesion in infantile eczema is characterized by papulation and vesicle formation, individual lesions at a given time often being in various stages of development. The vesicles rupture and exude a sticky, yellowish material which dries to form crusts. Scratching leads to the characteristic punctiform and excoriated appearance. When the crusts are removed, there is often bleeding from an inflamed moist surface. Milder lesions are less moist and inflamed, and scaling is frequently present, which may be a manifestation of an associated seborrhea. Severe and mild lesions may coexist in different parts of the body, and relatively inactive lesions may suddenly become acutely inflammatory. Thickening of the skin, formation of fissures and secondary infection with pustulation often follow scratching. Itching may be intense.

Infantile eczema occurs characteristically on the cheeks, forehead and scalp; occasionally behind the ears, on the neck and on the flexor surfaces of arms and legs. At first the skin is red and edematous, and when the swelling is extensive on the head and face, the appearance of the child may be greatly

distorted. Lesions on the trunk, abdomen and back tend to be drier and more circumscribed than elsewhere and are associated with more scaling. The entire body except the palms and soles may be involved. Occasionally a diaper dermatitis accentuates or localizes the eczematous eruption to this area.

In severe eczema infants are made uncomfortable and irritable by constant and intense itching, and loss of sleep may become serious. Affected infants are ingenious in their ability to rub and scratch itching parts despite restraining devices. Low grade fever may exist in the presence of superimposed bacterial infection. The regional lymph nodes become enlarged, but rarely suppurate. Splenomegaly is frequent. Most eczematous infants are overweight, but malnutrition may be present as a reflection of anorexia, chronic infection, persistent or recurrent diarrhea or dietary restriction.

Mild infantile eczema may be notably capricious. Many infants with an atopic family history have a mild eczematous rash only intermittently. Though these infants, like those with more persistent eczema, may subsequently have asthma, there is usually no necessity for restriction in the diet.

Flare-ups of eczematous lesions may follow prophylactic immunizations. The occasional development of generalized vaccinia in infants or children with eczema argues for deferment of smallpox vaccination unless there is a high probability of contact with the disease. Generalized vaccinia in eczematous infants may also occur from contact with a sibling or another child recently vaccinated, and such contacts should be scrupulously avoided. Kaposi's varicelliform eruption may result from superimposed herpes simplex on the eczematous lesion.

*Eczema in the older child*, whether or not previously present in early life, is similar to eczema in the adult, being characterized chiefly by thickening and lichenification. The lesions are usually symmetrically located in the flexures of the knees and elbows, about the wrists or on the back of the neck and ears. Scaling is frequent. Small, circumscribed, thickened, reddened, scaly patches may occur on the chest or back. The lesion is chronic, but acute exacerbations are common. Itching is intense, and infection and mechanical irritation from scratching play a large part in modifying the lesion. Dermato-graphia is not so prominent as in the infantile form of eczema.

So-called nummular eczema occurs in older



FIG. 419. Infantile eczema.

infants and children as localized patches originally composed of small vesicles and later becoming dry and crusting. They are scattered over the trunk and the extremities and may be associated with characteristic atopic eczema elsewhere on the trunk. The lesions tend to recur at the sites of first appearance. Localized infection in the skin is thought to have some etiologic significance. Hill maintains that removal of environmental allergens and foods is not helpful in this form of eczema unless it is associated with typical atopic eczema.

**Differential Diagnosis.** The diagnosis of infantile eczema is based on the characteristic eruption about the face and head, the itching, family history of atopy, eosinophilia and the demonstration in most cases of protein sensitivity.

*Seborrhea* does not have the characteristic vesiculation of eczema; the lesion is dry, and the scales are yellow and greasy. There is little itching, but severe inflammation and moisture may be present. The distribution may be patchy, as in dry eczema, but it often begins as "cradle-cap." When seborrhea is the sole manifestation, the differentiation is clear. The disturbance is not so persistent as eczema and yields readily to salicylic acid ointments. The two diseases may occur together, seborrhea usually preceding the atopic eczema.

*Leiner's disease* (p. 1284) is regarded by

many as a severe form of seborrheic dermatitis and has the essential characteristics of that disease. *Papular urticaria* has more distinct papules with little or no vesiculation and is found most frequently on the extensor surfaces of the arms and legs. *Scabies*, when complicated by scratching, may present some difficulties in diagnosis. It rarely involves the face, except in the breast-fed infant, and commonly is present in other members of the household. The characteristic burrow can usually be discovered. *Diaper dermatitis* can be excluded by a rapid response to treatment (p. 1298). *Papular eczema* involving the buttocks may resemble *congenital syphilis*, which must be excluded by appropriate tests. *Moniliasis* in very young infants with lesions particularly in the diaper area must be differentiated. Some of these infants have had oral thrush in the newborn period. Skin cultures will aid in the diagnosis. *Eczematoid eruptions* secondary to chronic skin infection and to purulent draining ears and sinuses must also be differentiated.

**Treatment.** The results of treatment in severe eczema may be far from satisfactory, but most patients can be significantly helped by therapy. Success will depend in large degree upon the mother's understanding of the disease. She will need to know that infantile eczema has exacerbations and remissions and that it may be discouraging from time to time. Infantile eczema will ultimately



disappear spontaneously in most instances, usually by the second or third year of life.

Whenever possible, the infant with eczema should be treated at home. In severe eczema, however, especially when secondarily infected or when mother and child are both exhausted, care in the hospital may become necessary. Strict isolation of the infant to prevent cross infection is necessary for his own protection and for that of others.

The treatment of infantile eczema can be considered in three categories: local, specific and nonspecific.

**Local treatment.** This is the most important factor in the treatment of eczema. Scratching and rubbing, which will encourage inflammatory activity, must be prevented. Scratching can largely be prevented by placing heavy cardboard cuffs about the elbows. The fingernails should be cut close and kept clean to prevent infection. The hands may be encased in cotton stockings. Heavy cellophane sheeting placed under the infant will prevent rubbing on the bedding. When the eczema is extensive, moist or infected, the clothing is best removed and the child placed under a heat tent to prevent chilling. Otherwise a light cotton diaper and loosely fitting cotton nightgown may be worn. Overdressing and too warm bed coverings aggravate the disease by inducing sweating.

No woolen garment should come in contact with the skin of an eczematous infant.

The infant can be bathed if water does not irritate his skin; mineral oil can be used for tender, inflamed areas. A mild soap may be used for cleansing. If it produces irritation, a soap substitute can be used. A hexachlorophene product, such as pHisohex, is particularly helpful in the presence of infection.

Ointments and lotions are the most important elements of local treatment. Different types of lesions may occur on various parts of the body at the same time and require different types of care. Ointments should not be used when there is weeping. When there is induration, the ointment should be gently but thoroughly rubbed in. The ointment or lotion should be kept constantly on the skin, regardless of the frequency of application.

Associated seborrheic dermatitis of the scalp can be controlled by application of 1 or 2 per cent salicylic acid ointment under a thin cotton cap. This procedure is continued for three to five days, no attempt being made to cleanse the scalp between the daily applications of the ointment. On the final

day a thorough shampooing with castile soap or pHiso-hex and water will usually clear the scalp. Occasionally the treatment may need to be repeated.

It is difficult to keep medication applied to the face. When a thick mass of scabs and crusts covers the surface, it is removed as much as possible by gentle wiping with gauze saturated with liquid petrolatum. Saline soaks, kept continuously wet for a day or two, are also helpful in removing encrustations. A facial mask of gauze is easily prepared.

During the acute inflammatory phase of the eczema, infection of the skin seriously affects the course of the disease. If there is not too much oozing, an ointment containing bacitracin or bacitracin with neomycin may be effective in controlling the infection. Some clinicians prefer an antibiotic lotion for this stage and feel that there is less danger of sensitization than with an ointment. Antipruritics in the form of menthol, phenol or chlorobutanol (Chlorotone) may be added to the ointment or solution. In the presence of severe infection systemic antibiotic therapy is indicated; because of the lesser chance of sensitization, it is actually preferable to local therapy in all instances. If, after the crusts have been removed, a wet oozing surface remains, a mild astringent lotion should be applied to dry the surface before applying tar ointment. One of the following lotions may be sponged on frequently for two or three days:

	Gm. or ml.
Burow's solution.....	16.0
Water.....	240.0
or	
Potassium permanganate.....	0.4
Water.....	120.0

1 teaspoonful of this solution to 1 quart of water gives about a 1:10,000 dilution of permanganate.

A 3 per cent Burow's solution containing 200 mg. of neomycin to 8 ounces of solution is recommended by Osborne for this purpose.

When the surface is dry, red and papular, an ointment containing tar, such as the following, is most effective:

	Gm.
Crude coal tar.....	3.0
Zinc oxide.....	5.0
Starch.....	50.0
Petrolatum, to make.....	100.0

The tar and the zinc oxide are combined, the starch is incorporated in the petrolatum, and the 2 mixtures then combined.

If the area is highly inflamed, Lassar's paste can be used as a protective coat before applying tar.

Coal tar ointment should be applied as often as necessary to keep the skin covered. Some patients find coal tar unusually irritating, and in this case the concentration of the tar should be reduced one half. Tar should not be used where there is pustulation. When the eczematous lesions are dry, thickened and localized in small patches, crude coal tar may be applied twice a day and dusted over with talcum powder. A satisfactory ointment is 5 to 8 per cent liquor carbonis detergens in a vanishing cream base. One to 3 per cent crude coal tar in Lassar's paste may also be useful. A number of proprietary tar ointments, both black and white, are available and are often less messy than compounded ones. A small area should be tried initially to determine the degree of sensitivity to tar. Overtreatment may produce a wrinkled and drawn appearance of the skin and fresh papulation. Tar contains phenol, and for this reason not more than one fourth of the body surface should be covered at one time. Exposure of the parts covered with tar to direct sunlight should also be avoided, since tar is a photosensitizer. The areas of eczema on the trunk and extremities should be kept constantly bandaged and uncovered only to apply fresh ointment.

Each day before applying fresh tar ointment the old should be carefully removed with liquid petrolatum.

The ointment should be kept carefully sealed in jars to prevent evaporation of the volatile ingredients. Tar may be removed from linens by rubbing both sides of the material with lard, then washing with soap and water.

If large areas of the body are covered with papulovesicles, a starch bath before the daily application of an ointment may be useful.

When much of the infiltration, papulation and itching have disappeared, the tar ointment is discontinued and a milder one is applied; petrolatum or a simple zinc oxide paste may be useful.

Hydrocortisone ointment (1 or 2.5 per cent) containing an antibiotic is useful for the inflamed, scaly, rather superficial lesions. It should be applied twice daily and rubbed in gently. When the eczema clears, the therapy should be discontinued and resumed if the lesions return.

Small oozing cracks behind the ears may

be painted with plain crude coal tar. If they are wet, a neomycin-Burow's solution lotion may be applied until the moisture has disappeared.

Mild eczematous lesions, consisting only in patchy redness with a slight thickening and scaling, require little treatment. All sources of irritation such as soaps, water and rough clothing should be avoided. The involved areas should be cleansed with petrolatum or a detergent solution or ointment and a mild tar ointment as liquid carbonis detergens applied.

The local treatment of chronic eczema (neurodermatitis) in older children may be even more difficult than that of the infantile form. There is a tendency to recurrence, and itching is intense. Control of scratching is important, but complete restraint of the older child is not feasible, and partial restraints are unsatisfactory. Crude coal tar ointments are helpful. They must be vigorously rubbed in and then covered with cotton bandages. When the legs are involved, cotton overalls or long stockings help in the control of scratching. Treatment should be continued for some time after the lesion has cleared. If infection is present, antibacterial therapy may be indicated. Roentgen treatment is said to be helpful in chronic cases, but beneficial results may be only temporary, and the dangers of treatment are considerable.

Antihistaminic drugs have not been of great benefit in eczema. The itching may be ameliorated to some extent. Oral therapy is probably preferable to local use, since there is less likelihood of sensitivity developing.

**Specific treatment.** The specific treatment of eczema involves detection of the specific allergens, followed by their removal from the diet or environment or by hyposensitization (see p. 1309). Attention is first directed toward foods as possible allergens, but it should be remembered that contact with wool and with dust and other inhalants may also be causative factors.

In the infant whose diet is limited, elimination diets are the most helpful method of testing (p. 1412). Skin testing is not very helpful in infants for reasons previously noted, though it may be of considerable help in older children. If the offending foods are eliminated and adequate local treatment has been instituted, improvement should be apparent within a week or less. New foods may then be added in small amounts at weekly intervals.

If skin testing is to be carried out, it may



be necessary to use the passive transfer method (p. 1308) in the infant because of dermographism or extensive eczema.

If the eczema is mild, the diet may not need to be altered and treatment may be limited to local measures. Even in mild cases, however, the removal of orange juice should be tried.

Breast-fed infants with eczema should not be weaned except when an item in the mother's diet which cannot be removed is responsible. An elimination diet for the baby consists in restricting intake to breast milk, for the mother in the avoidance of likely allergens or, if indicated, a rigid elimination diet.

Wool should be removed from the immediate environment of the child. Every effort should also be made to eliminate sources of house dust and other inhalants which may be causative. Hyposensitization with house dust may also be tried when the skin test to this substance is positive. Hill recommends smaller doses of the antigen than those used for allergic rhinitis.

**Nonspecific treatment.** Nonspecific measures in the treatment of eczema have been discussed (p. 1311). Measures promoting mild dehydration are particularly helpful in the management of eczema and should be used in association with local and specific measures. In infants it is difficult to reduce the fluid intake without reducing the caloric intake, since many drink little or no water. A lower sodium intake may decrease the tendency to water retention. In debilitated infants, however, dehydrating measures must be avoided.

In stubborn, diffuse eczema corticosteroids may be used systemically as well as locally as previously mentioned. Hormonal therapy should not replace other sound therapeutic measures.

The treatment of skin infection or infection elsewhere in the body with an appropriate orally or parenterally administered antibiotic is an essential part of therapy.

#### ATOPIC ERYTHRODERMA

Some highly allergic infants have a diffuse form of eczema which often leaves the palms and soles as the only areas of skin free of involvement. The presence of a large element of seborrhea in the rash separates this particular form of infantile eczema from the more usual variety. The skin is red, thickened, fissured and scaly. There are varying degrees of edema of the skin and subcutane-

ous tissues during the acute phase and during exacerbations. The vesiculation characteristic of infantile eczema is rarely present. The scaling and thickening of the skin which are striking features of seborrheic dermatitis dominate the picture and produce a strong resemblance to Leiner's disease. In the acute stage the feet and hands are usually cold and bluish. Itching is intense, and much traumatic irritation may result if the child is not properly restrained. General lymphadenopathy is commonly present.

These children are sick: there is loss of appetite, undernutrition and often diarrhea. Irritability may be great, and there may be fatigue from loss of sleep. Eosinophilia and the presence of passive transfer antibodies in the circulation attest the atopic nature of the illness. Passive transfer antibodies against milk, egg, feathers and dust are commonly found.

The course is chronic. Rarely does the eruption clear in less than a year. There are periods when there is spotty clearing of the skin, which soon, however, becomes involved again. Finally, after many months, and with little evidence that the disease is influenced by therapy, there is a gradual disappearance of the eruption.

These children often have other allergic manifestations. They are highly susceptible to infection. Infection in the skin plays a dominant role in the inflammatory features of the eruption, as it does in other types of infantile eczema.

**Treatment** is similar to that described under Infantile Eczema. Owing to the chronicity of the disease, rigid dietary restrictions are inadvisable. Treatment of any existing infection is an important consideration. Hill recommends that egg and wheat be removed from the diet, that a mild tar ointment be used on the face and extremities and petrolatum on the trunk, and that the skin be washed twice a day with pHiso-hex. Temporary relief in critical situations can often be obtained from the use of corticosteroid.

MITCHELL I. RUBIN

#### REFERENCES

- Hill, L. W.: The Treatment of Eczema in Infants and Children. *J. Pediat.*, 47:141, 1955.
- Moro, E.: *Eczema Infantum and Dermatitis Seborrhoides*. Berlin, Springer, 1932.
- Sulzberger, M. B., Witten, V. C., and Smith, C. C.: Hydrocortisone (Compound F) Acetate Ointment in Dermatological Therapy. *J.A.M.A.*, 151:468, 1953.

## URTICARIA AND OTHER ALLERGIC ERUPTIONS

### URTICARIA

The urticarial wheal (hive), the characteristic allergic lesion, is produced by dilatation and increased permeability of the capillaries. It consists of a central edematous area with areolar flush.

**Etiology.** Allergy cannot in all instances be proved to be the cause of urticaria. It seems to be the factor more frequently in children than in adults, foods being the commonest excitants. Though any food may be causative, seafood, especially shellfish, berries, chocolate, egg and milk are the most common offenders. A food which has constantly produced hives may cease to do so when hyposensitization to it has developed after continual ingestion in its original state, or when its allergic potency has been decreased by cooking or other means. Infection and psychogenic factors, which are said to have etiologic significance in the adult, appear to play a minor role in the child.

Localized hives which result from insect bites are often confused with the allergic form. Irregular distribution on an exposed part of the body, the possible exposure to insect (mosquito) bites and the absence of any family or personal history of allergy suggest this etiology. The ingestion or injection of drugs such as penicillin, the sulfonamides, salicylates, phenolphthalein, barbiturates and arsenicals may also be responsible for an urticarial eruption. The reaction, especially to penicillin, may be delayed until after administration of the drug has ceased.

Urticaria also appears as a reaction to injected foreign serum (serum disease) and vaccine. When it follows blood transfusions, it most probably represents an allergic reaction to some antigen in the blood. Urticaria may be an early manifestation of rheumatic fever and is often associated with the severe form of the disease. It may in rare instances be caused by contact with certain foods, insects and silks, and by inhalants.

Physical allergy, especially to cold, is not an uncommon cause. Hives may occur after a cold bath or exposure to cold winds. This type of urticaria can be reproduced by placing iced compresses on the skin. Heat and sunlight can also produce hives.

Skin testing is of little help in the detection of offending allergens; a careful history and the use of elimination diets are most helpful.

**Clinical Manifestations.** The individual wheal may be a macular, erythematous lesion with little edema, or the edema may be the predominant feature with wide extension and pseudopodia. In the infant, hives are usually of the macular type. In severe urticaria small wheals coalesce into large patches which may cover large areas of the body. Frequently the urticarial wheals come out in crops, the older lesions fading as new ones appear. The eruption and the associated itching tend to be more intense at night. Itching often precedes the appearance of the wheal. The individual hive may persist for a few minutes to several hours or days. Those which persist a long time are more often macular, are pinkish, and have little or no edema. Urticaria may persist for some time after an offending food has been eliminated and in drug sensitivity for weeks after the drug has been stopped. Chronic urticaria is uncommon in childhood; the clinical manifestations are similar to those of the acute variety. Erythema multiforme-like lesions or angioneurotic edema is occasionally associated with typical urticarial lesions.

*Angio-edema (angioneurotic edema)*, or giant hive, is a tense, white, nonpitting edema unassociated with itching; it rarely lasts more than a few hours. It commonly occurs as a localized lesion of the ocular area, lips, ears, side of face, tongue or larynx, or may be diffuse and involve legs and arms. When the larynx is involved, tracheotomy may be required as a lifesaving measure. A familial tendency to the laryngeal form has been reported. It has been described in the newborn infant, but occurs more frequently in older children. Various cerebral and cranial nerve disturbances have been ascribed to angioneurotic edema. It may occur in the Schönlein-Henoch syndrome.

**Treatment.** Treatment of mild hives is entirely symptomatic. A cathartic may be given to hasten the elimination of the offending food, and the diet should be light and limited to accustomed foods. In severe cases epinephrine, especially in oil, may be beneficial, as are the corticosteroids. The antihistaminic drugs (p. 1320) have been particularly helpful in the treatment of urticaria.

Sedatives may be necessary when itching is intense. When a large part of the skin is involved, soothing baths may be helpful. Ice cold applications of bicarbonate of soda paste and calamine lotion are also helpful. In severe and persistent cases the nonspecific measures for hyposensitization in allergic children may



be tried. In children the disease is usually self-limited.

MITCHELL I. RUBIN

## REFERENCES

- Duke, W. W.: Clinical Manifestations of Heat and Effort Sensitiveness and Cold Sensitiveness. *J. Allergy*, 3:257, 1932.
- Glaser, J.: Allergy in Childhood. Springfield, Ill., Charles C Thomas, 1956.
- Grant, R. T., Pearson, R. S. B., and Comeau, W. J.: Observations on Urticaria Provoked by Emotion, by Exercise, and by Warming the Body. *Clin. Sc.*, 2:253, 1936.
- Hopkins, A. M., and Kesten, H. D.: Urticaria; Etiologic Observations. *Arch. Dermat. & Syph.*, 29:358, 1934.
- Lewis, T.: The Blood Vessels of the Human Skin and Their Responses. London, Shaw & Sons, Ltd., 1927.
- Morris, R.: Angioneurotic Edema. *Am. J. M. Sc.*, 128:812, 1904.

## ALLERGIC RHINITIS

### HAY FEVER, NONSEASONAL ALLERGIC RHINITIS, VASOMOTOR RHINITIS

**Etiology.** The types of noninfectious rhinitis common in adults also occur in children; these include atopic rhinitis (seasonal hay fever or pollinosis), nonseasonal allergic rhinitis resulting from the inhalation of dust and other antigens, and the so-called non-atopic vasomotor rhinitis resulting from intrinsic factors. MacKinney and Glaser found this symptom in about one third of their allergic patients.

**Clinical Manifestations.** Paroxysmal sneezing attacks characteristic of hay fever during the season of pollen prevalence are common in older children, rare in infants. The sneezing attacks come most commonly on awakening and during the early morning hours, but in more severe cases they recur throughout the day, and cease only with sleep. In mild cases stuffiness and itching of the nose may be the sole complaints; in others, in addition to the sneezing, there is nasal congestion and a profuse rhinorrhea of a thin, watery-mucoid material. The nasal mucous membrane is swollen, boggy and pale, at times almost white. With superimposed infection, which is common, a purulent discharge is present, and the mucous membrane is inflamed. Itching of the palate is common. In about one third of hay fever patients asthma is an associated manifestation.

Intense redness, edema and itching of the conjunctiva are not so common in the child

as in the adult, but may be the only symptoms of pollinosis and may occur seasonally in the child for several years before the onset of nasal symptoms. The intensity of the symptoms is not constant during any single day, nor from day to day during the season.

Eosinophilia (5 to 10 per cent) in the peripheral blood is commonly present; it may be found on some days and not on others. Eosinophilia of the nasal secretions of more than 3 per cent has diagnostic significance, since only rarely does it occur in nonallergic states. It may, however, occur without clinical signs of nasal allergy in a child of an allergic family. The swab used for obtaining nasal secretions must be thin and inserted into the posterior part of the nose, and allowed to remain there for about a minute to collect mucus. If the mucous membranes of the nose are greatly swollen, it is wise to shrink them with a decongestant agent before passing the applicator.

**Diagnosis.** The diagnosis of *hay fever* is established by positive skin reactions to specific pollens or fungi known to be present in the atmosphere at the time when the patient displays symptoms (see p. 1307). Though hay fever may be brought on by the ingestion of foods, most cases result from the seasonal inhalation of pollen or fungi. In order to make an appropriate selection of skin-testing antigens, the physician must know the common pollen offenders of his locality and their pollinating seasons. It is uncommon for pollen from wild or cultivated flowers to cause much trouble unless they are brought into the home. The pollens of most of these are transported by bees, butterflies and insects and, probably because of their weight, are not found in the air far from their source. The offending pollens come mainly from grasses and weeds and, to a less extent, from trees.

*Nonseasonal allergic rhinitis*, in contrast to hay fever, is fairly common during late infancy and early childhood. The usual complaint is that the child's nose is always stuffy, that he makes hawking sounds and is constantly rubbing or picking at his nose. These children seem to be unusually susceptible to colds, and postnasal drip and cough may persist for weeks or months after an acute respiratory infection. Infection may involve the sinuses; in older children mucous polyps may develop, and bronchitis with peribronchial thickening is not uncommon. These children tend to have respiratory disturbances

during most of the winter, but are free of them during the summer months, unless they are also pollen-sensitive.

It has been suggested, but not proved, that bacterial sensitization in the allergic child accounts for his peculiar susceptibility to respiratory infections and is responsible for their chronicity. It is not uncommon for children with an inherited allergic diathesis to retain colds for a long time. The allergic feature of nonseasonal allergic rhinitis often becomes apparent only from a careful history. Nasal and blood eosinophilia constitutes supportive evidence. Positive skin tests to one or more of the common environmental inhalants, such as house dust, feathers, cosmetics and animal hair, are usually obtained.

*Nonatopic vasomotor rhinitis* bears a close clinical resemblance to nonseasonal allergic rhinitis. True atopy, however, cannot be demonstrated, and a positive family history is usually lacking. Vasomotor rhinitis is more common in adults than in children. Some believe that this type of rhinitis results from certain intrinsic factors, as, for example, a low basal metabolic rate, and cite as evidence the relief some adults obtain with thyroid medication. These patients are especially sensitive to cold and drafts; their disturbance may be a sort of physical allergy.

**Treatment.** Measures for the treatment of hay fever have been outlined under Treatment of the Allergic State (p. 1309). The most desirable measure would be complete elimination of the antigen from the environment. However, because the commonly offending grasses and weeds are widespread, this is usually impossible. A decrease in the amount of inhaled pollen can be obtained by filtering the air coming into the room where the child spends all the night and several hours of the day. Since pollination of grasses and weeds is heaviest in the early part of the day, it would be best to keep the child's room closed during these hours and open it in the early evening. When possible, removing the child to a section of the country where the pollens to which he is sensitive do not exist is ideal. When the prevailing winds are from the ocean, the seashore may bring some relief. Long residence in a new section of the country, however, though removing the patient from old antigens, may bring him into contact with new ones to which he becomes sensitized.

Hyposensitization to the specific pollen or pollens to which the patient has been found sensitive should be tried when the preceding

measures do not bring satisfactory relief. When the child is sensitive to many pollens of a given species, treatment with a single representative of the group, because of cross immunization, is usually sufficient. The dosage to be used and the course of injections to be given are described on page 1309. Instillation of constricting agents into the nasal passages brings temporary relief. Aspirin is often helpful when sleep is disturbed. The various nonspecific measures designed to decrease the responsiveness to allergic reactions (p. 1311) are helpful in controlling the more severe cases.

The antihistaminic drugs are helpful adjuncts in the treatment of seasonal hay fever. Hyposensitization and antihistamine therapy may be combined. The dose of antihistaminic drug varies with each patient and, in a given patient, with the symptoms. Relief may be obtained with one antihistamine when another is unsuccessful; long-acting antihistamines are available. Side effects of antihistamines are fatigue, drowsiness, headaches, dizziness, gastrointestinal symptoms and occasionally insomnia, diarrhea or palpitation. Agranulocytic changes have been observed with long-continued administration of Pyribenzamine.

In nonseasonal allergic rhinitis attempts must also be made to determine offending allergens by a detailed history and by skin testing. Treatment consists in removing the offending antigen, such as house dust, fungi or animal danders, from the environment or in hyposensitization by serial injections. A positive skin reaction to dust is commonly obtained in this condition, and treatment with a stock dust extract or preferably with one prepared from dust collected in the patient's home by means of a vacuum cleaner is often beneficial.

In summer, when respiratory infections are at a low ebb, the patient with nonseasonal allergic rhinitis is usually free of symptoms. Autogenous bacterial vaccines made from nasopharyngeal cultures or from bronchoscopic aspirations and given at regular intervals over most of the fall and winter months have seemed to be of benefit in some instances, but there is also considerable skepticism concerning their effectiveness. The combined injection of dust extract and a bacterial vaccine has seemed to be better than the use of the vaccine alone. Some observers believe that vaccine therapy is beneficial in a non-specific manner. Tonsils and adenoids should be removed only if infected; the operation



should not be performed during pollen seasons, since there is suggestive evidence that asthma may be induced in this manner in allergic children.

In persistent and severe cases removal of the patient to a warm, dry climate for the fall, winter and early spring seasons may be distinctly beneficial. The child will, of course, retain his allergic sensitizations, and nasal catarrh may persist. As the child grows older there is a tendency to lose the susceptibility to infections, and the catarrhal symptoms become less prominent, though hay fever or asthma may develop.

## ASTHMA

**Etiology.** Asthma is an allergic pulmonary disorder characterized by paroxysms of an expiratory type of dyspnea with wheezing and by generalized obstructive emphysema. The similarity between induced anaphylaxis in the guinea pig and human asthma strongly suggests a common mechanism for these two conditions. Infantile eczema and allergic rhinitis are common forerunners of asthma.

There is an apparent tendency in allergic persons for areas of localized edema to develop, especially in their upper and lower respiratory passages; this has been termed the "exudative diathesis." Frequently, after hearty laughter or vigorous activity, they have considerable secretion in their bronchi which produces a cough and, in some instances, mild respiratory distress with wheezing respirations. Exposure to cold, inhalation of cold air, smoke or mildly irritating gases may also induce a mild asthmatic attack. Psychic factors also seem to play an important etiologic role; smooth muscle and vasomotor tone are greatly influenced by emotional factors.

The frequency with which respiratory infection precedes the asthmatic attack has led many workers to consider bacterial sensitization the most important cause of asthma in children. There is little evidence to support this view, but considerable that infection often precipitates the asthmatic attack.

The common occurrence of asthmatic attacks at night has been variously explained. In some cases nocturnal attacks may depend on the presence of a feather pillow, cotton mattress or other inhalant antigen in the bedroom. Another possibility is that during sleep the cough reflex is depressed, permitting secretions to accumulate and obstruct the bronchial lumens, or the reduced vital capac-

ity resulting from the horizontal posture may also help to induce respiratory distress.

**Pathology.** The greatest changes are in the smaller bronchioles. In the early stage of the acute attack the essential changes are spasm of the bronchiolar musculature and edema of the mucous membrane, each of which obstructs the flow of air. The mucous membrane is pale and boggy. As the attack continues, thick, tenacious mucus fills the tubes, further obstructing the passage of air. In the acute case the muscular spasm soon relaxes, the patient coughs up the mucus, and the attack subsides within a few hours to two or three days. When infection is present, vascular congestion and polymorphonuclear infiltration of the bronchial walls, with increased exudation into the bronchial lumen, increase the respiratory embarrassment.

During the asthmatic attack not all the inspired air is exhaled; some of it is trapped in the alveoli, resulting in generalized obstructive emphysema. Wheezing results from air passing through the narrowed bronchiolar lumens, and rales are produced by the bronchial secretions. One or more of the larger bronchi may be completely obstructed by tenacious mucus, in which case atelectasis may develop. In the chronic forms of asthma, which are uncommon in children, the lining of the bronchioles is thickened by increased vascularization and eosinophilic infiltration. The goblet cells are increased; hyalinization of the basement membrane occurs, and the musculature and mucous glands are hypertrophied. As a result of long-standing respiratory obstruction, persistent emphysema develops. The dome of the diaphragm is depressed, reducing its functional activity, the ribs are maintained in the position of inspiration, and the respiratory effort becomes ineffective. When an acute asthmatic episode supervenes, breathing is almost impossible, and death from cardiac failure may occur.

**Differential Diagnosis.** As Jackson has emphasized, all that wheezes is not asthma. An aspirated foreign body may produce a distinct respiratory wheeze which must be differentiated from that of true asthma. Cardiac asthma is rare in children.

In so-called *asthmatic bronchitis* there is a certain amount of respiratory distress and wheezing, and musical rales are present on auscultation. There is no eosinophilia and no relief from epinephrine. In some children this tendency is so marked as to suggest a peculiar constitutional type of reaction. As

the child grows older the tendency to spasmodic bronchitis disappears. During the first attack it is not always possible to determine whether allergic asthma is a factor. The presence of a positive personal or familial history of allergy, of eosinophilia, and of response to epinephrine suggest an allergic basis for the attack.

Generalized obstructive emphysema in infants is most often due to factors other than allergy, such as primary bronchiolitic infection or infection superimposed upon aspiration pneumonia or infection associated with cystic fibrosis of the pancreas.

**Clinical Manifestations.** Asthma is uncommon in infancy, becoming more frequent after two or three years of age. Attacks of asthma which do occur in infants may be somewhat atypical. Acute respiratory distress, more evident in expiration, with shocklike symptoms may constitute the principal manifestation. Wheezing and musical rales may be absent. It is essential to recognize that asthma may present such a clinical picture in the infant and that the administration of epinephrine may be lifesaving. When the asthmatic attack is due to pollen sensitivity, there is little difference in the symptomatology of the child and the adult. Nasal congestion with sneezing and watery discharge usually precedes the attack by a few hours to a few days, and the child is often thought to have a head cold. Fever is usually absent, even in the presence of active infection. A slight cough may precede the attack, at this time musical rales may be heard, and the patient may complain of a sense of heaviness in the chest.

An attack of asthma may be ushered in with great suddenness, often during the night, with respiratory distress and noisy, wheezing breathing. The older child sits up in bed in an effort to secure better aeration. Sweating is prominent, the facial expression anxious, and the child appears in great distress. Respirations are thoracic; the chest is distended and the abdomen fixed. Expiration is prolonged, and most of the wheeze occurs during this phase of breathing. A short, ineffective or deep harassing cough may be more or less continuous, further exhausting the child.

The chest is hyperresonant to percussion, the breath sounds are weak, and when little exchange of air occurs, not much wheezing will be heard. Sibilant and musical rales often obscure the breath sounds. Occasionally a

bronchus becomes plugged with the thickened tenacious mucus and produces atelectasis in the supplied lobe. The mediastinum is then shifted toward the involved side. Heart action is rapid and during severe attacks may be weak; cardiac failure is uncommon in children. The neck veins are distended, and cyanosis may be marked.

When treatment is effective, the attack may be abruptly terminated. Otherwise it may continue for several days, gradually decreasing in intensity, but often with intervals of exacerbation.

The sputum may contain plugs of mucus in spirals, and eosinophils. The blood cell count in uncomplicated cases is little changed except at times for a moderate increase in eosinophils. In the absence of infection the erythrocyte sedimentation rate is normal.

The presence of acute infection modifies asthma in many ways. The onset is less abrupt, but the difficulty in respiration progressively increases to the typical asthmatic type. The response to epinephrine is poor, owing to the inflammatory changes. Fever and leukocytosis are likely to be present. Recovery is slow, and it is often a week or several weeks before the patient is completely restored to good health. Musical rales and cough persist long after evidences of dyspnea have gone. Recurrent attacks of bronchopneumonia may complicate the course of chronic asthma, and roentgenograms taken between acute episodes show evidence of bronchial and peribronchial thickening.

*Status asthmaticus* is intractable asthma which may persist for days with little relief even during sleep, resulting in great exhaustion of the patient. In rare instances it may occur early in the course of asthmatic disease, but is more common in cases of long standing. Death from asthma is rare, but may occur during status asthmaticus.

**Prognosis.** Though there is a tendency for asthma in children to subside at puberty, many cases continue throughout life and even become worse. Children who lose their asthma may acquire hay fever or some other allergic phenomenon. Allergic sensitivities change; the child who loses his sensitivity to foods may become sensitive to an inhalant.

The prognosis of asthma is greatly influenced by management, especially when one is able to identify a causative antigen or antigens. Best results are obtained when treatment is begun early. In some instances there appears to be some intrinsic factor which



cludes control and makes the prognosis less hopeful. Chronic respiratory infection obviously has an unfavorable influence.

Rackemann and Edwards determined the status of 449 adults twenty years after the onset of asthma during childhood. Of these, 30 per cent were entirely relieved of their symptoms; 19 per cent had no symptoms because they successfully avoided the offending causes of their asthma; 21 per cent no longer had asthma, but had some other allergic manifestation, usually hay fever; 26 per cent still had asthma of some degree, but in only 11 per cent was it considered serious; only 1 per cent had died of asthma. Asthma seen after thirteen years of age tends to have a less favorable prognosis.

**Treatment.** The most successful therapy is elimination of the offending allergens. Since in many cases the allergens cannot be determined, and in others cannot be successfully removed, other methods of treatment must be applied. Hyposensitization to antigens thought to be causative as revealed by a carefully taken history, by skin tests or by elimination regimens is often successful. The methods of testing for specific allergens and for hypersensitivity have been described on page 1307. Though asthma is more often caused by inhalants than by ingested foods, elimination diets are at times indicated as diagnostic and therapeutic procedures. Complete or partial elimination of pollen or other environmental allergens as described under the treatment of allergic rhinitis is often effective in preventing the asthmatic attack. Nonspecific methods to decrease the responsiveness of the allergic patients (p. 1311) should be carried out. When such factors as exertion, emotional upsets, exposure to cold and inhalation of irritating gases and chalk have been found to induce an attack, they should be avoided.

Epinephrine is by far the most effective drug for the relief of asthma, improvement usually being manifest within a few minutes after its injection. There is no reason to withhold it until the attack has become severe or the child is exhausted. There is little evidence that doses of 0.2 to 0.3 cc. of a 1:1000 solution, injected hypodermically several times a day for many days, are harmful. Small doses are as effective as larger ones in relieving the asthmatic attack, will not evoke the disagreeable side effects of pallor, tachycardia and sweating, and may be repeated every hour or half-hour if necessary. Though the response to epinephrine is not so striking when an in-

fection is present, it should still be administered.

Long-acting preparations of epinephrine in oil, 0.5 to 0.7 cc. of the latter, injected intramuscularly, may provide relief for twelve to sixteen hours. If a separate injection of the standard epinephrine is made simultaneously with the first injection of the one in oil, an immediate as well as a prolonged effect may be obtained.

Epinephrine may also be effectively administered by pharyngeal spray in a 1:100 dilution by the parent or the older child himself. A special glass nebulizer is required; benefit will result only if the epinephrine is sprayed deeply into the pharynx at the time of a full inspiration. Two or three compressions of the bulb of the atomizer will deliver sufficient epinephrine to bring relief of symptoms within a few minutes. If need be, the application may be repeated in one-half to one hour, but too frequent use may injure the bronchial mucous membrane. Under no circumstance should the 1:100 dilution of epinephrine be injected hypodermically; serious or even fatal reactions may occur.

There is rarely indication for the intravenous administration of epinephrine. It may be used as an emergency measure in severe status asthmaticus, but even in this case only small amounts diluted in saline solution should be injected intravenously.

Occasionally some resistance to the therapeutic effect of epinephrine is acquired after prolonged use, and larger doses are required to obtain the desired effect. The temporary use of aminophylline has been said to restore the normal reaction to epinephrine.

Ephedrine sulfate or hydrochloride is useful in controlling mild attacks of asthma and for the relief of cough. The dose for infants is about 8 mg. and for older children 15 mg. Ephedrine, 15 mg., may be combined with phenobarbital, 15 mg., and aminophylline, 30 to 60 mg., in a cough syrup (doses are average for a child of five years). Some believe that acetylsalicylic acid heightens the effect of ephedrine and combine the two in powders. Aqueous solutions of ephedrine may be used locally for the relief of nasal congestion.

Aminophylline (ethylenediamine) is an effective bronchodilator. In severe cases it may be injected intravenously in doses of 3.5 mg. per kilogram. The injection should be given slowly over a period of at least ten minutes. It may be administered undiluted, but preferably should be diluted in 150 to

200 cc. of 10 per cent glucose solution. If vomiting is induced, subsequent doses should be smaller or injected more slowly. It may not be repeated in less than six hours, and preferably less frequently. Nausea, circulatory disturbances and syncope may result from overdosage, and fatalities have occurred. Aminophylline is especially indicated when epinephrine has lost its effectiveness. It may be given orally in doses of 5 mg. per kilogram for the control of mild episodes or as a prophylactic measure, when it may be combined effectively with ephedrine and phenobarbital. Good results may also be had with rectal administration of aminophylline in a suppository in doses of 7 mg. per kilogram.

Antihistaminic drugs are useful in the treatment of asthma, but less so than in hay fever or urticaria.

In severe and uncontrollable asthma, especially in status asthmaticus, a corticosteroid may bring about dramatic relief. Improvement is often noted within four or five hours, but may be delayed. Therapy in full dosage may be necessary for only a few days, since benefit may persist after treatment has been stopped. In the chronic forms of asthma more prolonged therapy with smaller doses may be necessary. During hormonal therapy other methods of treatment should not be neglected.

The atropine group of drugs dries secretions and makes their expectoration more difficult. These effects often outweigh the benefits obtained from decrease in the spasm of bronchial musculature.

Fumes from the combustion of stramonium leaves may relieve a mild attack, but other forms of therapy are so much more effective that this method is now little used.

Potassium iodide is a valuable drug in the treatment of long-standing asthma because of its property of liquefying bronchial mucus. The drug should be given in increasing doses until there is an increase of bronchial secretion, and then the dose reduced slightly so that overproduction of mucus will not aggravate the cough. The patient should be watched closely for toxic effects; if these occur, the drug should be discontinued. Syrup of ipecac may also be used as an expectorant; if vomiting is produced, other expectorants may be used. When secretions are sticky and thick, it is important to provide a generous fluid intake.

Sedation is often necessary during the asthmatic attack so that apprehension may be

relieved and sleep obtained. Phenobarbital can be used with safety in relatively large doses. Chloral hydrate is useful when the patient is stimulated rather than sedated by barbiturates. Morphine should never be used during an asthmatic attack, since it produces bronchial spasm and may so depress the cough reflex that the child is actually drowned by the accumulated secretions. Paraldehyde diluted in olive oil and administered rectally is a most effective and prompt sedative, an effect usually being produced within fifteen minutes and lasting ten to twelve hours. Overmedication must be avoided.

Oxygen is of great value in reducing anoxia and cyanosis and is best administered in a tent. Its effectiveness is said to be increased when given in combination with helium in a ratio of 20 per cent oxygen to 80 per cent helium. The combination of carbon dioxide in a 10 per cent mixture with oxygen is said to be of help in liquefying the mucoid secretions. The humidity of the room atmosphere or oxygen tent should be kept relatively high.

In status asthmaticus when all else fails or when extensive atelectasis exists as the result of a plugged bronchus, bronchoscopic aspiration may free the airway.

When bacterial infection complicates the asthmatic episode, specific antimicrobial therapy is indicated. Every effort should be made to prevent respiratory infections as a prophylactic measure for the reduction of asthmatic attacks. Removal to a warm, dry climate during the winter season may be the only means of reducing the incidence of respiratory infections. A feather pillow, however, may cause as much trouble in the deserts of Arizona as on the damp, windswept North Atlantic coast.

Bacterial vaccines have been used extensively in attempts to reduce the incidence of respiratory infections and to induce hypersensitization to bacterial antigens. Theoretically, autogenous vaccines prepared after determining sensitivity to the organisms by skin testing should be more effective than the usual stock vaccines. In most cases vaccine therapy seems of little value. Most observers feel that beneficial results, if any, are due to nonspecific effects, and some suggest the use of a single bacterial vaccine (*Staphylococcus*) in all cases. The combination of dust extract with a bacterial vaccine is widely used.

In patients with recurrent or chronic asthma, when infection in the upper respiratory tract is difficult to control and the adenoid tissue is hyperplastic, irradiation



with radium is used to reduce the lymphoid hyperplasia. This method is not without serious danger and certainly is at best rarely indicated and should be used only by persons skilled in the use of radium.

In all cases the general health of the child should receive adequate attention. This includes a properly balanced diet and the proper amount of sleep at night, and afternoon rest periods when they are indicated. Attention should be given to the control of house dust and other inhalants within the home, including strong odors from foods to which the child is sensitive. Removal of animal pets with fur or feathers from the household regardless of the results of skin tests is essential.

Emotional factors play a significant role in the production of asthmatic attacks, and family guidance and psychotherapy are often of great benefit.

MITCHELL I. RUBIN

#### REFERENCES

- Barach, A. L.: The Use of Helium in the Treatment of Asthma and Obstructive Lesions in the Larynx and Trachea. *Ann. Int. Med.*, 9:739, 1935.
- Glaser, J.: Allergy in Childhood. Springfield, Ill., Charles C Thomas, 1956.
- Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma. *J. Allergy*, 6: 150, 1935.
- Rackemann, F. M., and Edwards, M. C.: Asthma in Children (a Follow-up Study). *New England J. Med.*, 246:815, 858, 1952.
- Rogerson, C. H., Hardcastle, D. H., and Duguid, K.: A Psychological Approach to the Problem of Asthma and the Asthma-Eczema-Prurigo Syndrome. *Guy's Hosp. Rep.*, 85:289, 1935.
- Sherman, W. B., and Kessler, W. R.: Allergy in Pediatric Practice. St. Louis, C. V. Mosby Co., 1957.
- Shulman, L. E., Harvey, A. McG., Howard, J. E., and Schoenrich, E. H.: Clinical Studies with ACTH in Bronchial Asthma; in *Proceedings of the Second Clinical ACTH Conference*. Philadelphia, Blakiston Company, 1951, Vol. 2, p. 401.
- Tuft, H. S.: The Development and Management of Intractable Asthma in Childhood. *A.M.A. Am. J. Dis. Child.*, 93:251, 1957.

#### SERUM SICKNESS

**Etiology.** Serum sickness will occur in nearly all persons, whether atopic or not, provided the amount of foreign serum injected is sufficiently large. When 100 ml. or more of foreign serum are given to an adult, serum sickness will occur in 90 per cent of instances. If less than 10 ml. are given, only about 10 per cent of persons will have a reaction. Fresh serum evokes a stronger reaction than older, stored serum. The Negro

and the American Indian are said to be less susceptible than the white race, but age and sex do not appear to be influencing factors.

The serums from different animals vary in their capacity to evoke reactions. By far the commonest cause of serum sickness is the parenteral administration of horse serum. Hog serum is as antigenic as horse serum; beef serum produces fewer reactions; avian serum is reported to produce none at all, and human serum rarely produces serum disease. Penicillin may infrequently induce a similar clinical response.

The most widely accepted explanation for serum sickness which follows the first and only injection of a foreign serum is the one proposed by von Pirquet and Schick: The injection of the serum incites the production of antibodies, which unite with the remaining portion of antigen (serum) to produce the allergic reaction. Passive transfer antibodies appear about the same time (eight to twelve days) as specific precipitins. Heterophile antibodies are also frequently present after the administration of horse serum. These antibodies may persist for years.

In persons previously sensitized to horse serum a subsequent injection of this serum usually induces an immediate reaction. Minute amounts of horse serum (such as is contained in diphtheria toxin-antitoxin) are sufficient to sensitize a person for years. The ingestion of horse serum or horse meat also incites sensitivity to horse serum. Such persons react immediately or within a few hours after the injection of serum. The reaction is likely to be more severe than in the usual serum sickness and may be fatal. Most fatal reactions, resembling anaphylactic shock, have occurred in atopic persons sensitive to horse serum or dander.

Necrotizing arteritis and periarthritis of the small arteries and endocardial lesions have been described.

**Clinical Manifestations.** The reaction usually follows an average incubation period of about seven days; however, it may occur within a few hours or may be delayed as long as thirty-six days. The most striking or characteristic symptom is the skin eruption, the most common lesion an urticarial wheal. These occur first at the site of the serum injection and may spread out in concentric rings. Soon the eruption appears over the entire body, being more prominent in regions of local pressure. Less commonly the eruption may be erythematous, morbilliform or scarlatiniform. Rarely an exanthem occurs; its

absence is a differential point from the various exanthematous diseases. Purpura and exudative eruptions may occur in the more severe cases.

Angioneurotic edema often is a striking feature of the reaction. It may be limited to the eyelids, lips, tongue, pharynx, hands or feet, or it may be generalized, resembling the edema of nephrosis. Itching is marked in practically all instances. Generalized lymphadenopathy is frequently present, and the enlarged nodes are tender, especially those draining the injected area. The spleen is often enlarged. Swelling, redness, pain and stiffness of the joints, usually the larger ones, are not infrequent; a single joint may be involved. There may be widely distributed muscular pains, and headache and malaise are frequent. Fever may be an early or late manifestation, at times antedating the eruption by two or three days. It is usually remittent and varies considerably in degree. When it appears before the onset of the eruption, much diagnostic confusion may arise. In severe cases neurologic complications such as neuritis, polyneuritis and cerebral manifestations with delirium, vomiting and convulsions have been described. Evidences of damage to the central nervous system have persisted for several months. The blood shows a slight leukocytosis often followed by leukopenia with eosinophilia. The erythrocyte sedimentation rate is usually moderately elevated.

Serum sickness in the previously sensitized person usually presents the same symptoms as in the nonsensitized except that they are manifest within a few hours and are more often associated with asthmatic symptoms and circulatory disturbances resembling anaphylactic shock.

**Prognosis.** Serum sickness is a self-limited disease. In the usual case it lasts one to three days; in about one third of the cases it lasts four to seven days, but may last even longer. In some instances the symptoms may subside and recur once or twice after intervals of a few days; a plausible explanation is that various fractions of the serum have different "incubation" periods.

**Prevention.** Before the injection of any foreign serum, the recipient should be tested for sensitivity. Normal horse serum rather than the therapeutic horse serum should be used, since falsely positive reactions may occur when the therapeutic serum is used as the testing material. An intradermal injection of 0.02 ml. of a 1:10 dilution of horse serum should be made. When there is a history of

asthma, hay fever or some other allergic disease, or when a hypersensitivity to horse serum or dander is known to exist, 0.02 ml. of a 1:100 or, preferably, a 1:1000 dilution of the serum should be used. If the weaker dilutions do not induce a reaction, a stronger one should be used after twenty minutes. In hypersensitive persons even this small amount of serum may produce severe generalized or even fatal reactions. Hypersensitivity varies, and the person may be able to take the second injection of serum with little effect. With a history of horse dander sensitivity, therapeutic serums from another animal species should be secured if possible. The ophthalmic test may also be used as a guide in determining the degree of sensitivity in the patient, using a drop of a 1:10 dilution for the first test and undiluted serum for the final test. Antihistaminic drugs have been recommended as prophylactic agents in serum disease.

**Treatment.** Epinephrine should always be available when the skin test is made for serum sensitivity or when serum is injected. It is of great value in controlling the anaphylactic symptoms as well as the urticarial eruption. Several doses may be required to keep the symptoms under control. Ephedrine may be used in the milder cases or after epinephrine has partly controlled the symptoms. The antihistaminic drugs and, in severe cases, a corticosteroid should be given for about seven days.

Cold compresses of a 5 per cent solution of sodium bicarbonate and starch baths help relieve the itching. Histaminase may be tried, but has not been particularly effective. Salicylates and sedatives may help make the patient more comfortable.

MITCHELL I. RUBIN

#### REFERENCES

- Kojis, F. G.: Serum Sickness and Anaphylaxis. *Am. J. Dis. Child.*, 64:93, 313, 1942.
- Pirquet, C. F. von, and Schick, B.: *Die Serum Krankheit*. Vienna, Franz Deuticke, 1905.
- Rose, B.: Studies on Blood Histamine in Patients with Allergy. II. Alterations in the Blood Histamine in Patients with Allergic Disease. *J. Clin. Investigation*, 20:419, 1941.
- Rutstein, D. D., Reed, E. A., Langmuir, A. D., and Rogers, E. S.: Immediate Serum Reactions in *Man. Arch. Int. Med.*, 68:25, 1941.
- Sherman, W. B., and Kessler, W. R.: *Allergy in Pediatric Practice*. St. Louis, C. V. Mosby Company, 1957.

#### GASTROINTESTINAL ALLERGY

**Etiology.** Gastrointestinal symptoms, such as vomiting and diarrhea, may accompany



other allergic manifestations, and under these circumstances do not necessarily represent an antigen-antibody reaction in the intestinal wall as the shock organ. There are instances, however, when the gastrointestinal tract does represent the shock organ in the allergic response, and the symptoms produced depend on such typical lesions of atopy as edema, excessive secretion of mucus and smooth muscle spasm in the intestinal wall. Edema of the tongue and palate has been noted when certain foods are eaten. Topical application of foods to exposed intestinal mucosa (colostomy) or the rectal mucosa through a proctoscope in sensitized persons produces localized edema with discharge of mucus. Intestinal spasm has been demonstrated roentgenographically, and pylorospasm by increased gastric peristaltic waves, when offending allergens are ingested.

The frequency of gastrointestinal allergy is difficult to estimate, owing to the varied causes of diarrhea, vomiting, colic and abdominal pain in children and the limitations of specific diagnostic procedures.

**Clinical Manifestations.** The chief manifestations of gastrointestinal allergy in children are vomiting, colicky abdominal pain, and diarrhea. Colicky pain and diarrhea, the stool containing much mucus and sometimes blood, are more characteristic of intestinal allergy in young infants. Fries points out that the portion of the alimentary tract involved determines the location of the abdominal pain. There is wide disagreement as to the frequency with which infantile colic is caused by allergic hypersensitivity; most observers believe it is infrequent.

In a group of newborn infants who had allergic intestinal symptoms after sensitization to cow's milk the clinical pictures were strikingly similar. About three weeks after cow's milk feeding had been instituted colic appeared and became progressively worse. The infants seemed excessively hungry, but gained weight at more than the usual rate. Within a few days after the onset of abdominal symptoms, loose stools appeared and soon contained mucus and bright red blood. The amounts of blood varied from small pinhead-sized clots well mixed with the slimy stool to profuse hemorrhage containing no fecal matter. In two patients the colicky pains were associated with visible, large, gastric peristaltic waves, indicative of pylorospasm. The bleeding and clotting times were normal. In each case there was prompt and complete disappearance of the blood from the stools

within forty-eight hours after withdrawal of cow's milk from the diet. The mucus in the stools and the colic disappeared shortly afterwards. Most of these infants subsequently had eczema; one had asthma. Bachman and Dees consider cow's milk responsible for most instances of gastrointestinal allergic disorders.

Symptoms resembling those of celiac disease are infrequent in older infants with milk allergy. Davidson and Burnstine reported a celiac-like disorder in a three-months-old infant fed cow's milk. The disturbance was characterized by steatorrhea in which both saturated and unsaturated fatty acid fractions increased in the stool with ingestion of milk. They demonstrated that steatorrhea occurred when betalactoglobulin was fed, and the diarrhea and steatorrhea were relieved when the substance was removed from the diet. This is one of the few instances in which a celiac-like syndrome was proved to result from ingestion of a purified protein substance. The celiac syndrome induced by the feeding of wheat and rye gluten is considered not to be a hypersensitivity phenomenon by most workers. This does not preclude the possibility that celiac disease may be caused by hypersensitivity to other foods.

Henoch's purpura with hemorrhage, edema of the intestinal wall with occult blood in the stools, and ecchymoses in the peritoneum are occasional allergic manifestations. Mucous colitis is occasionally seen, and the so-called spastic colon is not an uncommon finding in asthmatic children.

**Diagnosis.** There is too great a tendency to brand all sorts of gastrointestinal disturbances as allergic; the diagnosis of gastrointestinal allergy is most difficult to prove. The diagnosis is aided if there is a family history of allergy or if the patient evidences other allergic manifestations. Skin tests are generally unreliable. Diagnosis is based principally on the disappearance of symptoms when a suspected food is removed and on the return of symptoms when it is again ingested. This therapeutic test has greater significance when the test substance is as purified as possible and is in small quantity. An intestinal disorder following food ingestion does not prove the existence of allergy; the disorder may result from food "intolerance." The leukopenic index does not seem to be a reliable test for the demonstration of food allergy. Large numbers of eosinophils in the mucus of the stools are suggestive of allergy in persistent gastrointestinal disturbances; their absence does not exclude the diagnosis.

**Treatment.** Treatment of gastrointestinal allergy consists in elimination of the offending food. When an essential food is involved, substitution must be made with discrimination; in place of cow's milk, goat's milk or one of the milk substitutes may be prescribed. When the symptoms are mild, alteration of the antigenicity of cow's milk by cooking may suffice. Oral hyposensitization may be successful. Belladonna or one of the other antispasmodics may be helpful in counteracting intestinal spasm. In allergic families every effort should be made to have the infant breast-fed.

MITCHELL I. RUBIN

#### REFERENCES

Bachman, K. D., and Dees, S. C.: Milk Allergy. *Pediatrics*, 20:400, 1957.

- Davidson, M., and Burnstine, R.: Steatorrhea Related to a Factor in Cow's Milk. *A.M.A. Am. J. Dis. Child.*, 93:45, 1957.
- Glaser, J.: Symposium on Colic-Moderator. *Pediatrics*, 18:828, 1956.
- Lippard, V. W., Schloss, O. M., and Johnson, P. A.: Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein. *Am. J. Dis. Child.*, 51:562, 1936.
- Pratt, E. L.: Food Allergy and Food Intolerance in Relation to the Development of Good Eating Habits. *Pediatrics*, 21:642, 1958.
- Rubin, M. I.: Allergic Intestinal Bleeding in the Newborn; A Clinical Syndrome. *Am. J. M. Sc.*, 200:385, 1940.
- Walzer, M., Gray, I., Strauss, H. W., and Livingston, S.: Studies in Experimental Hypersensitiveness in the Rhesus Monkey. IV. The Allergic Reaction in Passively Locally Sensitized Abdominal Organs (Preliminary Report). *J. Immunol.*, 34:91, 1938.



# The Eye

## EYES OF THE NEWBORN INFANT

The eyes at birth are physiologically and anatomically immature. This immaturity is only relative, since the body as a whole grows seven times as much as the eyes after birth. Furthermore, the eye develops earlier and more fully in the embryonic stage than do most other parts of the body.

At birth the eye is three quarters of the adult size. The orbital outlet is circular rather than horizontal. The cornea measures 10 mm., compared with the 12-mm. diameter of the adult cornea. The sclera is thin, resulting in a bluish tint. The lacrimal gland is small, and no tears appear when the baby cries until the third or fourth week after birth. The macula is not completely developed until shortly after birth; the fovea continues to be further differentiated for about sixteen weeks. The angle of the anterior chamber contains mesodermal tissue, in some cases until the third postnatal month. Medullation of the optic nerve is not completed until the third postnatal month.

The eyes remain closed most of the time in the early postnatal days and are sensitive to light. By the end of two weeks the infant is able to look at large objects, but does not follow them. By four or five weeks he can look at relatively small objects, and by eight to ten weeks he follows moving objects and turns his head away from bright light. Then there is a gradual increase in visual acuity, binocular vision and binocular movements, including rotations, convergence and conjugate movements.

The baby's eyes should be examined with and without dilatation of the pupils, preferably before he leaves the hospital.

The neonatal fundus, particularly in the premature infant, shows gray pallor of the nerve head, absence of pigment and grayness in the periphery of the retinas; the veins and arteries are more nearly alike in size and color than in the adult. Remnants of the hyaloid artery and of the pupillary membrane

are more marked in the newborn and continue to atrophy.

Intracranial hemorrhage in the newborn is usually associated with hemorrhage in the fundus without papilledema. Unfortunately the fundus is rarely examined to detect this diagnostic aid.

## EXAMINATION

**General Examination.** Examination of the eyes of a child can be more thorough than is generally believed.

The *eyelids* are examined for crusts, ulceration of the margins and position of the lacrimal puncta. Pressure with the index finger over the lacrimal sac may express mucous or mucopurulent material through the puncta. The ability to open and close the lids should be tested.

The *conjunctiva* is examined for color, smoothness, thickness, secretion, injection, follicles and papillae, and for the presence of a foreign body. Everting the upper lid is a maneuver worth learning to execute smoothly. The child is asked to look down at his toes; the examiner then grasps the lashes with his right thumb and index finger; he pulls the lid downward and away from the globe, placing a probe, or his other index finger, at the upper level of the tarsal plate. The right fingers pull the eyelid upward and slightly outward, over the finger or probe. The lid is kept everted by holding the thumb against the brow and reminding the child to keep looking downward. Foreign bodies are usually found in the concavity just above the margin of the lid.

The *sclera* is examined for blueness, indicating thinness. The intraocular pressure can be estimated by palpation with both index fingers through the skin of the lid above the tarsus. It can be measured accurately only with a tonometer after local anesthesia (Pontocaine or Ophthaine, 0.5 per cent) or under general anesthesia.

The *cornea* is examined for luster, ulcera-

tion, foreign body, new blood vessels, and scars. The diameter of the cornea should be appraised. Megalocornea is a benign condition to be differentiated from a large cornea which is part of generalized enlargement of the globe in congenital glaucoma. Microcorneas are often associated with other congenital anomalies and sometimes herald glaucoma. Keratoconus is not common in children.

The *anterior chamber* is examined for depth by estimating the distance between the cornea and the iris. A small bright beam of light held at an oblique angle while the examiner looks through a magnifying glass will detect cells or fibrin or vitreous in the chamber.

The *iris* should be examined for color, surface markings and for reaction to light and to accommodation-convergence. The latter is tested by observing both pupils in equal light while the patient looks at a distant object and then at the examiner's finger. Adhesion of the iris to the cornea or the lens should be looked for.

The clarity of the *lens* can be examined by the ophthalmoscope with a plus 8 lens held a few inches away from the patient's eye.

**Fundal Examination.** Dilatation of the pupil is essential for adequate examination of the *fundus*, especially in children who tend either to watch the ophthalmoscope light or to look around the room. Dilatation can be done quickly and effectively with one drop of 5 per cent Neosynephrine plus 5 per cent eucatropine (Mydriatin or Eucadryl) in a solution of methyl cellulose. Homatropine is also effective, but atropine is not safe for the newborn infant except in ointment form, which prevents absorption from the nasal mucous membrane. Cyclogyl is an excellent cycloplegic agent. The lens and vitreous are examined for opacities. The nerve head is examined for shape, color, character of its margins, type of cupping and evidence of edema. The macula should be examined for the cherry-red spot of Tay-Sachs disease and for chorioretinal lesions which usually indicate toxoplasmosis. Each vein and artery should be followed from the disk to its termination. Much more of the fundus can be seen if the child is directed to look up, down, right, and left as the doctor examines the corresponding portions of the fundus. One should not hesitate to examine children under general anesthesia if the information desired is of sufficient importance. If the examination is done under anesthesia, it is

essential to have forceps to steady and move the globe, which rolls upward during sleep.

**Visual Tests.** Testing of visual acuity can be accomplished after three and one-half years of age by the use of a Snellen **E** chart, consisting of rows of the letter **E** in various sizes corresponding to the regular visual test chart. The **E**'s have their "fingers" pointing upward, right, down, and left. Cooperation is obtained more easily by having the child place his fingers on the chart itself, indicating the position of the "fingers" of a few of the **E**'s; the chart is then moved 20 feet away, and the child is asked to continue to show which way the "fingers" point by extending his own fingers in the same direction. Picture charts are less accurate.

Before the age of three and one-half years vision can be determined roughly by testing the pupillary reactions to light or by determining the response of the child to a rubber ring, a 1-inch cube or marbles of various sizes and colors. His ability to watch a light with each eye separately is another good rough measure of visual acuity. If the child loses interest or behaves badly when one eye is covered, but cooperates well when the other eye is tested, vision is probably reduced considerably in the first eye.

The *field of vision* can be tested by the confrontation method until the child is old enough to cooperate on a perimeter. With patience and a projection-type of perimeter accurate visual fields can be elicited at an earlier age than one would suppose.

*Color blindness* can be tested by use of colored wools or having a child trace numbers on an Ishahara or A.O. Color Chart with his finger. Defective color vision is much more frequent in the male than in the female. "Color ignorance" refers to inability to tell shades of color; this condition responds to education.

Mothers inquire about and suspect *mirror vision* far more often than it occurs. It is probable that children often reverse letters on an experimental basis, just as they use toys in unexpected ways. This is a transient form of mirror vision. Rarely one sees a child who actually has true mirror vision. Patient re-education of the child's reading habits is then necessary. The parents should be reassured that the eyes and brain are both normal, and that the problem is to teach the child to interpret what he sees as other people do.

Subnormal *dark adaptation* is difficult to test in young children. Vitamin A deficiency is the only causative condition amenable to



treatment. Retinitis pigmentosa and choroideremia and atrophy of the optic nerve represent reduction in the peripheral field, rather than poor dark adaptation.

**Examination by the Child's Physician.** Routine examinations of the eyes should include (1) the use of a Snellen E or letter chart; (2) examination of motility of the eyes by checking rotations, the near-point of convergence and movements with the cover-test as described under *Strabismus*; and (3) examination of the media and fundi with an ophthalmoscope.

Visual screening tests of children in offices and in schools has proved to be effective. The Atlantic City eye test\* can be done rapidly, provides adequate information, does not require a skilled examiner or extensive equipment and is readily interpreted. It tests visual acuity and muscle balance and provides a rough test of the child's refractive error. After testing the visual acuity with the Snellen chart, a + 1.75 lens is placed before each eye. If the child can then read the preferred chart, he *fails* the test. The muscle balance is checked by the use of a green rectangle in which a red dot should be seen. If the red dot is outside the rectangle, the child has more than one prism diopter of hyperphoria or more than 4 prism diopters of esophoria or exophoria. Children who have any abnormality should be referred for more precise diagnosis.

**Examination by an Ophthalmologist.** The optimal schedule for examination by an ophthalmologist is (1) in the neonatal period; (2) before entering school (age four years); (3) at or just after puberty; and (4) about eighteen years. In addition, examination is indicated whenever vision for either distance or nearness is defective; whenever strabismus is noted, since poor vision from disuse is usually not correctible after the sixth year of life; and at any sign or symptom of disease of the eye.

**Cycloplegics** which are used include atropine, 0.5 to 1.0 per cent, scopolamine, 0.2 per cent (each in an ointment rather than solution to lessen absorption from the nasal mucosa) and homatropine, 4 per cent, in children over twelve years of age. Cyclogyl, however, is the one of choice at all ages. It is almost as effective as atropine, acts more rapidly and paralyzes accommodation for only twenty-four hours, as compared with five days for atropine and scopolamine.

\* Can be obtained from William Freund, 1415 Pacific Ave., Atlantic City, N.J.

**Table 117. Common Ocular Therapeutic Agents\***

*Irrigating Solution*

For ocular irrigation: physiologic saline solution

*Astringent Solution*

	Gm. or Ml.
Zinc sulfate.....	0.065
Epinephrine (1:1000).....	4.00
Zephiran chloride (1:20,000).....	30.00
One drop in each eye every three hours	

*Mydriatic Solutions*

Homatropine hydrobromide.....	2% solution	} Mydriatin or Eucadryl
Eucatropine.....	5% }	
and		
Neosynephrine.....	5% }	} Eucadryl
in methyl cellulose 1%		

*Miotics*

Eserine salicylate.....	0.25-0.5% solution
Pilocarpine hydrochloride.....	1-4 % solution
Carcholin.....	1.5% solution

*Sulfonamides*

30% sodium sulfacetamide solution; 10% ointment

*Antibiotics*

Penicillin.....	10,000 units per ml.
Terramycin (standard preparation)	
Aureomycin (standard preparation)	
Streptomycin.....	5000 10,000 units per ml.

*Other Ointments*

Zinc oxide.....	20%
Ammoniated mercury.....	1%
Atropine.....	0.5 or 1%

*To Demonstrate Denuded Areas of Cornea and Conjunctiva*

Fluorescein soluble 2% solution (this solution is easily contaminated and should be replaced frequently)

*Antiseptic Drops*

Mercuraphen.....	1:10,000
Metaphen.....	1:5000

\* All the solutions listed are now packaged sterile in plastic squeeze bottles which are not readily contaminated.

## REFRACTIVE ERRORS

### HYPEROPIA

#### (FARSIGHTEDNESS)

The hyperopic eye is shorter than normal, so that the focused image falls posterior to the retina. Only hyperopia over 4 diopters is considered abnormal in children; in hyperopia of slight degree the power of accommodation is sufficient to supplement the refracting power, but its constant use may cause headache and ocular discomfort. The total refractive error is determined under atropine cycloplegia. Refraction is indicated in children with poor vision, lack of interest in read-

ing or looking at picture books, headache, eye pain, strabismus, corneal disease, inflammations of the lid, unexplained vomiting, facial tic, torticollis or vertigo. Proper lenses provide a correction adequate for distinct vision and prevent fatigue.

## MYOPIA

### (NEARSIGHTEDNESS)

The myopic eye is longer than normal, so that the focused image falls anterior to the retina. There is poor vision for distant objects, and accommodation does not improve it. Proper lenses for full correction of the refractive error must be worn constantly, and re-examination should be performed semi-annually for the first few years and then annually. Children of myopic parents should be examined at an early age because of the hereditary tendency.

## ASTIGMATISM

In astigmatism there is a difference in the refractive power of the various meridians of the eye. The child may appear to be a careless reader because a distorted image is obtained. Symptoms include headache, eye pain, fatigue, nervousness and conjunctival irritation. Astigmatism is usually combined with myopia or hyperopia. Cylindric or spherocylindric lenses give an optical correction of the defect. Slight degrees of astigmatism often do not require any correction; moderate degrees usually require glasses for reading, movies, television, and so forth; severe degrees require that glasses be worn constantly.

Paralysis of accommodation may be due to diphtheritic paralysis of the ciliary muscle or to other neurologic conditions.

## STRUCTURAL DISTURBANCES

### ORBIT

*Exophthalmos* is a protrusion of the eyeball caused by edema, inflammation, tumor, or injury to the orbit, by enlargement of the eyeball from various causes, by dilatation of the adjoining cavities, by exophthalmic goiter, by thrombosis of the cavernous sinus and, in some cases, by paralysis of ocular muscles. Diplopia may be a prominent symptom. *Exophthalmos* produces conjunctival congestion and epiphora, and also, if it interferes with mobility of the eyeball and closure of the lids, keratitis from exposure. *Exophthalmos* may be simulated by myopia or retraction of the upper eyelid.

*Enophthalmos* is rarely encountered. Apparent enophthalmos is seen in Horner's syndrome or with ptosis from any cause.

*Retrobulbar hemorrhage* with proptosis is a rare lesion in the newborn infant.

## EYELIDS

*Ectropion* is an eversion of the lids with exposure of the conjunctival surface of the upper or lower lid. The chief symptom is epiphora resulting from eversion of the puncta. Secondarily there may be excoriations and eczema of the lower lids, redness and hypertrophy of the exposed conjunctiva and exposure keratitis. *Ectropion* may result from a cicatricial contraction following wounds, burns or operations, from chronic conjunctivitis and blepharitis, from facial palsy or spasmotic contracture of the orbicularis muscle due to acute conjunctivitis and blepharitis. If a pressure bandage does not correct it, surgery may be necessary.

*Edema of the lids* may be secondary to inflammatory, traumatic, systemic or allergic factors. It is a prominent sign in trichinosis.

*Entropion* is an inversion of the margin of the lid. The cicatricial type is due to changes in the conjunctiva and the tarsus. The spastic type is due to spasm of the palpebral portion of the orbicularis muscle and affects the lower lid. The cornea is irritated and injured mechanically. Treatment is usually surgical.

## LACRIMAL APPARATUS

*Epiphora* (watery eye) is an overflow of tears, dependent upon increased secretion from exposure, irritation of foreign bodies, or inflammation; or upon eversion of the puncta with contraction of the canaliculus, or upon plugging of the nasolacrimal duct.

## CONJUNCTIVA

*Chemosis* is edema of the bulbar conjunctiva and results from trauma, local irritation, allergic reactions or trichinosis.

*Hyperemia of the conjunctiva* is caused by local irritations such as foreign bodies, dust, exposure to bright light, acute coryza or allergy.

*Pterygium* is a triangular fold of membrane occupying the palpebral fissure and extending from the bulbar conjunctiva onto the cornea. The apex is united to the cornea and is usually blunt; the base spreads out and merges with the conjunctiva. A pterygium should be removed before the pupillary area of the cornea is involved.

*Subconjunctival hemorrhage* is manifest by



bright or dark red patches on the bulbar conjunctiva. This condition is seen after injuries, operations and inflammation of the eyeball, and in children especially after sneezing or coughing. It may be a manifestation of any of the blood dyscrasias or of scurvy. Sometimes the hemorrhage occurs without any exciting cause, and the child is unaware of its existence. It occurs relatively frequently in newborn infants. The blood is absorbed within a week or two.

*Symblepharon* is a cicatricial attachment from the conjunctiva of the lid to the eyeball, affecting usually the lower lid. It follows operation or injuries, especially burns from lye, acids or molten metals. It may interfere with motion of the eyeball and cause diplopia. The band should be separated and the raw surfaces kept from uniting again during the process of healing. Oral mucous membrane grafts may be necessary.

### CORNEA

*Kerato-ectasia* is a protrusion of the cornea following inflammation without perforation. The bulging portion is opaque. It may follow thinning from an ulcer which has not perforated or may be due to softening of the cornea after interstitial keratitis. There is always a reduction in vision.

An *opacity* of the cornea which is faint and cloudlike is termed a *nebula*; one which appears as a gray spot in daylight, a *macula*; and a dense white opacity resulting from inflammation, ulceration or injury, a *leukoma*. Reduction of the opacity may occur, but superficial keratectomy, iridectomy for an artificial pupil, or corneal transplantation may be required to improve vision. Tattooing or coloring has been used to remove the disfigurement of a leukoma.

*Staphyloma* of the cornea is a total or partially bulging cicatrix in which iris tissue is included. It is usually one of the sequels of perforation of a corneal ulcer. There is almost always increased intraocular tension; the secondary glaucoma causes pain and may lead to blindness. Iridectomy may be necessary for partial staphyloma; enucleation, for total staphyloma.

### SCLERA

*Staphyloma* of the sclera is a thinning and bulging of the sclera which may occur over the ciliary body, the equator or the posterior portion of the eyeball and is found after chronic glaucoma, iridocyclitis, scleritis or injury to the sclera. Posterior *ectasia* is a com-

mon occurrence with high myopia. If the eyeball is greatly enlarged and causes much discomfort or disfigurement and is sightless, enucleation is advisable.

### PUPIL

The *Adie syndrome* consists of one myotonic pupil, which is larger than the other one, and is often associated with the absence of reflexes or a slow contracture of the pupil to continued direct light. The pupil remains contracted for a long period after the light stimulation has been removed. The normal pupil fails to contract to 2.5 per cent mecholyl, whereas Adie's pupil does contract. The cause of the syndrome is not known; no treatment is required.

*Horner's syndrome* consists in miosis, apparent enophthalmos, narrow palpebral fissure, hyperemic cheek and an absence of facial sweating. It is usually unilateral and is due to paralysis of the sympathetic nerve supply. The pupil contracts to light and dilates with a cycloplegic.

The *retrobulbar pupillary reflex* consists in a slight constriction to light by a dilated pupil which then immediately dilates further while the light stimulation is still present. It is usually seen in patients with retrobulbar optic neuritis, which is rare in children.

### CATARACT AND DISLOCATED LENSES

A cataract is an opacity of the lens or its capsule; it may be present at birth or develop during infancy or adolescence. No symptoms accompany the formation of an uncomplicated cataract, except gradual diminution of visual acuity. The so-called complicated cataract accompanies or follows other diseases of the eye, such as iridocyclitis, choroiditis, uveitis, glaucoma or retinitis pigmentosa.

During the first two months of pregnancy, when the eye of the fetus completes most of its structural differentiation, German measles in the mother may be responsible for cataract as well as for malformations of other organs of the fetus. Affected infants often have extreme idiosyncrasy to atropine; even after one or two symptomless ocular instillations there may be considerable constitutional disturbance with fever, restlessness and, on occasion, death.

Cataracts may develop in certain metabolic disturbances such as diabetes and parathyroid insufficiency, and after the intake of certain chemical compounds such as dinitrophenol and naphthalene. Cataracts are common in

galactosemia. *Zonular (lamellar) cataract* is the most important type of developmental cataract in children. It is almost always bilateral and usually symmetrical. The opacity of the lens is evident with focal illumination as a pearly-gray, round area in the center of the lens with concentric alternating rings of clear and translucent lens substance around it. Frequently the peripheral translucent area is capped by a few radially situated opaque spokes. Ophthalmoscopically, the opaque area is black against the red reflex of the fundus.

Traumatic cataracts result from penetrating wounds or contusions of the eyeball without visible perforation, and in such instances an intraocular foreign body should be suspected. The cataract usually develops rapidly and may be complicated by secondary glaucoma. Spontaneous absorption may result, leaving a clear black pupil. More often, however, part of the lens remains opaque and requires subsequent operation.

Whether to remove a monocular congenital cataract is a moot question. It probably should be done if the cataract is extensive. Binocular cataracts which fill the pupillary area, are associated with nystagmus or cause reduction in vision below 20/50, should be removed. The age for operation depends upon visual acuity. In general, one waits as long as possible, but operation should be done early if the pupillary area is completely covered, to avoid irrevocable amblyopia.

*Dislocation of the lens* may be congenital or follow injuries to the eye, and congenital dislocation may not make its appearance until the late teens. The latter may be associated with arachnodactyly (Marfan's syndrome) and with brachymorphism (Marchesane's syndrome).

## GLAUCOMA

All congenital or juvenile glaucomas are secondary in type. The term *hydrophthalmos* is used for congenital glaucoma resulting from a defective filtration angle of the anterior chamber; *buphthalmos*, for glaucoma of any cause other than a malformed filtration angle. Both produce enlargement of the globe, but *buphthalmos* often shows clinical signs of injury or disease which are lacking in *hydrophthalmos*. There is increased intraocular pressure which causes enlargement of the eyeball, since the cornea and the sclera yield because they are not firm enough to resist stretching. One or both eyes may be involved.

The cornea is enlarged, thin, bulging and

sometimes cloudy. The anterior chamber is deep, the pupil is dilated, and the iris is atrophied. The sclera is thin and bluish, the uveal pigment showing through. Glaucoma may occur on the same side as unilateral *nevus flammeus*. The disease is usually slowly progressive to blindness, although in some cases there is spontaneous cessation of enlargement with preservation of moderately good vision. When there is persistent pain in association with blindness, the eye should be enucleated.

Goniopuncture provides subconjunctival drainage of aqueous; it has been effective in about 75 per cent of patients with *hydrophthalmos*. Early operation is advisable.

*Secondary glaucoma (buphthalmos)* develops as a result of disease, injury or operation which causes an obstruction in the flow of the aqueous. The clinical picture varies with the disease it complicates. Treatment consists in removal of the cause when possible. Surgery may be necessary to relieve the pressure, but the prognosis is not good. Enucleation is indicated if vision is irreparably lost and the eye is painful.

## STRABISMUS

(CAST, SQUINT, CROSS-EYE, WALL-EYE, TROPIA, HETEROTROPIA)

Strabismus is an imbalance of the extraocular muscles. It is of considerable importance in pediatric practice, for it often results in other problems more damaging than the functional ones of amblyopia ex anopsia (poor vision from disuse) and absence of fusion. Owing to the cosmetic blemish, psychic problems may arise. Parents should never be told to "wait and let the child outgrow crossed eyes."

Transient overconvergence or pseudostrabismus does occur, but the differential diagnosis should be the responsibility of the ophthalmologist. Infants with strabismus should be referred to the ophthalmologist by one year of age.

Many times no definite cause can be assigned. Strabismus may be congenital, and at times it seems to be familial; in some instances there are causative birth injuries; often it is first noted following an acute disease. Few people have completely "normal" muscle balance (*orthophoria*); most have a tendency for the eyes to deviate in or out, up or down (*heterophoria*). A patient with a *phoria* can keep his eyes straight by exerting effort to maintain fusion. A patient with a *tropia* is unable to fuse, and there is then an actual



visible deviation, since the visual axes are not parallel. Some children have a phoria which at times becomes a tropia (or true deviation); this accounts for the parents' story of the eyes being straight except under certain circumstances.

Fusion may be possible in some fields of gaze, but impossible in others. For example, the child may see singly when he looks straight ahead or downward, but see double when he looks upward. He therefore does all he can to avoid looking up.

Two situations may give the appearance of strabismus when it is not there, or accentuate it when it is. These are epicanthal folds and the relative position of the eyeballs in the orbit. The latter represents a disparity between the anatomic axis and the visual axis.

Though there is a wide variation in the manifestations of strabismus, there are general categories which are helpful in planning the management of each case. *Paralytic (non-comitant) strabismus* is due to paralysis of a muscle. The eyes are straight except when they are moved in the direction of the paralyzed muscle; here double vision is present. In *nonparalytic (comitant) strabismus*, which is the usual type, all the muscles are capable of rotating the eyeball as they should, but they do not work together. The two eyes are in the same relative position no matter in which direction the patient looks. Double vision is not present.

There are lateral, vertical and mixed lateral and vertical types of strabismus. Paralysis of one of the vertically acting muscles may initiate the lateral imbalance. The child sees two images, one above the other and close together. He makes every attempt to avoid double vision. He may tilt his head, close one eye or allow one eye to deviate in or out in order to get the two images together or so far apart that they do not bother him. During this transient period of double vision the child may stumble, fall, over-reach or otherwise appear awkward. He may be fussy and difficult to manage. This is the ideal time to start covering one eye, since this prevents double vision and improves appearance by hiding the deviation. The procedure makes an alternator out of what would probably be a monocular squinter, and so promotes the development of good vision in each eye.

**Methods of Testing for Strabismus.** In very young infants one can tell whether or not the eyes are straight by observing the position of the light reflexes on the corneas when a light is held before the face. Each reflex should be in the center of the

pupillary space or at corresponding points in the two corneas, such as the corneoscleral junction nasally on one eye and temporally on the other.

For older children the best test is the "screen" or "cover" test, which is carried out by having the child look at or "fixate" a small light while a narrow card is used to cover first one eye and then the other. Absolutely straight eyes (orthophoria) make no movement whatever when the card is moved. If crossing (esotropia) is present, each eye will move outward to fix on the light. If the eyes are divergent (exotropia), each eye will jump inward to fix on the light. One watches always the eye which is just being uncovered. Measurement of the amount of deviation is obtained by holding prisms base-out or base-in before the eyes during the cover test. When the proper prism is found, no movement of either eye occurs.

The ocular rotations and the ability to converge should also be tested. The nearpoint of convergence is measured by bringing a small light or pencil slowly toward the nose, asking the child to follow the light. This nearpoint should be within 10 cm. of the base of the nose. It is a good idea to touch the child's nose playfully with the light or pencil. Almost every child will smile when this is done, and co-operation is better from then on.

When the rotations are tested, one should note the relative motility with both eyes open and with each eye closed. It is useful to tell the child to "follow the light and don't let it get away."

In performing these tests it is wise to move the light *slowly* and to move the card slowly from one eye to the other. Then neither patient nor doctor becomes confused. It is surprising how much information can be gathered in a very young child with so little equipment. During such examination the parent and office nurse should not talk or move about the room: a child's attention, once distracted, may not be regained at that session.

In *amblyopia ex anopsia* or monocular strabismus one eye is deviating all the time, while the other eye is always being used. The deviating eye, not being used for definitive seeing, fails to develop good central vision. As previously noted, central vision is not developed at birth. A child with an eye which deviates ignores the image in this eye (to keep from seeing double) so that central vision does not have a chance to develop. The eye does not lose vision, and the peripheral field of vision remains normal, but the eye does not develop its potential power of seeing straight ahead.

The nonsquinting eye develops normally, and the child does not show evidence of poor vision until this eye is covered; then the disparity in vision between the two eyes is striking. Patching of the good, or fixating, eye is essential. This must be done constantly for weeks or months, and care must be taken that the improved vision does not slip when the patch is taken off.

Treatment of amblyopia ex anopsia must be



FIG. 420. Patient wearing eye patch.

carried out before the age of six years and continued until ten years if necessary. About half of the children with strabismus are amblyopic, and about one out of 150 children has amblyopia. Amblyopia should be prevented rather than treated. Good results are obtained in 80 per cent of children up to two years of age, in 60 per cent of children from two to four years, and in only 40 per cent of those from four to seven years of age.

*Alternating strabismus* is a condition in which the right eye fixes while the left eye deviates, and vice versa. Since each eye is used part of the time for definitive seeing, vision is developed equally in the two eyes, and there is no necessity for patching either eye. These children do not have double vision, since they suppress the image in the non-fixing eye. Consequently they do not have binocular vision with depth perception, but they do not miss it, since they have never had it.

*Accommodative strabismus* depends upon the relation between convergence and accommodation, both of which are controlled by the third nerve and are called upon to function at the same time. Decided hyperopia necessitates excessive accommodation with accompanying overconvergence. Myopia is likely to be associated with divergent strabismus. Accommodative esotropia disappears under cycloplegia, and correcting lenses keep the eye straight by relieving or stimulating convergence. Good vision should be maintained in both eyes, but this is not automatically done in many cases. It is, therefore, sometimes necessary to use occlusion as well as

glasses. Orthoptic treatment is often effective by developing fusion. Operation is usually deferred until the child is grown and has shown whether or not he is able to keep his eyes straight without glasses. With cautious surgical intervention a good compromise can be made between the cosmetic and functional elements.

Glasses will help, but not entirely correct, the deviation in children with convergent strabismus who have some accommodative element and whose deviation does not depend completely upon the hyperopia. It is necessary to explain to parents that glasses alone are often not enough for the correction of strabismus and that it is important not to lose time in the development of good vision in each eye. Children with partially accommodative monocular strabismus are particularly likely to develop amblyopia ex anopsia. Occlusion, to be effective, must be continuous for prescribed periods; children will cooperate when the parental attitude is proper.

*Muscle exercises* (orthoptics) are of limited value. Their greatest help is in patients with divergence and in the postoperative course of children with monocular strabismus. Orthoptic treatment of children with pure alternating strabismus is a waste of time and may be a source of nervous fatigue to the child. When properly used in selected cases, orthoptics can render great help both in overcoming amblyopia and in improving fusion ability.

*Operative treatment* is reserved for those children who do not respond to the wearing of glasses or to exercises. A high percentage of patients with strabismus, particularly convergent strabismus, eventually come to operation. It is the only successful treatment for pure alternating strabismus. Monocular strabismus of even moderate degree should be operated upon as early as possible after treatment has overcome the amblyopia. Divergent strabismus offers less cosmetic blemish, and therefore treatment is often delayed; excellent results can usually be obtained, and binocular vision developed.

**Strabismus and Cerebral Palsy.** Children with cerebral palsy may have a variety of ocular palsies and as a result may have double vision in some directions of gaze. It is desirable to do away with double vision as soon as possible, especially since many of these children have severe problems in locomotion. There are two schools of thought concerning treatment: One group advises early operation



to secure a cosmetic result; the other group, which includes the writer, recommends alternate occlusion of each eye to ensure development of equal visual acuity and to avoid diplopia. This method also takes care of the cosmetic blemish, since the patch makes the one visible eye "look straight." The muscular imbalance often becomes less marked by the time the child is five or six years of age, when, if necessary, surgical correction of residual cosmetic defects can be undertaken.

## INFECTIONS

Pyogenic and viral infections of the external eye may have their origin during birth.

### ORBIT

*Orbital cellulitis* is an inflammation of the supporting cellular tissues that may terminate in suppuration and is accompanied by great swelling of the eyelids, chemosis, exophthalmos, impairment of the motility of the eyeball, and pain which is increased by pressure. Fever and at times cerebral symptoms are present. Complications of orbital cellulitis include optic neuritis, thromboses of the retinal veins and of the cavernous sinus and, occasionally, panophthalmitis. Orbital cellulitis is usually secondary to extensive disease of the nasal accessory sinuses, especially of the ethmoids, and less often to such neighboring foci as orbital periostitis or facial erysipelas, to injuries and foreign bodies or to blood stream infection. Treatment includes bed rest, hydration, hot compresses locally, antimicrobial therapy and, if necessary, incision and drainage.

### EYELIDS

*Blepharitis* is an inflammation that involves principally the margins of the eyelids and the skin around the bases of the cilia. Redness, scales, crusts and ulcerations may be present. The lashes are often matted by cellular debris and exudate. Sometimes some of the lashes may be lost, and trichiasis may result. Seborrhea is a common cause, alone, or complicated by secondary infection. Treatment of the seborrhea of the scalp and brows is essential to the clearing of marginal blepharitis (p. 1283). Staphylococcal infections of the glands of the skin and hair follicles and of the meibomian glands are common. If response to local treatment is not prompt, determination of the organism and the antibiotic to which it is sensitive is in order.

*Hordeolum* (sty) is an infection of the follicle of an eyelash, usually caused by staphylococci. It produces redness, swelling, pain, tenderness and sometimes preauricular adenopathy. It usually goes on to suppuration and drainage. Incision should not be done, but pulling the affected cilium often results in drainage. Hot saline compresses for fifteen minutes three times a day offer the greatest help. Sties tend to occur in series.

*Chalazion* is a chronic granulomatous inflammatory involvement of a meibomian gland. The basic lesion is a reaction to fatty secretion of the gland, which acts as a foreign substance. A chalazion may start as an acute inflammation with redness and swelling, or it may develop quietly as a hard, circumscribed swelling in the tarsal plate. It may develop as a polypoid mass on the under surface of the lid. The treatment consists of hot saline compresses. Use of other local medication is usually of no avail. Absorption is much more likely to occur in children than in adults, but incision and curettage are frequently necessary.

### LACRIMAL APPARATUS

*Congenital obstruction of the nasolacrimal duct* is due to failure of canalization of the lacrimal passage. *Congenital dacryocystitis* develops when the sac becomes infected. The contents of the sac usually liquefy and become purulent. This condition should be suspected when conjunctivitis, especially unilateral, persists for several weeks. Pressure on the lacrimal sac will regurgitate fluid through either punctum, and the quality of the fluid will indicate the degree of infection present. In some instances pressure on the lacrimal sac from above will force the fluid into the nose and re-establish drainage. In some instances probing of the nasolacrimal duct to expel the epithelial plug is necessary. Acute dacryocystitis should be treated expectantly until softening occurs. Specific antibacterial therapy is advisable in the more severe infections. Probing is usually postponed until the child is six months of age, but should be done at two or three months. Probing may be done without general anesthesia if the child can be satisfactorily restrained; otherwise light general anesthesia for a few minutes is sufficient.

*Acute dacryocystitis* occurs infrequently in children without congenital obstruction of the duct.

*Dacryoadenitis* produces swelling and ten-

derness in the upper temporal portion of the orbit. It occurs with systemic infections and not infrequently with mumps.

### CONJUNCTIVA

*Acute catarrhal conjunctivitis* is common in children, but not every injected eye should be regarded as a case of conjunctivitis. Foreign bodies beneath the lid and in the cornea and uveitis may closely simulate conjunctivitis, but fail completely to respond to treatment. Most patients speak of conjunctivitis as "pink-eye," which is the epidemic form of infection by the Koch-Weeks bacillus, for which 0.2 per cent zinc sulfate solution is a specific treatment. Other causative organisms are the Pneumococcus, Streptococcus, Staphylococcus and influenza bacillus. Viral infections are common and produce little secretion, but cause tearing and preauricular adenopathy. The most common cause is infection during or after a common cold.

Treatment consists in keeping the secretion cleansed from the eye by saline irrigations, local applications of 0.5 per cent silver nitrate by the physician, and sulfonamide or antibiotic therapy. Great care should be taken to avoid local sensitivity reaction, which may prove far more distressing than the original disease. In general, one should choose an antibiotic which is not used systemically; in this way danger of sensitization is greatly decreased. In this respect solutions are better than ointments. A bland ointment will prevent agglutination of the lids during sleep. Overtreatment should be avoided, especially since most forms of conjunctivitis are self-limited.

*Inclusion blennorrhea* is a viral infection transmitted in a variety of ways, including the genital tract at birth or in swimming pools. This is one of the viral infections which are effectively treated with a sulfonamide.

*Gonorrheal conjunctivitis* (p. 303) may be acquired during birth and become evident about the third day of life, or may be acquired after birth. Although formerly an important cause of blindness, its response to several of the antibiotics and to sulfonamides is extremely rapid.

Acute conjunctivitis complicating measles responds well to 0.2 per cent zinc sulfate solution.

Conjunctivitis may be a response to drugs such as atropine, to dyes, pollens, food or other allergens. Eosinophils can be found in scrapings of the conjunctiva. Symptomatic relief can be obtained from 1:4000 epineph-

rine hydrochloride solution or various antihistaminic solutions; most of the latter cause some burning. Systemic treatment with antihistaminics is advisable if the conjunctivitis is severe.

*Vernal catarrh* is an allergic disturbance which tends to occur in warm weather and to disappear with the onset of winter. Symptoms include lacrimation, intense itching and photophobia. In the palpebral form there are hard, flattened papillae on the upper palpebral conjunctiva, producing a cobblestone appearance, and a bluish-white color of the upper and lower palpebral conjunctivas as though covered with a thin layer of milk. In the bulbar form the conjunctiva adjacent to the limbus presents gelatinous elevations, which are rarely complicated by keratitis. The conjunctiva is congested and has a stringy mucoid secretion which contains eosinophils.

The symptoms can be relieved by irrigation with saline solution or an alkaline eye wash; if there is much mucus, soothing ointments, 1:3000 epinephrine, cold compresses and the wearing of dark glasses are indicated. If a definite sensitivity to protein can be proved, the protein should be avoided or the patient desensitized to it. Carbon dioxide snow may be used to destroy the papillae. When the cornea is involved, prompt and persistent treatment must be used to avoid ulceration.

The etiologic agent of *epidemic keratoconjunctivitis* is probably a filtrable virus which is transmitted by direct contact. At first there is the sensation of a foreign body under the eyelid with moderate itching and burning. Edema of the upper lid, chemosis, and edema of the semilunar fold and the caruncle develop, and there may be pain and discomfort on rotation of the eyeball. Within forty-eight hours large, translucent, oval follicles and considerable subconjunctival infiltration develop in the lower lid, in the upper retrotarsal fold and in the fornices. The preauricular lymph nodes become slightly tender, and symptoms of upper respiratory tract infection occur, with which there is a scratchy sensation in the throat and at times follicular pharyngitis. A pseudomembrane forms on either the upper or the lower lid by the third to the fifth day. Photophobia and blurring of vision develop when corneal opacities begin as subepithelial dots. The course is self-limited without permanent loss of vision. Symptomatic relief may be obtained from cold compresses. Virus antibodies can be demonstrated in the serum after the disease has run



its course. Simple hygienic measures seem to prevent transmission.

*Trachoma* is a serious contagious inflammation of the cornea and the conjunctiva which produces pannus of the cornea and scarring of the lids. It responds to sulfonamides and to several antibiotics, so that it is becoming a less serious public health problem.

## CORNEA

*Ulcer of the cornea* begins as a dull gray infiltration of a circumscribed portion of the cornea, followed by suppuration and extension in area and in depth. Sometimes there is a tendency to heal at one site and to advance in another direction, so that the ulcer changes its situation. A small, superficial ulcer heals within a few days. The ulcer may be detected by instillation of a drop of 2 per cent sterile fluorescein, which stains green all the ulcerated portions. There is usually grayish infiltration of the cornea immediately surrounding the ulcer and considerable ciliary injection.

The symptoms are pain, photophobia, blepharospasm, lacrimation and interference with vision. When the ulcer is deep, the symptoms are more pronounced, the complications and sequels more serious, and neighboring structures are involved.

*Hypopyon* is a collection of leukocytes in the anterior chamber usually secondary to a corneal ulcer, but it may follow injury and rarely accompanies unusual types of iridocyclitis. Deep ulcers of the cornea may heal with no damage except corneal opacity, but perforation is always a serious complication. Treatment of corneal ulcers is by hot compresses, atropine, antibiotics and, if necessary, local cauterization of the ulcer.

*Phlyctenular keratoconjunctivitis* is now relatively rare, owing to the decrease of tuberculosis and to the general improvement in nutrition. The phlyctenules are accumulations of lymphoid cells beneath the epithelium of the cornea or conjunctiva. They may rupture, form ulcers and heal slowly. Cortisone applied locally results in striking but temporary relief until other measures can be instituted.

*Interstitial keratitis* is a chronic cellular infiltration of the deeper layers of the cornea without ulceration. It is associated with uveitis and leads to discoloration, clouding and vascularization of the cornea. Both eyes are usually involved. The majority of cases are due to congenital syphilis, a few to tuberculosis. It is rarely the result of acquired

syphilis, but, when it is, it is likely to be unilateral. Vision may be greatly reduced, and other symptoms include photophobia, blepharospasm, lacrimation and pain. The symptoms persist for several months, the center of the cornea being the last part to clear. When response to treatment is good, the cornea will clear completely in a year or so, or there will remain merely a faint central opacity and ghost vessels, demonstrable with the slit lamp. In all cases iridocyclitis and choroiditis occur. These untoward effects may be responsible for the visual impairment. Local treatment with hot compresses and atropine should be used with antisyphilitic treatment. Cortisone may hold the keratitis in abeyance until penicillin therapy can be effective.

In *ultraviolet burns* of the cornea the widespread loss of the superficial cells of the corneal epithelium causes exquisite pain. Treatment consists in dilatation of the pupils with homatropine or Cyclogyl, instillation of a local anesthetic (Pontocaine or Ophthaine), and covering of the eyes. Healing requires twenty-four to forty-eight hours.

## UVEA

*Iridocyclitis*, an endogenous inflammation of the iris and ciliary body, is not common in children. It occurs as a manifestation of systemic diseases, such as syphilis, tuberculosis, brucellosis and parasitic infestation, and as a response to focal infection. It may be acute or chronic. The symptoms are photophobia, lacrimation, pain in the region of the fifth nerve and diminution of vision. The signs are contracted pupil, which may be irregular in shape and may react poorly, dullness of the iris pattern and cellular precipitates on the posterior surface of the cornea. Complications are secondary glaucoma, cataract and phthisis bulbi. The treatment consists of atropine locally, hot compresses and foreign protein therapy, and treatment of the systemic disease.

*Endophthalmitis* is usually a blood-borne infection and may start as a metastatic retinitis with involvement of the vitreous and the uveal tract. It occurs with meningitis, scarlet fever, measles and subacute bacterial endocarditis. It is serious and usually leads to blindness. Nematodes have been found in excised globes. The manifestations of toxoplasmosis are most notable in the retina.

*Panophthalmitis* is an inflammation of all the structures of the eye and is frequently suppurative. It produces pain, loss of vision

and severe congestion of the eyeball, eyelids and orbit. Treatment includes symptomatic measures and the use of antibiotic agents until it is safe to enucleate the globe.

## INJURIES

Injuries to the eyes of children are common. Small abrasions and superficial foreign bodies causing acute pain prompt the parents to consult a doctor immediately. Contrariwise, injuries which do not produce pain, bleeding, sensitivity to light, or blepharospasm tend to be ignored until late. These latter injuries may be intraocular foreign bodies, traumatic iritis, perforating wounds, dislocation of the lens and detachment of the retina, all of which are of major importance. A review of the results of injuries to the eye in children indicates that they should be the responsibility of the trained ophthalmologist from the outset.

Ecchymosis and edema are signs of injury to the eyelids. Ecchymosis (black eye) is usually of no great importance except when the eyeball is involved. Blood from a basal skull fracture may appear under the bulbar conjunctiva a day or so after the injury.

*Lacerations of the eyelid* are generally more extensive than they appear externally. A small wound on the skin surface may not reflect the extent of a laceration of the tarsus. With any history of injury, prompt and complete examination of the lids, conjunctiva, cornea and sclera is necessary, even if general anesthesia is required. One or two sutures properly placed in the lid margin may obviate the necessity for extensive plastic repair at a later date, and even blindness may be avoided by prompt suturing of perforating wounds.

Perforating wounds of the globe are always of major importance, even though the eye looks white and is not painful. Even tiny perforations may be complicated by sympathetic ophthalmia.

Large lacerations of the cornea and sclera require proper appositional suturing after excision of any free uveal tissue, vitreous, and damaged lens tissue. Large wounds with escape of vitreous and hemorrhage into the eye often involve the choroid and retina. Detachment of the retina may occur. Frank infection is surprisingly infrequent. Emergency treatment should consist in instillation of a *sterile* atropine solution and application of a *sterile* pad. No ointment should be applied to the eyeball. After repair of the globe foreign protein therapy, cortisone locally and

rest in bed are indicated until the true status of the eye can be determined.

*Sympathetic ophthalmia* is a plastic inflammation of the uveal tract in one eye occurring two to eight weeks after an injury to the other eye. The signs are photophobia, lacrimation, pain in the eye and dimness of vision for close work. Examination reveals circumcorneal injection, punctate deposits upon the posterior surface of the cornea, a contracted pupil, and sometimes increased intraocular tension. Later the iris is thickened and discolored, and its markings are obliterated by extensive posterior synechiae; exudate fills the pupil; the tension is diminished; opacities develop in the vitreous, and the lens becomes opaque. Finally, the retina may be detached, and the eyeball atrophies. The pathogenesis of sympathetic ophthalmia is not understood.

The best treatment is prophylactic. Removal of the exciting eye is not the cure for sympathetic inflammation. If the exciting eye has vision, it should not be removed merely because sympathetic inflammation is present. Active treatment includes the use of atropine, hot compresses, protection from light, cortisone and injection of a foreign protein (milk or typhoid vaccine). The early use of a sulfonamide or an antibiotic may materially alter the prognosis.

An injured eye should be enucleated if it is blind and painful, if iridocyclitis persists or if a foreign body cannot be extracted. Operative treatment to improve vision should be postponed for several months after evidences of inflammation have disappeared.

Sudden onset of pain with tearing and congestion of the conjunctiva is highly suggestive of a *foreign body* on the cornea or conjunctiva. Foreign bodies can be located by examination with a condensed light and a magnifying glass. Those on the cornea may be seen best with an ophthalmoscope. Irregularities in the surface may show the location of the foreign body. The instillation of 0.5 per cent Pontocaine will facilitate examination as well as removal of the foreign body. It is wise to be sure that the anesthesia is complete and that the patient is relaxed enough to hold still. Foreign bodies should be removed with an instrument which is not sharp enough to penetrate the globe and which will lift rather than dig out the foreign body. Atropine and an antiseptic ointment should then be applied, and a sterile pad fastened securely with adhesive tape. This keeps the medication in, the patient's fingers out, and the lids closed over the cornea to promote



healing without further abrasion. If a foreign body is suspected and none is found, the eye should be examined roentgenographically.

Fluorescein in a *fresh sterile solution* should be instilled to show up any abrasion of the surface; defects in the cornea are stained green; those in the conjunctiva, yellow.

*Burns* of the eye should be irrigated and covered with a bland oil or ointment and the eye bandaged. Initially, burns from acid appear to be more severe than those from alkali, but the latter are usually more serious. In powder burns the particles, when accessible, should be removed as soon as possible by copious irrigations. Pontocaine may be used to relieve the pain. Reparative operations may be necessary after the acute stage.

*Emphysema* of the lids usually denotes a *fracture* of the wall of the orbit, permitting communication with the nasal cavity. The lids will present a soft swelling of considerable size, and on palpation there is a sensation of crepitation. A pressure bandage will hasten disappearance of the air. A fracture of the anterior wall may be detected by an unevenness of the bone. If the inner wall is involved, there may be emphysema of the orbit. When emphysema is present, rupture of the eyeball has certainly not occurred.

## TUMORS

**Eyelid.** Benign neoplasms include papillomas, hemangiomas and dermoid cysts. Non-neoplastic growths which may be found on the lids are xanthoma, molluscum contagiosum and milium. These tumors should be removed if they interfere with function or are unsightly. Malignant tumors, carcinoma and sarcoma, are rare in children; when they occur, they should be widely excised.

**Conjunctiva.** Benign tumors, which may be excised if large or unsightly, include hemangioma, nevus, lymphangioma, lipoma, dermoid cyst and papilloma. Malignant tumors which call for wide excision are melanoma, epithelioma and sarcoma.

**Cornea.** Congenital tumors are known as dermoids. A small dermoid may be confined to the limbus, but larger ones may cover the corneal area completely. Such tumors are usually easily removed, but some extend into the eye.

**Iris.** A nevus is characterized by small, excessively pigmented patches. Melanomas are rare in children. Cysts of the pigment epithelium

are benign and require no treatment. Diktyomas arise from ciliary epithelium.

**Ciliary Body.** Cysts and sarcoma are rare.

**Orbit.** Benign neoplasms and other tumors, including dermoid cyst, neurofibroma, aneurysm, meningocele and osteoma, can usually be removed with preservation of the eyeball. Malignant tumors, such as sarcoma and carcinoma, require complete exenteration of the orbit. The leukemic-like infiltration of a chloroma into the walls of the orbit is not amenable to treatment. Early metastasis to the orbit may be the first clinical sign of a neuroblastoma, manifest by exophthalmos, ecchymosis of the eyelids, and papilledema.

**Retinoblastoma.** This is a relatively rare, malignant tumor which occurs almost exclusively in infants and young children. It has its onset in utero, and in many instances a familial pattern can be demonstrated. There are two types: (1) *exophytum*, in which several pinhead-sized nodes appear in the retina and spread in the subretinal space, detaching the retina; and (2) *endophytum*, in which the tumor grows primarily toward the vitreous, the retina remaining attached to the choroid. Initially, the mass appears in the form of a small, round, yellowish-white nodule, but it is soon surrounded by small satellites which spread on the inner surface of the retina with polypoid masses extending into the vitreous. There is no pigmentation in a retinoblastoma, in contrast to that of intraocular melanomas.

In about one third of instances there are bilateral tumors, each independent of the other. There may be a period of six to twelve months before the growth is sufficient to produce such clinical manifestations as dilatation, a peculiar yellow reflex behind the pupil and defective vision. The tumor may be seen with the naked eye or with the ophthalmoscope. If secondary glaucoma develops, the eye becomes hard, congested and painful, and the cornea becomes clouded. Various types of ectasias may occur, and the sclera may perforate. Proptosis develops as the tumor forms a large, fungating, ulcerating mass which bleeds easily and bulges forward between the lids. The tumor extends by way of the optic nerve, and metastases occur by way of the blood stream, especially when the choroid has been involved by extension. These are the most important prognostic factors. Death may result relatively early from cerebral involvement by way of the optic nerve.

Differential diagnosis includes a retinal de-

tachment, metastatic retinitis, exudative retinitis and choroiditis, massive retinal fibrosis from extensive hemorrhage at birth, persistent fibrovascular sheath of the lens, or retrolental fibroplasia.

The treatment consists in early enucleation of the involved eye with removal of the largest possible portion of the optic nerve. If the tumor is bilateral, and permission for enucleation of both eyes is refused, roentgen ray therapy and triethylene melamine may be given. The local complications of roentgen therapy may be severe. The presence or absence of tumor tissue in the severed end of the optic nerve determines the prognosis. Local recurrences may develop within four to twelve months.

## RETINA

The retina may show characteristic changes associated with certain systemic diseases. In leukemia there may be hemorrhages with white centers, dilatation and tortuosity of the veins and exudation. In rare instances in the diabetic child the retinal vessels may be full and of a light color, owing to lipemia. In chronic nephritis there may be retinal edema and occasionally flame-shaped hemorrhages.

*Chorioretinitis* occurs with syphilis, tuberculosis, toxoplasmosis and septic infections. There is a reduction or loss of vision in the part of the field corresponding to the area involved. The prognosis depends upon the location of the inflammation and the response to therapy. The areas involved are at first yellowish with ill-defined margins; later there is organization leaving atrophic areas which are whitish with pigmented margins. Vitreous opacities may be associated findings. Treatment should include rest, injections of foreign protein and specific measures directed against the cause.

In amaurotic family idiocy (Tay-Sachs disease) there is a cherry-red spot at the macula surrounded by a grayish-white zone somewhat larger than the size of the disk, and optic nerve atrophy develops.

In anemia the disk and the rest of the fundus are pale, and in long-standing cases the veins are dilated and tortuous. Hemorrhages occur with severe anemia. Pulsation of the retinal arteries may be seen with aortic insufficiency. Hemorrhage of the retina may occur in association with injury in the newborn infant with such disturbances as hemophilia, purpura and cardiovascular disease and with-

out any signs of inflammation. Massive retinal fibrosis may follow hemorrhage at birth; there is a reduction in vision and sometimes detachment of the retina.

Simple *optic atrophy* is differentiated from secondary optic atrophy by the blurred margins and secondary sclerotic changes in the arterioles near the disk in the latter condition. Optic neuritis and choked disk cannot always be differentiated ophthalmoscopically, but optic neuritis has all the cardinal signs of inflammation with diminished visual function. The choked disk is noninflammatory and does not interfere with normal visual acuity until the late stages, when secondary optic atrophy develops. Intracranial lesions affecting the optic nerve in front of the chiasm usually produce diminished central visual acuity early, and there is rapidly developing simple optic atrophy. Lesions in the region of the optic chiasm produce diminished visual acuity in both eyes, but it is usually more advanced in one eye; there are pallor of the disk, simple optic atrophy, and asymmetric visual field changes, bitemporal in type. Lesions affecting the optic tract and its radiations usually produce choked disks, without interference of the central visual acuity; there are characteristic symmetric field changes of the homonymous hemianoptic type.

Posterior fossa lesions usually produce nystagmus, ataxia and rapidly developing choked disks, with no associated visual field defects.

*Detachment* of the retina is likely to occur with severe myopia, iridocyclitis, trauma or retinoblastoma. There is diminution of vision with an associated field defect. The retina is gray, the vessels dark and tortuous, and a hole or tear may be observed except in association with tumors. The prognosis is generally poor in children, but operative treatment may be effective.

*Retinitis pigmentosa* is a chronic, progressive degeneration of the retina with atrophy and pigmentary infiltration of the inner layers. There is an increasing contraction of the visual field, producing night blindness; the central region is the last to fail. There is a ring scotoma which starts typically in the equatorial region and spreads peripherally. The arteries are threadlike, the entire fundus is pale, and the disk waxy yellow; the pigmentation is in the periphery. Cataract is a frequent terminal complication. In the Laurence-Moon-Biedl syndrome retinitis pigmentosa is associated with mental retardation, hypogenitalism, obesity and polydactyly.



## RETROLENTAL FIBROPLASIA

### (RETINOPATHY OF PREMATURITY)

One of the most notable phenomena of medical history has occurred during the past sixteen years: A completely new disease of the eye has been described, studied extensively and the means for its prevention established by cooperative clinical and laboratory research.

In 1942 retrolental fibroplasia was discovered as an acquired disease in premature infants. By 1948 the nature and clinical course of the disease were understood. In 1951 the relation of intensive oxygen therapy to the occurrence of the disease was reported, and by 1955 the pathogenesis had been proved. Today retrolental fibroplasia rarely occurs.

Briefly stated, a high concentration of oxygen causes vasoconstriction of incompletely developed retinal blood vessels in the premature infant, and secondary proliferation of endothelial cells in the layer of nerve fibers in the periphery of the retina leads to formation of new vessels in the retina and in the vitreous. Detachment of the retina may follow. Regression may occur at any stage of the disease, or partial or complete blindness may result.

Prevention of this disease by giving the least amount of oxygen necessary for survival of the infant has been eminently successful. Children who were born prematurely in the past decade or so are now being seen with various degrees of myopia as a result of previously undiagnosed retrolental fibroplasia. Properly fitted glasses produce improvement in such children.

Other conditions may simulate the disease by producing a membranous structure behind the lens. These conditions are retinoblastoma, metastatic retinitis, massive retinal fibrosis, tunica vasculosa lentis, congenital cataract, effects of German measles, encephalophthalmic dysplasia, detached retina and external exudative retinitis (Coats' disease). If very marked, the fundus reflex in patients with toxoplasmosis or medullated nerve fibers may also simulate retinopathy of prematurity.

## HYGIENE OF THE EYE

Children should be encouraged to read in a good light (100 to 150 watts) which comes from behind and does not produce reflected glare. Printed matter should be held at least 14 inches from the eye. The print should not

be too small. It is wise to have the book tilted to prevent reflection from glossy paper. Good posture while reading should be encouraged.

Television is not harmful to the eyes, although it frequently brings on symptoms of fatigue and "eyestrain." The child should sit 10 to 12 feet from the screen in a room which has some general illumination. The picture should be as sharply focused as possible to reduce fatigue. The content of the programs is more important than the eye symptoms. Television, like "comics," is likely to consume too much of the interest of the child and detract from the development of good reading habits. Allowing a child to watch television while wearing a patch is sometimes effective in the treatment of amblyopia ex anopsia.

There need be no restriction of children's reading because of their refractive errors or muscle imbalances.

## SIGHT-SAVING CLASSES AND SCHOOLS FOR BLIND CHILDREN

Sight-training classes have been established in public and in private schools for children whose vision has been reduced to such an extent that they are not capable of the requirements of the ordinary school curriculum. The training consists chiefly in following the regular school curriculum by means of books printed in large type on suitable contrast backgrounds so that ocular fatigue is minimized. Special attention is given to lighting and to correct reading posture. Under this regimen children with limited but not complete loss of vision can be adequately educated.

The cooperative system for educating partially sighted children is recommended rather than placing them in schools for the blind or special schools where they are grouped with children with other abnormalities, such as deafness or cerebral palsy. Even placement in segregated classes in public schools adds its stigma. The cooperative plan places the partially seeing children with the normally seeing children in regular classrooms. Projects requiring concentrated eye work by the partially sighted children are conducted in separate, specially equipped classrooms. The psychological advantages of this plan are tremendous, just as the term "semi-sighted" is preferable to "semi-blind."

When vision has been reduced to 10/200 or less, it is almost impossible for the child to continue in sight-training classes, and he

should then be enrolled in a school for the blind. Here he is taught one of the touch systems of reading. Emphasis is placed on the teaching of manual arts and the development of a sense of independence and self-sufficiency. Those schools which teach the parents as well as the child how to handle the problem of the visually handicapped are most effective.

Children who have never had vision do not miss it and are content with the world. They should be treated as normal children and neither pitied nor rejected. Parents often regard a blind infant with awe and must be taught how to handle the situation.

JOHN S. MCGAVIC

#### REFERENCES

- Adler, F. H.: *Gifford's Textbook of Ophthalmology*. 6th ed. Philadelphia, W. B. Saunders Company, 1957.
- Allen, J. H.: *Strabismus*, Ophthalmic Symposium. St. Louis, C. V. Mosby Company, 1950.
- Berens, C., ed.: *The Eye and Its Diseases*. 2d ed. Philadelphia, W. B. Saunders Company, 1949.
- Berens, C., and Zuckerman, D.: *Diagnostic Examination of the Eye*. Philadelphia, J. B. Lippincott Company, 1946.
- Clarke, C. C.: Age Factor in the Treatment of Amblyopia ex Anopsia. *Sight-Saving Rev.*, 20:151, 1950.
- Doggart, J. H.: *Diseases of Children's Eyes*. 2d ed. St. Louis, C. V. Mosby Company, 1950.
- Duke-Elder, W. S.: *Text-Book of Ophthalmology*. St. Louis, C. V. Mosby Company, 1932-57, Vols. I-VII.
- Dunham, E. C.: Retrolental Fibroplasia in the Premature Infant; A Review of the Literature. *Bull. W.H.O.*, IV:605, 1951.
- Dunnington, J. H.: Some Factors in the Surgical Treatment of Vertical Deviations. *Am. J. Ophth.*, 31:1404, 1948.
- Keeney, A. H.: *Chronology of Ophthalmic Development*. American Lecture Series No. 99. American Lectures in Surgery. Springfield, Ill., Charles C. Thomas, 1951.
- Krause, A. C.: Congenital Encephalo-ophthalmic Dysplasia. *Arch. Ophth.*, 36:387, 1946.
- Krimsky, E.: *Children's Eye Problems*. New York, Grune & Stratton, Inc., 1956.
- Mann, I. C.: *Development of the Human Eye*. 2d ed. New York, Grune & Stratton, Inc., 1950.
- Payne, B. F.: Cross-Eyed Children. *Arch. Pediat.*, 58:365, 1941.
- Reese, A. B.: *Tumors of the Eye*. New York, Paul B. Hoeber, Inc., 1951.
- Reese, A. B., and Blodi, F. C.: Retrolental Fibroplasia; Fifth Francis I. Proctor Lecture. *Am. J. Ophth.*, 34:1, 1951.
- Sanders, T. E.: *Pediatric Ophthalmology*. St. Louis, C. V. Mosby Company, to be published.
- Scobee, R. G.: *The Oculomotor Muscles*. 2d ed. St. Louis, C. V. Mosby Company, 1952.
- Symposium: Strabismus. *Tr. Am. Acad. Ophth. & Otol.*, 57:121, 1953.
- Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath behind Each Crystalline Lens; Preliminary Report. *Am. J. Ophth.*, 25:203, 1942.
- Wolff, E.: *Anatomy of the Eye and Orbit*. 3rd ed. Philadelphia, Blakiston Co., 1948.



# Unclassified Diseases

## AMYLOIDOSIS

This disease, uncommon in childhood, usually occurs in association with tuberculosis or chronic suppurative disease and consists in the deposition of amyloid in various tissues, especially in those of the kidney, spleen, liver, pancreas and adrenals. In recent years the incidence of the disease has declined because of the infrequent occurrence of suppurative foci.

Clinical amyloidosis usually becomes apparent within one to two years after a suppurative focus has developed; the clinical features depend on the organs involved and the degree of involvement. In *primary* amyloidosis there is no suppurative or tuberculous infection; deposition of amyloid is widespread. This type does not occur in childhood. The *secondary* type is most likely to develop as a result of caseous tuberculosis, especially in the presence of discharging sinuses. Recent reports stress the role of rheumatoid arthritis as a precursor of amyloid disease; it is estimated that between 10 and 15 per cent of patients with rheumatoid arthritis may suffer this complication. Amyloidosis should be suspected in any child with chronic disease who exhibits a gradually enlarging liver with or without splenomegaly in the early stages of the disease and without jaundice. Ascites and peripheral edema may occur late in the disease, and the skin has a peculiar waxy pallor. The urine is generally abundant and contains large amounts of albumin and waxy casts. The course is progressively downhill, and wasting is extreme. Death may occur from uremia, but in the majority of instances the original disease, rather than amyloidosis, is the cause of death.

Amyloid is principally protein in composition and has a sulfate-bearing polysaccharide fraction. It is thought to result from an allergic reaction between components of the serum globulin and certain fixed tissue elements. Amyloid is not seen within cells, but is in the intercellular tissues, which it damages by pressure or limitation of blood supply.

**Laboratory Studies.** As a result of the affinity of amyloid for various dyes, the Congo red test may prove helpful in the diagnosis of this condition. In this test (see Kolmer and Boerner) 1 cc. of 1 per cent aqueous solution of Congo red per 10 pounds of body weight is injected intravenously. Exactly four minutes later and again one hour after the injection 10 ml. of venous blood are withdrawn and the serum is separated. If possible, urine should be collected at the end of one hour after the injection and its color noted. The two specimens of serum are compared in a colorimeter, using the four-minute sample as the standard. The standard is set at 10 ml., and the one-hour sample is then read. The calculation  $\frac{\text{ml. 1-hour sample}}{\text{ml. 4-minute sample}} \times 100$

yields the percentage of dye remaining in the plasma. In normal subjects less than 40 per cent of the dye disappears from the blood in one hour. In amyloidosis 60 to 100 per cent of the dye may disappear within four minutes. If the dye is found in the urine and if there is a reduction of more than 40 per cent in the blood, the possibility of lipoid nephrosis must be considered in the differential diagnosis.

Gingival biopsy may prove helpful in the diagnosis of amyloid disease. A negative test for amyloid does not, however, exclude the diagnosis.

**Treatment.** Prophylaxis of amyloid disease is more effective today with the appropriate use of antibiotic therapy to control pyogenic infections. There is some evidence that administration of desiccated powdered whole liver is of value in treatment of the disease.

SYDNEY S. GELLIS

## REFERENCES

- Eisen, H. N.: Primary Systemic Amyloidosis. *Am. J. Med.*, 1:144, 1946.
- Jacobi, M., and Grayzel, H.: Generalized Secondary Amyloidosis; A Clinicopathological Study of 84 Cases. *J. Mt. Sinai Hosp.*, 12:339, 1945.

Kolmer, J. A., and Boerner, F.: *Approved Laboratory Technic*. 4th ed. New York, D. Appleton-Century Co., 1945.

Rosenblatt, M. B.: *Clinical Considerations and Treatment of Amyloidosis*. U. S. Armed Forces M. J., 2: 739, 1951.

## SARCOIDOSIS

Sarcoidosis, a disease of obscure etiology, has been noted in children, although it is uncommon below the age of ten years. It has not been possible to observe this disease in a sufficiently large number of children to define the clinical pattern adequately in this age group. Most of the manifestations of sarcoidosis in preadolescent children have been extrapulmonary, whereas in adults the lesions have usually been pulmonary, with or without associated lesions in the skin, bones, eyes, and viscera.

The pathologic abnormalities noted in sarcoidosis simulate those observed in chronic granulomatous diseases, especially tuberculosis. *Mycobacterium tuberculosis* has not been demonstrated in these lesions, and most patients with sarcoidosis do not have dermal reactions to tuberculin.

The *epidemiology* is obscure. Observations made on adults in the U.S. Army have shown that Negroes are more commonly affected than white persons and that most patients, regardless of race, have come from rural communities in the southeastern United States.

Uveoparotid fever in children has been described with painless swelling of the parotid or salivary glands, fever and uveitis. Disseminated sarcoidosis involving most of the viscera has also been reported. Pulmonary involvement in the adolescent child and young adult is extremely variable in its extent and characteristics. Parenchymal infiltrates, miliary nodules and hilar and paratracheal lymphadenopathy have been observed singly or in combination in such patients.

Owing to the protean manifestations of sarcoidosis, the *differential diagnosis* is extremely broad. The diseases to be considered include tuberculosis, the various pulmonary mycoses and inflammatory ocular lesions such as phlyctenular conjunctivitis. Sarcoidosis, in adults at least, is commonly associated with hyperproteinemia and hyperglobulinemia; hypercalcemia may also be present. Multiple cystic lesions in the bones of the hands and feet have been noted in some adults. There are no specific diagnostic tests, although the Nickerson-Kveim test, consisting in formation of a granuloma several weeks after intradermal injection of material from a sarcoid lesion, is positive in the majority of active adult cases. Biopsy of affected areas is probably the most valuable diagnostic study.

*Treatment* is symptomatic and supportive. Corticosteroids cause resolution of the inflammatory ocular lesions.

The *prognosis* of sarcoidosis in children is not established, but many adults show spontaneous recovery after a prolonged illness of several months' to several years' duration.

ROBERT H. HIGH

## REFERENCES

- Castellanes, A., and Galan, E.: Sarcoidosis (Besnier-Boeck-Schaumann's Disease): Report of a Case Simulating Still's Disease. *Am. J. Dis. Child.*, 71: 513, 1946.
- Longcope, W. T., and Freiman, D. G.: A Study of Sarcoidosis. *Medicine*, 31:1, 1952.
- Michael, M., Jr., Cole, R. M., Beeson, P. B., and Olson, B. J.: Sarcoidosis. Preliminary Report on a Study of 350 Cases, with Special Reference to Epidemiology. *Am. Rev. Tuberc.*, 62:403, 1950.
- Ricker, W., and Clark, M.: Sarcoidosis. A Clinicopathologic Review of Three Hundred Cases, Including Twenty-Two Autopsies. *Am. J. Clin. Path.*, 19:725, 1949.
- Thornhill, P. S., and Thornhill, E. H.: Boeck's Sarcoid with Nodular Iritis in a Child. *Am. J. Dis. Child.*, 64:262, 1942.



# Neoplasms and Neoplastic-like Tissues

Cancer is one of the leading causes of death in childhood; from three to twenty years of age it is responsible for more deaths than any other disease. What appears to be an increase in the incidence of cancer in recent years is probably in large part the result of decreased mortality from other causes, especially infectious diseases. Although cancer now accounts for approximately 18 per cent of the deaths from disease in children one to fourteen years of age, it continues to be a relatively rare cause of morbidity. As a result, the experience of any physician with neoplasms in early life is likely to be limited, and their importance is often not appreciated.

*Benign tumors* are far more frequent in early life than malignant ones, and many of the benign ones represent hamartomas rather than true neoplasms.

*Hamartomas* are tumor-like congenital malformations resulting from overdevelopment of one or more tissue elements normally present at the site of the tumor, e.g., hemangiomas and osteochondromas. In general they tend to grow concomitantly with the rest of the body and thus do not exhibit the relatively uncontrolled growth characteristic of true neoplasms.

*Malignant neoplasms* have been reported in almost all sites of the body during early life. There are certain sites of predilection, however, which differ sharply from the common locations of cancer in adults. Thus the skin, gastrointestinal tract, lung, prostate and uterus are rare sites of cancer in infants and children, whereas the central nervous system, eye, renal and adrenal regions, hematopoietic system, soft tissues and bones are common sites. Sarcomas are far more common in children than are carcinomas; in adults the reverse is true. Encapsulation of a neoplasm is often considered to be indicative of benignancy in adults, but certain malignant tumors in children, e.g., Wilms' tumors, are often initially encapsulated. Increased cellularity, invasion of adjoining tissues and the presence of mitotic figures are commonly associated with cancer in adults, yet their

occurrence in hemangiomas in infants is entirely compatible with a benign clinical course. Similarly, the presence of incompletely differentiated tissues in a congenital teratoma need not be indicative of malignancy, but may merely reflect incomplete differentiation of the body tissues at this age. Conversely, the juvenile nasopharyngeal angiofibroma may be responsible for death because of its invasiveness, yet its histologic appearance may be that of an innocuous lesion.

The natural course and the therapeutic response of tumors in infants and children cannot always be predicted accurately on the basis of experience with neoplasms in adults. The clinical manifestations of malignant neoplasms in infants and children are often quite different from those encountered in adults. The rapid progression of certain neoplasms in early life may be responsible for a clinical pattern suggestive of an acute infectious process rather than a neoplastic one. In many instances, however, neoplasms in children manifest themselves as abnormal solid masses.

*Every abnormal solid mass in an infant or child should be regarded as a malignant neoplasm until its exact nature is determined by histologic examination of the removed tumor.* Needless palpation of the mass should be avoided, and complete removal should be effected after as brief a time as is consistent with adequate clinical evaluation and preparation for operation. This period usually need not exceed twenty-four to forty-eight hours. Treatment other than by surgical excision should not be instituted until an unequivocal diagnosis has been established by histologic study. Observance of these principles should prevent a number of needless deaths from cancer in infants and children.

## TUMORS OF THE NOSE, SINUSES, PHARYNX, EAR AND ORAL CAVITY

Nasal Polyps. See page 745.

*Juvenile nasopharyngeal angiofibromas* are relatively rare benign neoplasms occurring

almost exclusively in males and primarily between the ages of ten and twenty years. Nasal obstruction and epistaxis are the most frequent clinical manifestations. The tumors arise in the nasopharynx and may expand into the palate or face or invade the maxillary sinuses or orbit. Metastases do not occur, but recurrences following attempted removal or irradiation are common. The tumors are highly vascular, and bleeding may be serious or may render operative removal impossible. Although spontaneous regression may occur with sexual maturity, it is probably uncommon.

**Chordomas** (p. 1369) of the base of the skull may project into the nasopharynx, or the initial manifestations may be those of an intracranial tumor. Owing to their location, operative removal is impossible.

**Teratomas** may arise in the base of the skull, in the roof of the pharynx or in the hard or soft palate and project into the mouth, nasal cavities or cranial cavity. Some of the well differentiated teratomas projecting from the mouth have been described as parasitic fetuses and referred to as epignathi. Histologically, teratomas in this location are benign, but their location may preclude operative removal.

**Osteoma.** See page 1366.

**Papillomas** are rare benign epithelial tumors composed of irregular polypoid masses. They may be single or multiple; they arise from the nasal mucosa more often than from that of the paranasal sinuses. Clinically, they may be confused with nasal polyps. Repeated recurrences are common, and malignant transformation has been reported.

**Adenomas** are benign tumors arising from the glands of the mucous membrane of the nasal and paranasal cavities and are most frequently located in the nasal cavity and ethmoidal region; those in the latter site may erode the cribriform plate. The symptoms are related to nasal obstruction or swelling, and nasal bleeding is common. Recurrences may follow removal.

**Mixed tumors of salivary gland origin** (p. 1349) may arise in the mucous membranes of the nose, paranasal sinuses or the palate. Palatal tumors commonly arise from the posterolateral portion of the hard palate and project into the floor of the nasal cavity and maxillary sinus. The symptoms are those of nasal obstruction. Difficulty in swallowing may be noted in association with palatal tumors. The tumors may be well circumscribed and erode the adjoining bone or may be

poorly circumscribed invasive lesions. Clinical or pathologic differentiation of benign and malignant tumors may be difficult or impossible. Metastases are infrequent. Some of the tumors, especially those in which the epithelial elements predominate, may respond to irradiation.

**Benign Osteoblastoma.** See page 1366.

**Ameloblastomas.** See page 1369.

**Carcinoma of the nasopharynx** or of the tonsil may be a poorly differentiated epidermoid growth, which has been referred to as a transitional cell carcinoma or a lymphoepithelioma. A distinction between such neoplasms and lymphosarcomas arising in the lymphoid tissue of the nasopharynx may be impossible. The primary neoplasm in the nasopharynx may be a diffuse, infiltrative, nonulcerated lesion; at times it may be so small that it is overlooked, and the initial manifestation may be metastases in the cervical lymph nodes. These tumors are radio-sensitive.

**Chemodectomas (nonchromaffin paragangliomas)** are rare tumors arising in the chemoreceptor system, e.g., the carotid and aortic bodies, the ganglion nodosum of the vagus nerve and the glomus jugulare. They may arise in more than one site in an individual patient. The clinical manifestations are dependent upon the site of origin. Those arising in the glomus jugulare are manifest by the presence of an aural polyp which tends to bleed profusely and to recur, by chronic otorrhea, deafness, facial paralysis and osseous destruction in the region of the middle ear. Although the neoplasm invades adjoining tissues, metastases are infrequent.

**Nasal glioma** is a rare tumor-like mass of astrocytes, sometimes with an admixture of ganglion cells, usually found in infants. It may occur as a small subcutaneous nodule over the bridge of the nose or intranasally, where it must be differentiated from an encephalocele.

**Congenital Macroglossia.** See page 636.

**Lymphangioma of the tongue** (p. 1359) may be localized or diffuse. It may be responsible for macroglossia at birth, or a localized lesion may spread to cause macroglossia after some months or years. The lesion is usually a cavernous type of lymphangioma, and the overlying epithelium is thickened and hyperkeratotic. Multiple superficial ulcers may occur, and intermittent glossitis is a common complication. There may be associated lymphangiomatous involvement of the lip, especially the lower one. Localized



tumors are best treated by surgical excision; diffuse forms infrequently respond to irradiation.

**Hemangioma of the tongue** may be localized or diffuse. It is a less frequent cause of macroglossia than is lymphangioma, from which it may be distinguished by its deep red color and tendency to bleed.

**Neurofibroma** may be responsible for unilateral macroglossia. It usually develops before the age of three years and is often associated with neurofibromas of the skin and *café-au-lait* spots.

**Myoblastoma** is a small, superficial benign tumor composed of large granular cells, which may occur in the tongue, especially on the dorsum or along the margins. A derivation of these tumors from neural tissue rather than from skeletal muscle has been suggested. Myoblastoma of the *gum* may be present in newborn infants.

**Epulis** is a term commonly used for any tumor-like growth of the gums, many of which are probably reactive rather than neoplastic. They are pedunculated or sessile growths which may recur after simple removal, but do not metastasize. Histologically, they consist predominantly of fibrous tissue or may contain numerous multinucleated giant cells.

The **lingual thyroid** is a mass in the region of the foramen caecum at the base of the tongue which must be differentiated from a thyroglossal duct cyst. It represents residual thyroid tissue along the course of the primitive thyroglossal duct; in some instances there may be complete failure of descent of the thyroid, in which case removal of the lingual thyroid is followed by hypothyroidism.

**Embryonal rhabdomyosarcoma.** See page 1364.

## TUMORS OF THE SALIVARY GLANDS

**Mikulicz's Syndrome.** See page 638.

**Mixed tumors of salivary glands** are uncommon neoplasms in children. The parotid gland is most frequently affected, the tumor appearing as a round firm mass behind the ramus of the mandible. Histologically, various admixtures of epithelial and mesenchymal-like tissues are present, hence the term "mixed" tumor. Although metastases are infrequent, recurrences are likely.

**Mucoepidermoid tumors** of the salivary glands occur much less frequently than mixed tumors, from which they may be clinically indistinguishable.

**Hemangioma of the parotid gland** is commonly discovered at or soon after birth. It is a bluish, rapidly growing tumor which histologically may be misinterpreted as an angiosarcoma. Treatment is by prompt surgical excision.

## TUMORS OF THE NECK

**Adenomas of the thyroid** are encapsulated neoplasms which do not invade normal tissue or metastasize. They are usually solitary, but multiple adenomas may be present. Clinical and pathologic differentiation of nodular goiter from true neoplasms of the thyroid may be difficult or impossible. The presenting complaint is that of a mass in the region of the thyroid without evidence of dysfunction of the gland. Any nodule in the thyroid should be removed and examined histologically; differentiation of benign adenoma and carcinoma, however, is not always possible.

**Carcinoma of the Thyroid.** See page 1173.

**Teratomas** of the neck may be located within the thyroid or may be independent of this gland. The neoplasms are usually present at birth. They consist of solid and cystic areas containing a variety of well differentiated tissues.

**Thyroglossal Duct Cyst and Branchial Cleft Cyst; Hygroma Colli; Malignant Lymphoma.** See pages 639, 1360 and 992.

## TUMORS OF THE MEDIASTINUM

Most tumors arising in the anterior mediastinum are teratomatous or lymphomatous in origin, whereas most of those arising in the posterior mediastinum are neurogenic. They should be differentiated from cysts of the trachea and bronchi and from neuroenteric cysts and duplications of the esophagus.

## TUMORS OF THE THYMUS

**Primary malignant neoplasms** of the thymus are rare, but may arise from the lymphoid elements (lymphosarcoma) or from the epithelial elements of the organ (thymic carcinoma). The latter neoplasms are often poorly differentiated, with little or no attempt at formation of Hassell's corpuscles, and commonly contain an admixture of lymphocytes. As a result, histologic differentiation of thymic lymphoma and carcinoma may be difficult or impossible. The neoplasm surrounds and may compress the structures in the superior mediastinum, the manifestations being those of cough, dyspnea, and dilation

of the superficial veins of the head, neck and upper thorax. Roentgenographic examination reveals a mass in the anterior-superior mediastinum (p. 998). The neoplasms are usually radiosensitive. The thymus may be involved in mediastinal lymphosarcoma, leukemia or Hodgkin's disease.

**Benign thymomas** are rare neoplasms. They consist of an epithelial reticulum infiltrated with lymphocytes. Myasthenia gravis may be associated with hyperplasia of the thymus or with a benign thymoma.

#### OTHER TUMORS OF THE MEDIASTINUM

**Teratomas** are located in the anterior mediastinum, usually in its superior aspect. Many are benign cystic neoplasms, commonly referred to as *dermoid cysts*. However, since dermoid cysts appear to be merely cystic variants of the more solid teratomas, they need not be considered separate entities. Symptoms may not be apparent until adult life. Dyspnea, cyanosis and cough may be manifestations, and expectoration of hair and sebaceous material may occur if the tumor perforates into a bronchus. Infection of the cystic mass may produce symptoms simulating a pneumonic process. Rarely the neoplasm extends into the suprasternal or supraclavicular area. Compression of the superior vena cava causes dilation of the veins of the head, neck and upper thorax. Roentgenographic examination reveals a circumscribed mass extending from the anterior mediastinum into one hemithorax; when teeth or skeletal elements are demonstrable roentgenographically, the nature of the mass is established.

The neoplasms may be composed of one or more cysts; less frequently they are predominantly solid tumors. The cysts contain sebaceous material, hair or mucoid material. Histologically, almost any type of tissue may be present, especially in the solid neoplasms. Malignant teratomas are usually solid or finely cystic tumors containing actively proliferating, poorly differentiated tissue in addition to more mature elements; the malignant element may be carcinomatous, or multiple tissues within the neoplasm may behave in a malignant manner. Mediastinal teratomas should be surgically removed.

**Lymphoma, Neuroblastoma, Ganglioneuroma, Neurilemmoma, Neurofibroma.** See pages 992, 1355, 1356 and 1363.

**Cystic hygromas** (p. 1360) are usually associated with cervical hygromas.

**Mediastinal lipomas** may arise in the sub-

pleural fat and project into the pleural cavity, the cervical region or through an intercostal space. They may sometimes be identified by their radiolucency and may be suspected when there is extrathoracic extension of a mediastinal tumor.

#### TUMORS OF THE HEART

Primary tumors of the heart are rare in infants and children, and differentiation of certain benign tumors from hamartomas may be difficult or impossible. The majority of the tumors are benign, although instances of sarcoma and malignant teratoma of the heart are recorded. The diagnosis is usually not suspected during life; in a number of instances the tumors have been associated with sudden death. Diagnosis may rarely be suggested by the clinical manifestations and may be confirmed by angiocardiographic studies.

**Rhabdomyoma** of the heart is often associated with tuberous sclerosis (p. 1079). It probably represents a hamartoma rather than a true neoplasm.

**Myxomas** of the heart involve primarily the left atrium. They are usually polypoid tumors which project into the cavity of the atrium. The clinical manifestations may be those of mitral stenosis, sometimes associated with attacks of syncope and progressive cardiac failure.

**Fibroma** of the heart may be responsible for sudden death. The tumors are usually well circumscribed intramural masses, some of which may represent hamartomas rather than true neoplasms.

**Lymphangioma** of the heart may be associated with heart block. Occasionally extracardiac lymphangiomas are also present.

**Sarcomas** of various types have occurred as primary neoplasms of the heart. More than one half of these involve the right side of the heart, and involvement of the right atrium may be responsible for the superior vena caval syndrome.

#### TUMORS OF THE LUNG

Primary neoplasms of the lung are rare, although pulmonary metastases from various sites are relatively common. Every effort should be made to determine whether there is a primary extrapulmonary neoplasm whenever a pulmonary tumor is demonstrated; furthermore, removal of a suspected malignant neoplasm from any site should be pre-



ceded by roentgenographic examination of the chest in search for pulmonary metastases.

**Bronchial adenomas** are firm spherical tumors which project into the lumen of one of the larger bronchi. Ulceration of the overlying mucosa is usually a late feature. These neoplasms initially produce partial and later complete bronchial obstruction, with resultant emphysema followed by atelectasis; the initial symptoms may be those of hemoptysis, pneumonia, or bronchiectasis secondary to bronchial obstruction with retention of secretion. The neoplasm consists of cords or nests of small, round, uniform cells in a vascular stroma. Since the tumors often penetrate the bronchial wall, they should be surgically excised, even if this requires lobectomy or pneumonectomy.

**Hemangiomas** of the lung are rare and may be associated with similar lesions elsewhere. They may be demonstrated roentgenographically. Dyspnea, cyanosis, polycythemia and clubbing of the fingers and toes may be present and lead to an erroneous diagnosis of congenital heart disease. At times a bruit may be audible over the tumor. Surgical excision is the treatment of choice, but the tumors may respond to irradiation.

**Hamartomas** are usually small subpleural nodules, which only rarely reach such a size as to require surgical intervention; they are usually incidental findings at postmortem examination. Most pulmonary hamartomas have been found in adults and consist principally of cartilage.

**Adenomatoid Malformations of the Lung.** See page 781.

**Sarcoma** of the lung is rare in children; some of the reported instances probably represent metastases, and others may be posterior mediastinal neuroblastomas or undifferentiated bronchogenic carcinomas. Detailed histologic studies and careful search for an extrapulmonary source must be made before the diagnosis of primary pulmonary sarcoma can be accepted.

**Sarcomas** are massive tumors which may involve an entire lung. Cavities may occur as a result of necrosis within the neoplasm. The pleura, ribs and vertebrae may be involved, but distant metastases are infrequent.

**Bronchogenic carcinoma** is rare in children. The clinical manifestations may be those of infection, emphysema or atelectasis. Cough is usually present. Surgical excision is the treatment of choice, but the prognosis is poor.

## TUMORS OF THE GASTROINTESTINAL TRACT

**Adenomatous polyps** are usually located in the rectum and sigmoid (p. 684), but also occur elsewhere in the colon, stomach and small intestine. They are usually solitary. There may be no symptoms, or they may be responsible for abdominal pain, obstruction (especially intussusception) or hemorrhage.

**Hemangiomas of the intestine** may be diffuse infiltrating lesions with resultant thickening of the wall and narrowing of the lumen, or localized tumors projecting into the lumen of the bowel. They are at times multiple and may be associated with hemangiomas elsewhere. The manifestations are those of hemorrhage, intestinal obstruction or intussusception.

**Leiomyomas of the intestine** are rare in children; they may be responsible for intussusception.

**Carcinoids** are usually located in the appendix, less frequently in the terminal ileum, in a Meckel's diverticulum or in other parts of the gastrointestinal tract. Appendiceal tumors are often associated with obstruction of the appendiceal lumen and the clinical manifestations of acute appendicitis. Tumors of the ileum may be asymptomatic or may be responsible for intestinal obstruction. They are usually slowly growing tumors, but are probably best regarded as low grade malignant neoplasms. Metastases from appendiceal carcinoids are rare, although the muscularis and serosa are often invaded by the tumor. The higher incidence of metastases from extra-appendiceal carcinoids may be related to the later onset of symptoms with resultant delay in removal of the neoplasm.

**Lymphosarcomas** occur in the small intestine or, less frequently, in the appendix and stomach. They may be polypoid intraluminal masses or diffuse areas of infiltration of the wall of the bowel. Cures may be obtained by surgical removal.

**Multiple polyposis** is a rare, often familial condition characterized by the presence of innumerable sessile and pedunculated tumors, usually involving the colon. It should not be confused with the presence of isolated or scattered adenomatous polyps. Areas of pigmentation may be present in the mucous membranes of the lips and mouth and in the skin (Puetz-Jeghers syndrome), especially with polyposis of the small intestine. The disease may be asymptomatic or may be mani-

fest by abdominal pain, hemorrhage or intussusception. Malignant change occurs with sufficient frequency to warrant resection of the affected segment of the bowel.

### TUMORS OF THE LIVER

Metastatic neoplasms of the liver in infants and children are more frequent than primary ones, and may arise from various neoplasms, especially from a neuroblastoma. There are usually no manifestations other than hepatomegaly; in rare instances the clinical pattern of glycogen storage disease has been produced.

**Infantile hemangioendothelioma** is the usual vascular tumor of the liver in infants, cavernous hemangiomas similar to those encountered in adults being rare. The tumors are commonly multicentric within the liver, and extrahepatic hemangiomas are present in some instances. The multiplicity of the lesions and the active proliferation of vessels within them may suggest a malignant neoplasm, but they probably represent vascular hamartomas rather than true neoplasms.

Clinical manifestations are commonly present in the first weeks of life. An abdominal mass is often the only presenting complaint, but anemia and rarely ascites and jaundice may be present. In some instances cardiomegaly and evidence of congestive heart failure may lead to an erroneous diagnosis of congenital heart disease; cardiovascular manifestations have been attributed to arteriovenous shunts within the tumor. Fatal hemorrhage may occur spontaneously or after biopsy. The solitary tumors are probably best treated surgically. Multicentric tumors of the liver should be treated by irradiation, although spontaneous regression may occur in some instances.

**Adenomas** are rare solitary circumscribed neoplasms composed of hepatic cells without well defined hepatic cords. They are not associated with cirrhosis and should be differentiated from the adenomatous hyperplastic nodules associated with hepatic damage. The tumor may reach a large size and probably may undergo malignant change; differentiation from carcinoma may be difficult. They should be treated by surgical excision.

**Hamartomas** are usually solitary encapsulated tumors which may reach a large size. They are not associated with cirrhosis, and the manifestations are those of an abdominal mass. The tumor may be pedunculated or

located deep within the liver. The tumors consist of the tissues normally found within the liver, but arranged in a disorderly manner. They are not true neoplasms, but opinions differ as to whether they represent malformations or regenerative hyperplastic nodules secondary to injury. Easily resectable lesions should be surgically removed, but others are probably best left untreated after the diagnosis has been established by biopsy. There is no evidence to indicate that they become malignant.

**Mesenchymal hamartomas** of the liver are not related to the hamartomas described above. They are cystic masses which usually manifest themselves during infancy. The presenting complaint is that of an upper abdominal mass which may increase rapidly in size, owing to the accumulation of fluid within the lesion. The tumor is usually located near the lower margin of the liver. It may project into the pelvis and can often be outlined roentgenographically. The tumor can usually be identified grossly by its multicystic appearance. It is poorly demarcated from the adjoining hepatic parenchyma. Histologically, it consists of connective tissue containing cystic spaces, many of which may have no demonstrable lining cells. Small numbers of hepatic cells and bile ducts are present, especially about the periphery of the lesion. The tumor should be surgically excised, but it is probably unnecessary to sacrifice a margin of normal hepatic tissue about it, since recurrence would seem to be unlikely.

**Carcinoma** (hepatoma) of the liver, although relatively uncommon, should be considered in the differential diagnosis of an abdominal mass. The tumor may be present at birth, and in somewhat over half of the reported instances symptoms have developed before two years of age. The manifestations are usually those of gradual abdominal enlargement with the presence of a palpable mass. Pain may precede the presence of a palpable mass, and fever often occurs late in the course of the disease. Icterus and ascites are usually absent. Occasionally demineralization of the skeleton and an increase in the lipid fractions of the blood may be associated with carcinoma of the liver. Roentgen films may reveal calcification within the neoplasm. The average duration of life after the onset of symptoms is about four months.

The neoplasm may consist of a solitary mass, or multiple nodules of neoplastic tissue



may be distributed throughout the hepatic parenchyma. Cirrhosis is unusual in association with these tumors in infants and children. Histologically, they consist of closely packed hepatic cells with varying degrees of differentiation (hepatocellular carcinoma). The neoplastic cells may be well differentiated, and the lesion may thus be interpreted erroneously as a benign adenoma. Carcinoma arising from the bile ducts (cholangiocellular carcinoma) is a much less frequent type of neoplasm in children.

Small amounts of osteoid are occasionally present in hepatocellular carcinomas. In certain neoplasms, osteoid, cartilage and squamous cell carcinoma, as well as hepatocellular and cholangiocellular carcinoma, are intimately admixed with sarcomatous elements; these are referred to as *hepatic mixed tumors*. However, small amounts of osteoid are occasionally encountered in hepatocellular carcinomas, and there is no sharp line of division between these and mixed hepatic tumors.

Treatment of carcinoma of the liver consists in surgical excision. Care must be taken, however, to differentiate between nodular areas of regenerating hepatic tissue associated with cirrhosis or hepatitis and true neoplasms.

**Teratoma** of the liver is a rare tumor which is usually recognizable at or shortly after birth. They tend to have a bizarre lobated structure. They contain a variety of tissues foreign to the liver and derived from multiple germ layers, e.g., skin, brain, bone, intestinal glands.

**Mesenchymomas** of the liver are composed of a mixture of mesodermal elements, i.e., angiomatous, fibrous and undifferentiated mesenchymal tissue. Epithelial elements are usually absent. Although those occurring in the liver usually appear to be malignant, some have been successfully resected.

**Sarcoma** of the liver is rare. The neoplasms are often undifferentiated and are classified with difficulty. Embryonal rhabdomyosarcomas have been reported as arising in the liver as well as within the common bile duct.

**Ectopic adrenal tissue** may occur beneath the hepatic capsule, and rarely benign or malignant adrenal cortical tumors may arise in the liver. The diagnosis of such an *adrenal rest tumor* within the liver probably should not be made unless evidences of adrenal cortical hyperfunction are present or the hormones are identified within the tumor.

## TUMORS OF THE PANCREAS

**Adenoma of the Islets of Langerhans.** See page 1217.

**Adenocarcinomas** are extremely rare neoplasms in infants and children. The manifestations include anorexia, icterus, a palpable abdominal mass, and diarrhea; a celiac-like syndrome may occur as a result of the neoplasm. The tumor may be so undifferentiated that histologic distinction between carcinoma and sarcoma may be impossible.

**Lymphosarcoma.** (See also page 992.) Primary lymphosarcoma of the pancreas is extremely rare, but has been reported during the neonatal period.

## TUMORS OF THE KIDNEY

**Embryoma of the kidney (Wilms' tumor)** is one of the most common abdominal neoplasms of early life. The majority appear during the first four years of life; rarely it may be manifest at birth or initially in adult life. The tumor is usually unilateral. Similar neoplasms occasionally arise in the retroperitoneum independent of the kidney.

The presenting complaint is usually that of an abdominal mass. Hematuria is usually absent. Fever and leukocytosis may occur as a result of hemorrhage and necrosis within the tumor. Physical examination reveals a firm, nontender mass, which may extend to the midline and down into the iliac fossa; it does not commonly cross the midline as a neuroblastoma is likely to do. Pyelography reveals no characteristic pattern, but distortion of the renal pelvis is common; lateral displacement of the affected kidney is less likely than with a neuroblastoma. Although such features may strongly suggest that the mass is a Wilms' tumor, no pathognomonic signs exist; an unequivocal diagnosis is established only by histologic examination.

Macroscopically, the neoplasm is encapsulated until a relatively late stage, when it may invade the renal pelvis and ureter, renal veins or perirenal fat (Fig. 421). The capsule of the tumor is continuous with that of the affected kidney, and subcapsular hemorrhage may be responsible for pain or for apparent rapid "growth" of the neoplasm. The regional lymph nodes and the lungs are common sites of metastases.

Histologic examination reveals a somewhat varied pattern in different neoplasms and in different parts of the same tumor. The most



FIG. 421. Wilms' tumor in lower portion of right kidney. The kidney and tumor have been hemisected.

common appearance is that of broad cords and sheets of undifferentiated mesenchymal cells separated from each other by loose connective tissue, and containing tubules in varying stages of differentiation; this sarcomatous and carcinomatous pattern has given rise to the terms "adenosarcoma" and "mixed tumor of the kidney." Other structures may also be present, which include abortive glomeruli, skeletal and smooth muscle fibers, squamous epithelium and cartilage. Since all these elements are readily derived from mesenchymal tissue, these neoplasms should not be regarded as teratomas.

When a persistent abdominal mass which *could* be a retroperitoneal neoplasm is present, surgical exploration is indicated. Preliminary studies should be conducted promptly (twenty-four to forty-eight hours) and with as little trauma as possible; unnecessary palpation of the tumor should be avoided. Pyelography is indicated to determine the location of the mass, if possible its nature, and in particular to demonstrate that the opposite kidney is functioning adequately. The surgeon should be prepared to remove the mass or to perform other appropriate measures, e.g., drainage and/or plastic repair of a hydronephrosis. Preoperative roentgenograms of the chest should be made in an attempt

to exclude the presence of pulmonary metastases.

Although cures of Wilms' tumors may occur after irradiation alone, histologic examination of tumors removed after a course of roentgen therapy commonly reveals neoplastic cells. Preoperative irradiation is generally contraindicated, since by such treatment of occasional benign or non-neoplastic lesions may be needlessly irradiated, with injurious sequelae. During the operative procedure ligation of the renal veins and ureter prior to manipulation of the mass is important in preventing spread of the neoplasm by these routes. The perirenal fat and any regional lymph nodes encountered should be removed. Postoperative irradiation to the site of the neoplasm is currently used, even though there is evidence to suggest that permanent damage to the opposite kidney may rarely be produced.

The prognosis of Wilms' tumors, although grave, is not as hopeless as formerly considered. In recent years the experience in certain medical centers has been highly encouraging; in one reported series apparent cures were obtained in 47 per cent of the entire group, and 80 per cent of the infants less than twelve months of age survived two years or longer. The accumulated data of Abeshouse from a rather large number of sources disclose a survival rate of only 20 per cent two years after removal of the tumor; at ten years only 5 per cent had survived. Late recurrences or metastases are less common in infants than in older children. If recurrences or metastases have not occurred after a period equivalent to that of the age of the patient at the time of removal of the neoplasm plus nine months, the probability of cure is good. However, Abeshouse records deaths from the neoplasm as long as twenty years after removal of the primary tumor. It is difficult, however, to be as pessimistic as this last report would appear to justify, in view of the much better results which have been obtained in centers where there is considerable interest in this problem as compared with the general experience throughout the country.

**Hypernephroma (renal cell carcinoma),** the common renal carcinoma in adults, is extremely rare in children.

**Adenomas** or small benign growths composed of epithelial elements may occur in association with angiomas of the retina and cerebellum and with cysts of the pancreas and kidney (*I Lindau's disease*); they probably are hamartomas rather than true neoplasms.



**Hamartomas** or small fibrous nodules may occur in the renal medulla or less frequently in the cortex; they are not sharply limited and may contain tubules as well as connective tissue, smooth muscle and fat.

Multiple tumors of varied histologic structure may be present in each kidney in patients with *tuberous sclerosis* (p. 1079); rarely renal insufficiency may occur as a result of these tumors.

## TUMORS OF THE ADRENAL

**Neuroblastoma** is one of the most common malignant neoplasms in infants and children. Although commonly arising in the adrenal medulla or periadrenal tissue, it may arise at any site along the sympathetic chain, e.g., the retroperitoneum, posterior mediastinum or the cervical ganglia. The majority occur in the first three years of life and may even be widely disseminated at birth. Bilateral involvement of the adrenal glands may occur. The presenting complaint is commonly that of an abdominal mass, but at times the primary tumor is small, and the initial complaints are referable to metastatic lesions, e.g., pain in the extremities as a result of osseous metastases, exophthalmos from orbital metastases, or massive hepatic enlargement. Fever and leukocytosis may be present, and the clinical manifestations may suggest an infectious rather than a neoplastic process.

A neuroblastoma in the adrenal or periadrenal region often crosses the midline, in contrast to a Wilms' tumor. Roentgenographic examination commonly reveals lateral and downward displacement of the kidney on the affected side; focal areas of calcification are more often present in neuroblastoma than in Wilms' tumor, and distortion of the renal pelvis is more common in the latter neoplasm. However, intrarenal neuroblastomas may occur and be macroscopically indistinguishable from Wilms' tumor.

The tumor is initially encapsulated, but later may extensively infiltrate the surrounding tissues. The aorta, inferior vena cava, ureter and renal pedicle may be completely surrounded by neoplasm, making complete surgical excision impossible. Removal may also be impaired by extensive areas of hemorrhage and necrosis within the tumor. Metastases are often widespread, common sites of involvement being the liver, bones, orbits, meninges and lymph nodes. The osseous metastases may be extensive, and aspiration of bone marrow may reveal characteristic

pseudorosettes even in the absence of roentgenographic changes. Roentgenograms of the skeleton often reveal widespread destructive lesions of many bones, with multiple areas of rarefaction (Fig. 422). In the long bones the destructive process and associated periosteal reaction may simulate the appearance of osteogenic sarcoma or, more frequently, of Ewing's tumor (Fig. 425) or of acute leukemia; bilateral symmetrical involvement of



FIG. 422. Roentgenograms revealing metastatic neuroblastoma involving the tibias and tarsal and metatarsal bones. Note the tendency toward a symmetrical distribution of the lesions. Extensive periosteal new bone formation is present in the right tibia; the appearance simulates that of a primary neoplasm of bone.

the long bones and pelvis is often present. Ewing's tumor (p. 1368) and the osseous metastases of neuroblastoma may also be similar histologically, and every attempt should be made to exclude the latter before accepting a diagnosis of Ewing's tumor.

The neuroblastoma may show varying degrees of differentiation toward mature ganglion cells, or rarely toward mature chromaffin tissue. The more undifferentiated neoplasms, in which pseudorosettes are not apparent, may be misinterpreted as malignant lymphomas. Better differentiated areas reveal the classic pseudorosettes or, less frequently, immature or mature ganglion cells. However, all grades of differentiation may be present in a single neoplasm, and examination of multiple sections may be necessary before the neuroblastic nature of the lesion can be established. Many have been erroneously referred to as lymphosarcoma or undifferentiated sarcoma.

The diagnostic study of a patient suspected of having a neuroblastoma is similar to that described under Wilms' tumor. Roentgenograms of the skeleton and chest and a pyelogram should be obtained. Examination of material aspirated from the bone marrow may aid in establishing the diagnosis.

*Treatment* consists in surgical removal of the primary neoplasm, followed by irradiation of the operative site; if complete surgical excision is impossible, removal of as much of the neoplasm as can safely be performed should be attempted. Some systemic antineoplastic agent such as Aminopterin, nitrogen mustard or a corticosteroid is used as an adjuvant in our clinic. Localized metastases which are apparent initially or appear later and which are not readily removable surgically are treated with roentgen irradiation. A number of recoveries after hepatic metastases and even a few after localized skeletal metastases are recorded.

Spontaneous cures of neuroblastoma are extremely rare. In recent years recoveries following therapy have been reported with increasing frequency and certainly justify treatment of any patient who is not in a terminal condition. The results of therapy are probably dependent upon the age of the patient as well as upon the stage to which the disease has advanced at the time therapy is instituted; the prognosis is definitely better in infants than in older children.

**Ganglioneuromas** are composed of ganglion cells, Schwann cells and neurites and

are apt to occur at a slightly older age than are neuroblastomas; the majority are found before the age of twenty years. They arise from the sympathetic ganglia in the retroperitoneum, posterior mediastinum, cervical region or adrenal medulla or rarely from ganglia in other locations. The tumors are encapsulated and often attain a large size before clinical manifestations appear. They are usually solid tumors without the extensive areas of hemorrhage or necrosis common in the neuroblastoma. Completely differentiated ganglioneuromas are benign neoplasms; the less differentiated forms, however, contain immature ganglion cells or neuroblasts and may metastasize. Many sections of these neoplasms should be examined histologically in order that less differentiated areas may not be overlooked.

**Pheochromocytoma; Adrenal Cortical Tumors.** See pages 1192 and 1189.

## OTHER RETROPERITONEAL TUMORS

**Retroperitoneal teratomas** are the third most frequent type of retroperitoneal neoplasm in infants and children, neuroblastoma and Wilms' tumor being more common. Approximately half of retroperitoneal teratomas are found during the first year of life. They are usually large tumors arising high in the retroperitoneal region; they may occupy one side of the abdomen or cross the midline. The presenting complaint is usually that of an abdominal mass; many of the masses show no apparent growth over a period of several months. Roentgenographic examination often reveals areas of mineralization within the tumor, in addition to displacement of the kidney or ureter. Clinical differentiation of the teratoma from neuroblastoma or Wilms' tumor may be impossible. Prompt surgical removal preceded by pyelograms and roentgenograms of the chest and skeleton is the treatment of choice.

**Pelvic and retroperitoneal teratomas** are large tumors arising in the presacral region. They extend upward into the retroperitoneal tissues and may extend outward into the buttock.

**Sacrococcygeal Teratoma; Chordoma.** See pages 685 and 1369.

**Tumors of the soft tissues of the retroperitoneum** (p. 1362) include benign and malignant tumors derived from adipose or fibrous tissue and malignant tumors derived from skeletal muscle. They are usually bulky



neoplasms which clinically may be indistinguishable from the more common retroperitoneal neoplasms: Wilms' tumor, neuroblastoma and teratoma.

**Retroperitoneal lipoma; retroperitoneal lymphoma.** See pages 1362 and 992.

**Retroperitoneal lymphangiomas** are large cystic tumors composed of dilated lymphatics, which may occur independently or in conjunction with similar tumors in the mesentery.

**Retroperitoneal hemangiopericytoma.** See page 1359.

## TUMORS OF THE BLADDER AND PROSTATE

Neoplasms of the bladder are rare. The majority are rhabdomyosarcomas, although leiomyosarcomas, myxomas, papillary carcinomas of low grade malignancy and hemangiomas have been reported.

Rhabdomyosarcomas (p. 1364) may originate in the bladder or prostate. They usually occur in the first decade and have been reported at birth. They are bulky masses, often with a grapelike configuration (sarcoma botryoides) and usually can be palpated through the rectum. Clinically they are manifest by obstruction to the flow of urine, hydro-nephrosis with secondary pyelonephritis, frequency, dysuria and hematuria. Metastases are usually relatively late, but early extension to contiguous structures is common. The prognosis is extremely grave. Radical surgical extirpation is the treatment of choice, possibly followed by irradiation.

## TUMORS OF THE TESTIS

The highest incidence of testicular neoplasms in early life is during the first three years. The majority of the tumors are malignant, embryonal carcinoma being the most common type; seminomas are extremely rare in infants and children. The presenting complaint is usually that of painless swelling of one testis. The tumor is firm, cannot be transilluminated, and the overlying skin is often discolored, but not adherent to the mass. In some instances the initial complaint is that of a palpable abdominal mass, the result of metastases from an unrecognized testicular neoplasm.

**Embryonal carcinoma** is the most frequent type of testicular neoplasm in infants and children. Metastases are especially likely to be located in the iliac and periaortic lymph

nodes and lungs; involvement of the left supraclavicular lymph nodes may follow intrathoracic metastases. The prognosis is grave, but cures have been obtained.

**Teratomas** contain various tissues derived from different germ layers and may consist of both fetal and adult structures. They are all considered malignant tumors, since in large series in adults there has been no relation between the clinical behavior and the apparent differentiation of the elements within the tumor. Teratomas may contain admixtures of other germinal tumors, i.e., seminoma, embryonal carcinoma or choriocarcinoma.

**Seminomas** consist of sheets of rather uniform cells separated by trabeculae of connective tissue in which lymphocytes are often present. The prognosis is better than that associated with the other malignant testicular neoplasms.

**Testicular choriocarcinomas** are neoplasms containing villous-like arrangements of cytotrophoblasts and syncytial trophoblasts. Pure choriocarcinomas are less frequent than are choriocarcinomatous foci in other testicular neoplasms, especially in embryonal carcinomas and teratomas. Gynecomastia and urinary chorionic gonadotropin may be present in association with choriocarcinoma, but may also occur with embryonal carcinomas.

**Testicular adenocarcinoma with clear cells** has been described as a distinctive type of neoplasm of infants. It is a locally invasive tumor which may metastasize, but cures have occurred after orchiectomy and postoperative irradiation. The cell of origin of the neoplasm is not established.

**Androblastomas** are rare testicular tumors comparable to ovarian arrhenoblastomas (p. 1358). They may be present at birth.

*Treatment of neoplasms of the testis* consists in orchiectomy preceded by ligation of the spermatic cord as high as possible. Adjuvant therapy is dependent upon the type of neoplasm, but it should be recognized that different types of neoplastic cells may occur within a single tumor. Seminomas, which are highly radiosensitive, are probably best treated by orchiectomy followed by irradiation to the entire periaortic chain of lymph nodes as well as to the left supraclavicular lymph nodes. Embryonal carcinoma and choriocarcinoma are less radiosensitive and are best treated by orchiectomy and resection of the iliac and periaortic lymph nodes to the level of the renal pedicles, followed by irradiation. A

similar operative procedure should be performed for teratomas, but the value of postoperative irradiation in these tumors is questionable.

**Interstitial Cell Tumor.** See page 1197.

## TUMORS OF THE OVARY

Ovarian neoplasms in infants and children are rare. The manifestations are usually pain and an abdominal mass; torsion of the pedicle may be associated with nausea and vomiting, the clinical findings suggesting a diagnosis of acute appendicitis.

**Teratomas of the ovary** may be cystic benign tumors (dermoid cyst) or predominantly solid neoplasms, the former being somewhat more common. Over half of the solid teratomas in children are responsible for death. Ovarian teratomas are usually unilateral and are palpable through the abdominal wall or by rectal examination. Roentgenograms may reveal areas of calcification within the mass. Rarely isosexual puberty may occur in association with choriocarcinomatous elements in a teratoma of the ovary. *Treatment* is by surgical excision.

**Cystadenomas of the ovary** are less frequent than teratomas. They are usually unilateral and benign. They may be serous or pseudomucinous. Simple cysts probably represent non-neoplastic follicular cysts or unilocular serous cystadenomas. Treatment consists in surgical excision.

**Carcinomas of the ovary** in children are usually solid unilateral tumors which are initially encapsulated. They should be treated by surgical excision; the value of postoperative irradiation is questionable.

**Dysgerminomas** are probably derived from undifferentiated cells which have not yet developed male or female characteristics. They occur predominantly after the age of ten years. There may be associated genital hypoplasia or pseudohermaphrodis, but the neoplasm does not secrete hormones. More than one fourth of the tumors are bilateral. They are solid tumors, often with areas of hemorrhage and necrosis; histologically they resemble seminomas of the testis. The tumor is radiosensitive and is probably best treated by surgical excision and postoperative irradiation.

**Arrhenoblastomas** are masculinizing tumors of the ovary occurring principally in adults; they have been observed in adolescent girls, but not in prepuberal children.

**Granulosa Cell Tumor.** See page 1201.

## TUMORS OF THE VAGINA AND UTERUS

**Sarcoma botryoides** is a descriptive term referring to a polypoid, grapelike malignant neoplasm of mesenchymal origin. They are predominantly embryonal rhabdomyosarcoma (p. 1364), but those arising from the vaginal wall or cervix uteri and projecting into the vagina or externally through the vulva may also contain areas of cartilage or other mesodermal elements. They frequently invade the bladder, and determination of the site of origin may be impossible. They are most frequent in the first few years of life. The manifestations are urinary frequency, bloody or profuse foul-smelling vaginal discharge and the presence of multiple polypoid "grapelike," edematous or hemorrhagic masses protruding into the vagina. Metastases may occur to the lungs and other viscera as well as to lymph nodes. The prognosis is extremely grave. They should be treated by radical surgical excision, including hysterectomy and possibly postoperative irradiation.

## TUMORS OF THE SKIN AND SOFT TISSUES

**Hemangiomas** are probably congenital malformations (hamartomas) rather than true neoplasms, but they may exhibit various neoplastic qualities. They are the most common tumors in infants and children, the majority being present at birth or developing within the first year of life. With rare exceptions the tumors are benign, and treatment is largely for cosmetic purposes.

**Capillary hemangiomas (strawberry nevi)** are well circumscribed, slightly elevated, bright red to deep purple tumors which incompletely blanch on pressure. They consist of multiple lobules of small capillaries interspersed with cords of cells resembling endothelium, but without distinct vascular lumens. *Hemangioendotheliomas* are probably only variants of the capillary hemangioma in which the predominant pattern is that of endothelial proliferation with sparsely developed vascular lumens. Hemangiomas, especially in infants, may reveal active cellular proliferation with scattered mitotic figures and invasion of surrounding tissues or even of veins; in spite of such histologic findings they almost always behave clinically as benign tumors. They may be treated by application of carbon dioxide snow or dry ice, irradiation or surgical excision (p. 1274), but in the majority of instances they will spontaneously regress over a period of a few years. Accord



ingly, unless they are in a location where they interfere with function, they are probably best not treated.

**Cavernous hemangiomas** are poorly circumscribed, blue or purple elevated tumors which tend to extend more deeply into the subcutaneous tissues than do the capillary hemangiomas. They consist of numerous cystic vascular spaces containing blood. Mixed forms of cavernous and capillary hemangiomas are common. Cavernous elements which do not regress spontaneously are probably best treated by surgical excision. Cavernous hemangiomas may occur in sites other than the skin, e.g., in bone, liver and in the tongue. In skeletal muscles they manifest themselves by pain and the presence of a diffuse mass which decreases in size with elevation of the part; foci of calcification may be demonstrable by roentgenographic examination. Hemangiomas of the intestine, which may be capillary or cavernous, may be responsible for hemorrhage and intussusception. *Diffuse hemangiomas* of an extremity may be associated with hypertrophy of the part and of the associated bone. Rarely large vascular tumors may be associated with thrombocytopenia, purpura and anemia.

**Nevus vinosus** (*nevus flammeus*, *portwine mark*) is usually located on one side of the face and may correspond to the distribution of the trigeminal nerve. It is a flat, irregular lesion which may be light pink at birth and later deep purple. It blanches on pressure. It consists of scattered dilated vessels in the superficial dermis. Treatment is unsatisfactory. A somewhat similar lesion is often present in the nape of the neck, over the bridge of the nose or on the eyelids of newborn infants; these usually disappear spontaneously.

**Cirroid aneurysms** (*racemose hemangioma*, *congenital arteriovenous fistula*) are rare lesions consisting of a pulsating mass of dilated, tortuous arteries, veins and capillaries. They may be associated with a nevus vinosus.

**Glomus tumor** is a small bluish tumor usually located on the extremities, especially in the subungual region. It manifests itself by excruciating pain, especially on contact. Histologically it resembles a cavernous hemangioma except for the presence of discrete glomus cells in the walls of the vessels. The tumor is benign, and treatment is by surgical excision. Such tumors are rare in children.

**Hemangiopericytomas** are rare tumors thought to be derived from cells normally

located just outside the basement membrane of the capillaries. The tumor may occur in the superficial soft tissues or in deeper tissues, e.g., the retroperitoneum. The vascularity of the tumor may not be apparent in routine histologic sections. The malignancy of the tumor varies and often cannot be correlated with its histologic pattern; congenital hemangiopericytomas are usually benign.

**Hereditary hemorrhagic telangiectasia** (*Rendu-Osler-Weber disease*) consists of multiple minute reddish-purple spots composed of thin-walled dilated capillaries and venules, occurring most frequently in the mucous membranes of the nose and mouth, but at times in the skin and in various viscera. There is a history of repeated hemorrhages, especially epistaxis, and of familial occurrence. Recurrent attacks of epistaxis may begin during childhood and may precede the appearance of the telangiectases.

**Angiomas of the retina** (*von Hippel's disease*) may be associated with cerebellar angiomas, cysts of the pancreas and adenomas of the kidney (*Lindau's disease*).

**Sturge-Weber syndrome.** See page 1080.

**Lymphangiomas**, which are less common than hemangiomas, are also probably malformations (hamartomas) rather than true neoplasms. They are often present at birth. The most common locations are on the neck and extremities. The various types of lymphangioma may be associated with each other in a given tumor, and other mesodermal elements, including smooth muscle, adipose tissue, foci of lymphocytes and hemangiomatous areas, may also be present. The tumors are benign, but, because of their infiltrative tendency, recurrences are common, and complete surgical extirpation may be difficult or impossible.

**Simple lymphangiomas** are rare, small, flat or verrucous lesions usually located on the face or neck. They consist of dilated lymphatic vessels in the superficial dermis.

**LYMPHANGIOMA CIRCUMSCRIPTUM** is a rare condition characterized by the presence of small groups of thick-walled vesicles. It may be present at birth or begin in infancy or childhood. The lesions are superficial simple lymphangiomas.

Diffuse lymphangiomas are poorly circumscribed tumors occurring in the skin, mucous membranes or muscles. They are usually congenital. In the tongue and lips they are responsible for macroglossia and macrocheilia, respectively. Diffuse lymphangioma of an extremity is responsible for one form of

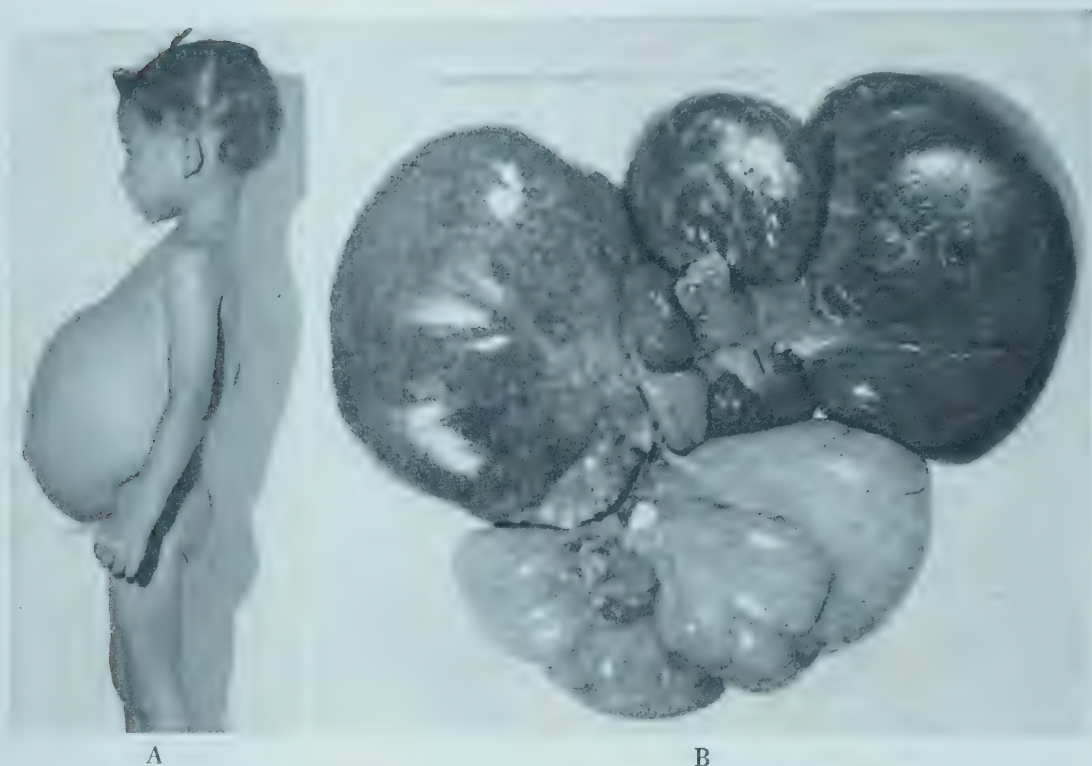


FIG. 423. A, Three-year-old girl with large multicystic cystic hygroma of the mesentery (mesenteric cyst). B, The cyst with its contents weighed almost 4000 gm.

elephantiasis (*elephantiasis lymphangiectatica*). It may involve an entire extremity or only a portion, e.g., the fingers or foot; there may be associated hypertrophy of the bone in the affected area. Histologically, the dilated lymphatic channels may be obscured by abundant scar tissue. The more localized lesions should be treated by surgical excision, but recurrences are frequent. Treatment of the more diffuse lesions is usually unsatisfactory; lymphangiomatous macroglossia may respond to irradiation.

**Cystic lymphangiomas (cystic hygromas)** are most frequently encountered in the neck (hygroma colli) and in the axillae, but may also occur in the inguinal and retroperitoneal regions. In the cervical region they may extend into the mediastinum, and rarely mediastinal hygromas may occur in the absence of a cervical component. *Omental* and *mesenteric* cysts (Fig. 423) are frequently cystic hygromas. *Sacral hygromas* may simulate lipomas or sacrococcygeal teratomas; they are sometimes connected with the spinal canal. Enlargement of cystic lymphangiomas may occur as the result of enlargement of the individual cysts, from the formation of new cysts or from hemorrhage into the cysts.

**HYGROMA COLLI** is the most common type of cystic lymphangioma. It is usually

demonstrable at birth as a soft, poorly defined mass, often in the posterior cervical triangle; many of the tumors can be transilluminated. Periodic fluctuations in the size of the mass are common, and rapid increase in size is often associated with hemorrhage into the cystic spaces. The size of the cervical component of a cervicomedial hygroma is greatly influenced by crying or by the phase of respiration. The tumors are often asymptomatic, but respiratory difficulty or difficulty in swallowing may occur with severe displacement of the trachea or esophagus.

The tumor may surround vessels and nerves, and the cystic spaces may project in various planes, making surgical excision difficult. They are lobulated, thin-walled cystic structures which are usually multilocular; the cystic cavities may be independent of one another or may communicate freely. The contents usually consist of clear colorless fluid, but this may be xanthochromic or bloody. The walls of the cysts are lined by endothelium and are composed of connective tissue, smooth muscle and foci of lymphocytes.

Cystic lymphangiomas should be treated not only for cosmetic purposes, but also to prevent complications such as infection and mediastinal compression. Hygroma colli and



ygromas of the mediastinum are best treated by surgical excision. Irradiation is sometimes used for tumors which are not surgically accessible, but in general the tumors are not susceptible to radiotherapy.

**Epidermoid cysts** are spherical, benign tumors often located in the skin of the neck, face or scalp; they are probably derived from congenital ectodermal rests and are not true neoplasms.

Epidermoid cysts in the calvarium are demonstrable roentgenographically as sharply demarcated defects surrounded by dense sclerotic bone.

**Dermoid cysts** are clinically indistinguishable from epidermoid cysts and probably have similar derivation; they should not be interpreted as teratomas. They are often located in the skin above the eye. Histologically they resemble epidermoid cysts except for the presence of skin appendages in their walls.

**Calcifying epitheliomas** are hard, sharply demarcated benign tumors of the skin which may arise at any site, especially in the face or upper extremities. Clinically they may be confused with epidermoid cysts, and pathologically they have been interpreted by some as representing proliferative and secondary degenerative changes in an epidermoid cyst. Their principal importance is the fact that histologically they may be interpreted erroneously as carcinoma.

**Pigmented nevi** in infants and children are usually clinically benign, even though their histologic appearance may simulate that of the malignant melanoma of adults. They may be present at birth as large, rough, dark brown or black areas, as in the "bathing trunk" nevus, sometimes with smaller nevi in the surrounding skin. Smaller nevi may first be noted in infancy, childhood or even adult life. The tumors may be located at almost any site, may be smooth or papillary, light brown to almost black, and may contain hair.

The histologic pattern of nevi in infants and children varies somewhat from that usually encountered in adults. Benign nevi in children tend to be more cellular than those in adults, are more likely to have multinucleated cells and may contain mitotic figures. Failure to recognize the occurrence of these features in the benign nevi of infants and children may lead to an erroneous diagnosis of malignant melanoma.

Certain nevi reveal an even more striking histologic similarity to that of the malignant

melanoma of adults and have been referred to as *juvenile melanomas*. They tend to be somewhat larger, purplish red rather than dark brown, hairless, and somewhat more elevated than the usual nevi in children. They are benign lesions which should be treated by conservative surgical measures.

Owing to their frequency, removal of all nevi is not feasible. Those on the genitals, palms of the hands and soles of the feet as well as those in other sites which are subjected to repeated irritation should be removed prior to puberty. The occurrence of increasing pigmentation, ulceration, rapid growth or a pigmented halo about a nevus is an indication for surgical excision of the growth with a wide margin of intact skin.

**Malignant melanomas** are rare prior to puberty. Histologically, they resemble the more active malignant melanomas of adults. They may occur in association with xeroderma pigmentosum. Malignant melanoma in the pregnant woman has been reported as metastasizing to the placenta and infant.

**Blue nevi** are usually smooth, firm, blue or bluish black nodules occurring on the face, buttocks, or dorsum of the feet or hands. The lesion may resemble a mongolian spot histologically, and cellular forms have been misinterpreted as malignant. Malignant transformation of a blue nevus, however, is rare.

**Dermatofibrosarcoma protuberans** is a slowly growing invasive tumor arising in the dermis. It begins as one or more hard, painless nodules which slowly coalesce, protrude from the skin and may ulcerate. The fibroblastic tissue within the neoplasm tends to form irregular strands and whorls. The tumor may recur locally over a period of many years, but metastases are rare.

#### TUMORS OF SKIN APPENDAGE ORIGIN

The classification of neoplasms derived from skin appendage is not entirely uniform, and differentiation between neoplastic and non-neoplastic lesions may be difficult. The tumors tend to be clinically benign, although in some the histologic pattern may suggest a malignant neoplasm. Only a few of the tumors of skin appendage origin will be discussed.

**Syringocystadenoma papilliferans** is a tumor derived from the ducts of apocrine glands. It usually occurs as a single plaque, most frequently on the scalp; minute cysts are sometimes visible within the lesion, the surface of which may reveal areas of crust-

ing. Histologically it consists of numerous villous-like processes which project into the lumens of the dilated ducts.

**Syringomas** occur as hundreds of small, soft, slightly elevated, yellowish pinhead-sized nodules, especially about the eyelids, chest, abdomen and anterior aspects of the thighs. They are found predominantly in females and develop at the time of puberty. Histologically they consist of numerous small cystic ducts located in the dermis. These are benign lesions which are probably not true neoplasms.

**Tricho-epithelioma** (epithelioma adenoides cysticum) usually occurs in females at the time of puberty. It is frequently familial. Multiple small discrete yellow to pink nodules appear on the face and occasionally on the upper trunk. The tumor is derived from hair follicles and may contain areas closely simulating basal cell carcinoma; rarely a basal cell carcinoma may develop in adult life.

**Cylindromas** (turban tumors) are multiple benign growths which are often familial. They occur predominantly on the scalp of females, sometimes appearing in early childhood or at puberty. They usually appear initially on the forehead as smooth, firm, freely movable, painless nodules. They increase in number and size throughout life, so that ultimately the entire scalp may be covered by a lobulated mass of lesions. The origin of these tumors is disputed. They are nearly always benign and are best treated by surgical excision.

**Nevus sebaceus** (Jadassohn) is a circumscribed, slightly raised firm yellow plaque usually occurring on the scalp or face and present at birth. It is composed of large numbers of sebaceous glands.

**Adenoma sebaceum** (Pringle). See pages 1079, 1139 and 1280.

#### **SQUAMOUS CELL CARCINOMA; BASAL CELL CARCINOMA**

These are rare in children, but may occur, especially in xeroderma pigmentosum.

#### **CUTANEOUS LEIOMYOMAS**

These occur as solitary or multiple small nodules in the skin. They may be tender and painful, but this may not be apparent for years after the tumor has been first noted. The tumors consist of bundles of smooth muscle derived from the arrectores pilorum muscles or from vascular walls. They are usually benign and are probably best treated by surgical excision; electrocoagulation and

freezing with carbon dioxide snow have been used for eradication of multiple tumors.

#### **TUMORS OF THE SOFT TISSUES**

Neoplasms arising from muscle, fat and connective tissue comprise a miscellaneous but important group of tumors of early life. They may arise at almost any site and vary from benign neoplasms such as the lipoma to highly malignant sarcomas; the latter may be so undifferentiated as to preclude accurate determination of their cell of origin. They may occur at any age; among sixty-six congenital malignant neoplasms, exclusive of retinal tumors (Wells), there were thirty-three examples of sarcoma of various types. The most frequent manifestation is a visible and/or palpable mass; clinical differentiation of benign and malignant neoplasms is often impossible. Every solid mass should be considered malignant until proved otherwise by histologic examination of the excised mass.

Only some of the more common tumors of the soft tissues and some of those which present particular problems in diagnosis and treatment will be discussed.

**Lipomas** are benign, sharply circumscribed, rounded, lobulated tumors which may reach an enormous size. They are radiolucent and may be transilluminated; rarely calcific deposits may occur within the tumor. Rapid enlargement of these tumors may suggest a malignant change, but actual malignancy developing within a pre-existing lipoma is rare.

The most common site of these tumors, which may be multiple, is in the subcutaneous tissue. Small congenital lipomas may arise from the deep fascia on the palmar surfaces of the fingers and hands. A subcutaneous lipoma in the buttock may simulate a sacrococcygeal teratoma. Lipomas arising on the inner surface of the masseter muscle may extend into the parotid gland and simulate primary tumors of this gland.

**Retroperitoneal lipomas** are rare tumors usually arising in the perirenal region, which may attain a large size and distort or displace the renal pelvis or ureter. They may be circumscribed, easily removable lesions or diffuse tumors which cannot be completely removed. Sarcomatous areas may be present within these neoplasms.

**Mediastinal lipoma.** See page 1350.

**Diffuse lipomatosis** of an extremity may be present at birth, with resultant massive enlargement of the part; associated deformities of the adjoining bones may be present. In



her instances they are manifest as ill-defined tumors usually located in skeletal muscle. Complete removal may be difficult or impossible, and recurrences are common. Such diffuse lipomatoses probably represent a hamartomatous malformation rather than a true neoplasm and, in spite of recurrences, could not be misinterpreted as malignant neoplasms.

**Fibromas** are benign circumscribed neoplasms derived from fibroblasts. Pure fibromas are relatively rare, many of the tumors referred to as such being neurogenic in origin.

**Juvenile nasopharyngeal angiofibroma.** See page 1347.

**Dermatofibromas (sclerosing hemangioma, histiocytoma, subepidermal fibrosis)** are solitary, slightly elevated benign tumors of the skin. They are usually small, varying in size to 1 cm. in diameter, and on section are yellow and firm. The tumor consists of spindle-shaped cells often arranged about small spaces suggesting capillaries; vacuoles of eosinoid material, granules of hemosiderin and multinucleated giant cells are often present. They are interpreted by some as sclerosing hemangiomas.

**Desmoids** are fibromas of the musculoaponeurotic sheaths, most frequently in the anterior abdominal wall of women. Their neoplastic nature is not accepted by all observers, but their clinical behavior, with infiltration of surrounding tissues, continued growth and repeated recurrences, is certainly that of a neoplasm of low grade malignancy. The tumor may be present at birth or may first be noted in later infancy or childhood. They arise from aponeuroses usually in the abdominal wall and often involve the entire thickness of the wall. They are usually poorly circumscribed tumors which may recur even after apparently complete excision. Histologically, their appearance is that of a fibroma with inclusions of residual skeletal muscle within the tumor. Treatment should be by wide surgical excision.

**Congenital generalized fibromatosis** is an extremely rare condition characterized by the presence of multiple firm, spherical or ovoid fibroblastic tumors involving superficial and muscular tissues as well as viscera and sometimes bones. The lesions are present at the time of birth and are widely distributed over the body, but the more superficial ones show some predilection for the trunk, thighs and shoulder girdles. One of the masses may be dominant and suggest a primary neoplasm, but the multiple nodules appear to be in-

dependent growths (possibly hamartomas) and not metastatic lesions. Death occurs in the neonatal period.

**Fibromatosis of the plantar fascia** is of importance because it may be erroneously interpreted as fibrosarcoma and amputation performed; fibrosarcoma is even more uncommon than fibromatosis. Fibromatosis is manifest as single or multiple nodular swellings, sometimes associated with pain. They are usually not adherent to the overlying skin, and contractures are rare. Instances of congenital plantar fibromatosis have been reported. The lesion consists of interweaving bundles of cellular tissue composed of spindle-shaped cells. It is not clear whether this is an entity distinct from juvenile aponeurotic fibroma. Treatment consists in removal of the plantar fascia; incomplete removal may be followed by recurrence.

**Juvenile aponeurotic fibroma** is a rare lesion of childhood, appearing as a firm, painless, noncircumscribed tumor in the palm of the hand or sole of the foot. It is not associated with contractures of the part and is not fixed to the skin. Roentgenograms may reveal focal areas of calcification within the tumor. Although some of the tumors may be discrete neoplasms with ill-defined borders, others appear to arise multicentrically and to infiltrate fat and skeletal muscle; this lack of delineation may in part be responsible for the recurrences which may take place. The tumor consists of numerous plump, rather uniform nuclei oriented in one direction and embedded in a stroma of closely packed collagen. Areas of calcification may be present. The neoplasm is benign, although it may recur one or more times. Surgical excision (not amputation) is the treatment of choice.

**Neuromas** are not true neoplasms, but consist of proliferative masses of Schwann cells, axon fibers and connective tissue which develop at the proximal end of a severed nerve. They may be extremely painful.

**Neurilemmomas (schwannoma, neurinoma)** are benign, solitary, encapsulated tumors which arise from the peripheral, sympathetic or cranial nerves. The acoustic nerve is the commonest site of neurilemmoma arising from a cranial nerve. Peripherally located tumors are not likely to become as large as those in the posterior mediastinum or retroperitoneum. The tumor may be solid or partially cystic. Histologically it is characterized by palisading of the nuclei.

**Neurofibromas** may occur as solitary tumors or may be associated with multiple

neurofibromatosis (p. 1079). It commonly grows at the end of a cutaneous nerve, producing small, nonencapsulated tumors which may be single or multiple. Histologically it consists of interweaving bundles of fibroblastic-like cells with varying amounts of collagen. *Plexiform neurofibromas* may occur as isolated lesions or in association with *elephantiasis neuromatosa*, in which severe thickening of the part may be associated with hypertrophy of the bone. *Intraspinal neurofibromas* may occur singly or in association with multiple neurofibromatosis. The tumors may be entirely intraspinal or may penetrate an intervertebral foramen and produce a paravertebral mass.

**Neurofibroma of bone.** See page 1366.

**Giant cell tumors of tendon sheath origin** are small firm tumors arising from a tendon sheath or less frequently from an articular capsule. They are most frequent on the flexor surface of the fingers, less often on the toes. They resemble a fibroma containing foam cells and multinucleated giant cells. The tumor is benign, but may recur if incompletely removed.

**Benign mixed mesodermal tumors** are rare tumors which are usually small, nonencapsulated, and located in the soft tissues. They may contain a variety of mesodermal elements, including adipose tissue, smooth muscle and angiomatous areas. Some of these may be hamartomas rather than true neoplasms. Treatment is by surgical excision.

**Myxomas** are rare neoplasms which may arise in different structures, the more frequent ones being the heart, soft tissues and genitourinary system. Tumors in the soft parts may be soft and semitranslucent if superficially located; these features may not be apparent in more deeply situated tumors. They should be treated by wide surgical excision; otherwise recurrences are frequent.

**Sarcoma of soft tissues.** A variety of malignant neoplasms of mesenchymal origin occur in the soft tissues of infants and children and may be present at birth. The presenting complaint is usually that of a palpable mass, at times only recently noted and in other instances of relatively long duration. Differentiation of benign and malignant neoplasms of the soft tissues is usually impossible clinically, and the nature of the neoplasm is established only by histologic examination. In general, treatment is by wide local excision with removal of a substantial margin of surrounding normal tissue; the edges of the resected specimen should be examined histologically in

order to determine adequacy of the removal. Inadequate removal of sarcomas of even low grade malignancy may be followed by repeated recurrences or even by metastases. Sarcomas are usually radioresistant, but occasionally they may show some response to irradiation. Metastases are usually hematogenous rather than lymphogenous.

**Fibrosarcomas** vary from well differentiated tumors which are readily cured by local excision to highly undifferentiated neoplasms which are fatal in spite of wide excision. The better differentiated fibrosarcomas merge imperceptibly with the benign fibromas, whereas the fibroblastic origin of some of the highly undifferentiated neoplasms may be impossible to establish.

**Neurofibrosarcomas** (*neurogenic sarcoma*) may occur in patients with multiple neurofibromatosis or as solitary neoplasms; differentiation of the latter from fibrosarcoma may be impossible.

**Liposarcomas** are malignant tumors derived from fat and may occur at an early age. Only small amounts of fat may be demonstrable in some of these neoplasms. Although best treated by surgical excision, some of the tumors may respond to irradiation.

**Rhabdomyosarcomas** are malignant mesenchymal neoplasms revealing varying degrees of differentiation toward skeletal muscle. The more differentiated (but still highly malignant) neoplasms usually arise in the skeletal muscle of an extremity and are manifest by the presence of a mass deep in the affected part; they are rare in infants and children. Less differentiated neoplasms (embryonal rhabdomyosarcomas) tend to arise in the urogenital system and in the region of the head and neck, especially in the orbit, nasopharynx, soft palate, middle ear and maxillary sinuses; less frequently they may arise in an extremity. These are predominantly neoplasms of infants and children and may even be noted at birth. Embryonal rhabdomyosarcomas arising just beneath the mucous membrane of a hollow viscus or a body cavity may assume a grapelike or polypoid configuration and are referred to as sarcoma botryoides. The presenting complaint is usually that of a mass in the affected site, often with ulceration and secondary infection. The neoplasms are infiltrative and rapidly growing and may metastasize widely. The treatment of choice is wide surgical excision followed by irradiation. The prognosis is grave, but cures have been effected.

**Alveolar soft part sarcomas** occur pre-



ominantly in the muscles of the extremities of females. They are usually slowly growing tumors which may recur locally and may metastasize years after removal of the primary neoplasm. Their origin is not established, although some authors have suggested a relationship to nonchromaffin paragangliomas. Histologically they are characterized by a pseudoalveolar arrangement of the neoplastic cells in relation to delicate endothelial-lined vascular channels and septa. They should be treated by wide surgical excision.

**Leiomyosarcomas**, malignant neoplasms derived from smooth muscle, are rare in infants and children. They may arise in soft tissues as well as in the prostate and bladder.

**Synovioma** is a malignant neoplasm usually arising in the soft tissues near the knee; only rarely is the synovium of the joint involved. The neoplasm presents as a slowly enlarging mass involving the soft tissues. Recurrence is common, and the tumor metastasizes to regional lymph nodes, the viscera and bones. The prognosis is grave. Radical surgery is the treatment of choice, and some advise immediate amputation even for small circumscribed tumors.

## NEOPLASMS OF BONE

A variety of benign and malignant neoplasms of bone have been described in children in addition to non-neoplastic lesions which clinically and roentgenographically simulate true neoplasms. Roentgenographic studies are valuable for the detection and interpretation of osseous lesions, but diagnosis and treatment of suspected neoplasms of bone require clinical and *histologic* studies in addition.

### BENIGN NEOPLASMS AND NEOPLASTIC-LIKE LESIONS

**Osteochondromas** (*osteocartilaginous exostoses*) may be solitary or multiple. They probably represent anomalies of development rather than true neoplasms. Multiple exostoses are discussed on page 1244. The solitary osteochondroma is one of the most common of the benign osseous tumors. It is most frequently located at or near the ends of the long bones, especially the lower end of the femur or upper end of the tibia, but may arise from any bone which is preformed in cartilage. It usually manifests itself in childhood or adolescence by a bony protuberance; occasionally pain may result from a fracture through its stalk or from the development of an overlying bursitis. The tumor consists of

a bony mass near the epiphysis which protrudes in the direction of the shaft and is covered by a cap of cartilage. Growth of the mass tends to cease at or before cessation of skeletal growth. After cessation of growth the cap of cartilage may disappear, leaving only the residual outgrowth of bone (osteoma). Malignant transformation of an osteochondroma usually does not occur until after cessation of skeletal growth and is more frequently observed in the presence of multiple exostoses; the resultant neoplasm is usually a chondrosarcoma. It has been estimated that 5 per cent of patients with multiple exostoses will ultimately have malignant neoplasms from one or more sites. Surgical resection of the tumor should be performed whenever feasible as a prophylactic measure against malignancy.

**Enchondromas** are solitary benign cartilaginous tumors arising within the bones. They probably are hamartomas rather than true neoplasms. Skeletal enchondromatosis refers to the presence of such tumors in multiple sites; when the involvement is predominantly unilateral, the condition is referred to as Ollier's disease (p. 1245); when there are associated vascular malformations, it is referred to as Maffucci's syndrome.

Solitary enchondromas are usually located in cylindrical bones, especially in one of the short bones of the hands or feet. The initial symptoms are often pain and swelling following a pathologic fracture. Roentgenograms reveal a well circumscribed area of rarefaction within the bone, with or without expansion of it and attenuation of the overlying cortex; dense stippled foci representing areas of calcification are commonly present. There is usually no periosteal formation of new bone unless infraction of the cortex has occurred. Histologically, the tumors consist of lobules of atypical hyaline cartilage, the matrix of which may have undergone a myxomatous change. Malignant changes within an enchondroma may occur, but are not common. The development of chondrosarcoma in the short bones of the hands or feet is rare. Treatment of solitary enchondroma consists in curettage, and the introduction of bone chips or a bone graft if necessary.

**Benign chondroblastomas** are rare tumors derived from young cartilage cells. They occur predominantly in adolescent males and characteristically involve the epiphysal end of a long bone. The neoplasm manifests itself by pain which is often referred to the neighboring joint. Roentgenographically the lesion

appears as a rarefied mottled focus arising in the epiphysis, but sometimes extending into the adjoining metaphysis; it tends to be encircled by a narrow line of increased density. Histologically it consists of cellular areas of compact round or polyhedral cells, deposits of hyaline cartilaginous matrix, focal areas of calcification, necrosis and hemorrhage. The presence of multinuclear giant cells may lead to an erroneous diagnosis of giant cell tumor. Treatment consists in curettage with instillation of bone chips.

**Chondromyxoid fibroma** is closely related to benign chondroblastoma. It is a rare benign tumor usually encountered in the metaphysis of one of the long bones of the extremities. The lesion appears as an eccentrically located, expansile rarefied area in the metaphysis; the borders tend to be scalloped and well defined by a narrow band of opaque sclerotic bone. In small bones the roentgenographic appearance may be that of an expansile, pseudotrabeclated cyst occupying the entire width of the bone. Histologically the tumor consists of lobulated masses of closely packed cells embedded in a myxoid matrix; the latter may undergo extensive fibrosis, and in some areas recognizable cartilaginous matrix may be formed by the neoplastic cells. The tumor, although rare, is of importance because it may be confused with a malignant tumor, especially a chondrosarcoma. Curettage followed by instillation of bone chips usually suffices to cure the tumor, but recurrences may take place.

**Osteomas** are benign tumors composed of osseous tissue which arise in the bones of the face or skull and may project from the surface or extend into the orbit or paranasal sinuses. Other growths indistinguishable from true osseous neoplasms may represent the end stage of an osteochondroma or may be the result of reactive non-neoplastic formation of bone.

**Osteoid osteoma** is most frequently located in the tibia or femur, but may occur in other bones. The predominant symptom is pain, often with localized tenderness; swelling and, rarely, slight local heat and redness may be present. Roentgenograms may not demonstrate a distinctive lesion in the early stages. Characteristically, however, there is a small radiolucent area surrounded by a zone of sclerotic bone; the latter may extend well beyond the lesion and may obscure the area of radiolucency. In some instances the central nidus may be radiopaque and thus not be

visible within the dense peripheral sclerotic bone.

The tumor consists of a central nidus of sharply circumscribed osteoid tissue with varying degrees of mineralization. The dense peripheral zone noted on the roentgenogram consists of reactive, non-neoplastic bone. The tumor is benign and can be cured by complete removal of the nidus; failure to remove the nidus is followed by a recurrence of symptoms.

**Benign osteoblastoma** (osteogenic fibroma, ossifying fibroma, fibrous osteoma) is a rare neoplasm composed of a fibrous matrix with areas of osteoblastic activity, osteoid tissue and bone. It occurs predominantly in children and young adults and involves especially long bones, vertebrae and the maxilla and mandible. Roentgenographically, it is a well circumscribed lesion which may expand and attenuate the cortex; its inner border tends to be limited by a zone of sclerotic bone. Although the lesion is clinically benign, its histologic features may simulate those of an osteosarcoma as well as a variety of neoplastic and non-neoplastic lesions of bone. Complete clinical and roentgenographic data, as well as the histologic findings, must be carefully evaluated before accepting a diagnosis of benign osteoblastoma.

**Nonosteogenic fibroma** is a benign tumor which usually occurs near the end of the diaphysis of one of the long bones, especially in the lower extremity. The lesion may be asymptomatic, or pain, sometimes interpreted as arthritis, may occur. Roentgenograms reveal a rarefied, trabeculated lesion with a sharply outlined margin of sclerotic bone; the lesion is usually eccentrically located within the bone. The tumor consists of bundles of spindle-shaped connective tissue cells with no attempt at the formation of bone. Abundant hemosiderin pigment, multinuclear giant cells, foam cells and collagen may be present. The lesion can be successfully treated by curettage. Spontaneous healing may occur, however, and there is considerable doubt as to the neoplastic nature of the lesion.

**Neurofibromatosis** (see also p. 1079). Neurofibromas may involve the bones directly, with extensive destruction and deformity, or they may be associated with skeletal abnormalities such as scoliosis, pseudarthrosis, skeletal enlargement of part or of an entire extremity, or a defect in the wall of the orbit with unilateral pulsating exophthalmos.



**Giant cell tumors** are rare in childhood, since they characteristically occur in the ends of long bones after closure of the epiphyses. The majority of lesions interpreted as such are probably solitary unicameral cysts.

**Hemangiomas** may occur as primary osseous lesions or in association with hemangiomas in the adjoining soft tissues. Primary osseous hemangiomas are located especially in the vertebrae, although they may also occur in other sites. Roentgenographically, they may appear as pseudotrabeclated, cystic expansile lesions. In the skull a so-called sun-ray appearance may be noted on the roentgenogram. Hemangiomas of the vertebrae may involve two or more adjoining vertebral bodies and produce a vertical striated appearance; collapse of the vertebrae with pressure on the spinal nerve rootlets may be responsible for symptoms.

**Epidermoid Cyst.** See page 1361.

**Eosinophilic Granuloma.** See page 1004.

**Solitary unicameral cysts** are common lesions occurring in the metaphyses of long bones, especially in the upper ends of the tibia and humerus and lower end of the femur. They rarely occur after closure of the epiphysial line. The lesion is often symptomless until pain occurs after a pathologic fracture.

The lesions probably begin in the metaphysis, and growth of the bone displaces them away from the epiphysial plate. It causes a central rarefaction of bone, often with a pseudotrabeclular pattern (Fig. 424); the defect is usually no wider than the adjacent metaphysis, although expansion of the shaft may occur. The cortex is attenuated and may be fractured. The roentgenographic appearance may be similar to that of such conditions as fibrous dysplasia, enchondroma or eosinophilic granuloma. In contrast to the giant cell tumor and benign chondroblastoma, it does not cross the epiphysial plate.

The lesions are cystic and contain blood or fluid, which is often xanthochromic. The cyst is lined by a small amount of nonspecific vascular connective tissue containing deposits of hemosiderin, lipid-laden macrophages and multinucleated giant cells.

**Treatment** consists in curettage and packing with bone chips. Spontaneous healing may occur, especially after a pathologic fracture, but treatment is usually indicated.

**Aneurysmal bone cysts** may involve almost any bone; vertebral lesions probably constitute approximately one fourth of the cases. The presenting complaint is usually that of

pain, at times associated with a palpable mass; neurologic manifestations may be present with lesions of the vertebrae. Roentgenographically they appear as cystic expansile lesions which, especially in the long bones, tend to extend outward beyond the surface of the bone. Multiple incomplete septa are often visible within the radiolucent area. The expanded lesion is usually outlined by a thin shell of periosteal new bone, but rupture of this may occur with extension of the process into the adjoining soft tissues. Macroscopically, the cysts contain bloody fluid and soft, hemorrhagic or reddish-brown tissue; abundant blood may persistently obscure the operative field at the time of operation. Histologically they consist of pools of blood separated by septa of connective tissue; giant cells, hemorrhages and newly formed bone may be present within the septa. *Treatment* is indicated because of the tendency of the lesion

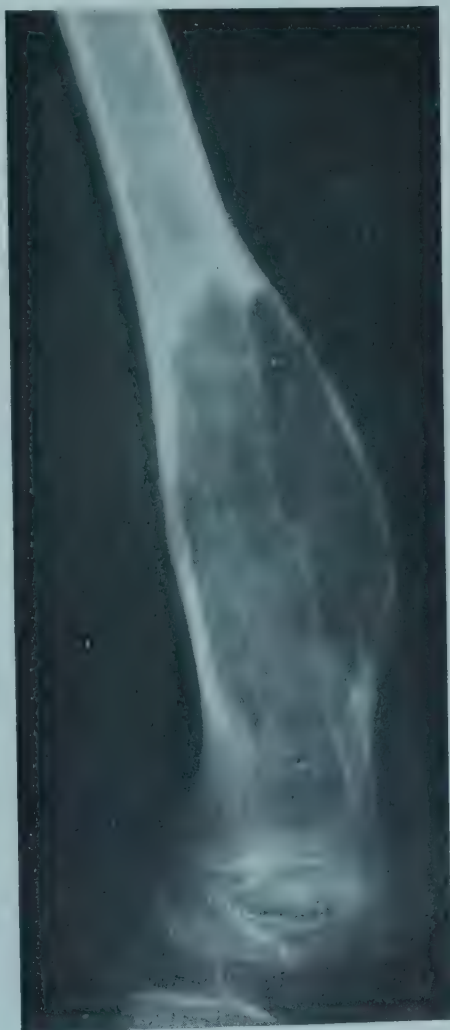


FIG. 424. Solitary unicameral cyst of lower end of femur. Note the "trabecular" pattern and expansion of the cortex. The epiphysis is intact, a characteristic of the lesion.

to progress and consists in curettage or less frequently in irradiation; even incomplete curettage may be followed by healing. The lesion probably is not a true neoplasm.

### MALIGNANT TUMORS OF BONE

By far the most frequent primary malignant tumors of bone are the osteosarcoma and Ewing's tumor, the majority of which occur between ten and twenty-five years of age, males being affected more frequently than females. Osteosarcoma characteristically involves the metaphysial end of a long bone, whereas Ewing's tumor involves the shaft, but roentgenographic differentiation of these two neoplasms is not always possible. Of greater importance, however, is the fact that many, if not all, of the roentgenographic features of these tumors may be duplicated by non-neoplastic lesions of bone. Accordingly, treatment of lesions suspected of being malignant tumors of bone should not be instituted until an unequivocal diagnosis is established by histologic study of the tumor. Moreover, the pathologist is limited in his ability to establish a diagnosis on the basis of histologic studies alone. For example, an actively growing callus about a fracture may closely simulate the histologic appearance of an osteosarcoma, yet correlation of the material obtained at biopsy with the roentgenographic findings may clearly indicate the true non-neoplastic nature of the process. Thus the pathologist must evaluate all pertinent clinical, roentgenographic and surgical data before he arrives at a diagnosis.

**Osteosarcoma** (osteogenic sarcoma) is more common than Ewing's tumor. It usually begins at the lower end of the femur or the upper end of the tibia or humerus, but may arise at other sites. The presenting complaint is commonly that of pain and swelling of the affected part, which the patient may attribute to trauma.

Roentgenographic studies reveal varying degrees of destruction of bone and of new bone formation. Codman's triangle is a radiopacity at the end of the tumor where the periosteum has been elevated. Neither this finding nor the perpendicular striations of new bone in the subperiosteal neoplasm ("sun-ray appearance") are always present, nor are they pathognomonic of an osteosarcoma. An elevated serum alkaline phosphatase, indicative of new bone formation, may be present.

The neoplasm at the time of amputation usually occupies the medullary cavity and has



FIG. 425. Roentgenograms of a Ewing's tumor of the tibia. A, The initial film revealed only slight periosteal proliferation. B, Roentgenogram, taken 3 months later, reveals cortical destruction and proliferation of new bone, the latter assuming a "sun-ray" appearance in some areas.

penetrated the cortex to the subperiosteal zone; penetration of the periosteum into adjoining soft tissues may also occur. The cortex, even though penetrated by neoplasm, may appear relatively intact or may be extensively destroyed. Histologically the appearance is varied, but consists essentially of atypical mesenchymal cells with varying degrees of formation of typical or atypical osteoid tissue and true bone. Cartilaginous areas and areas of myxomatous tissue may be present. Osteosarcoma commonly metastasizes to the lungs, although other organs may also be involved; osseous metastases are rare. Amputation appears to offer the best possibility of cure. The mortality rate, however, is high, but Dahlin has reported 19 per cent of patients surviving five years.

**Ewing's tumor** may involve the same bones as does osteosarcoma; in addition, there is relatively frequent involvement of the flat bones and the ribs. The initial complaints are often similar to those associated with an osteosarcoma; fever and leukocytosis may occur with either tumor, but are more likely to be associated with Ewing's tumor.

Roentgenographically, the lesion produces a mottled area of rarefaction, often associated with increased density and periosteal forma-



tion of new bone (Fig. 425). The latter may be deposited in layers, resulting in an "onion-skin" appearance, but this finding is often absent and may appear in association with other osseous lesions. The roentgenographic appearance may closely simulate that of osteomyelitis, osteosarcoma, eosinophilic granuloma of bone or metastatic neuroblastoma (Fig. 425).

Gross examination of an affected bone usually reveals more extensive neoplastic involvement than was demonstrable roentgenographically. Histologically the tumor consists of sheets of uniform round or oval nuclei with little or no cytoplasm. The neoplastic cells do not form new bone. Extensive areas of hemorrhage and necrosis are commonly present. The histologic appearance may be indistinguishable from that of a metastatic neuroblastoma, and every attempt should be made to exclude the presence of an extra-osseous primary lesion.

Ewing's tumor usually involves a single bone when first recognized, but ultimately many bones may be affected. Metastases to the lungs are also common. *Treatment* is unsatisfactory. Although the neoplasm usually responds initially to roentgen therapy, cures are rare. The results following irradiation are probably comparable to those obtained by amputation.

**Primary reticulum cell sarcoma of bone** often arises in a long bone and may simulate Ewing's tumor both roentgenographically and histologically; it is not accepted by all observers as distinct from Ewing's tumor. Metastases to lymph nodes occur more frequently than in Ewing's tumor, and osseous metastases are infrequent. Irradiation is probably the treatment of choice. The prognosis is more favorable than that of Ewing's tumor.

**Chondrosarcoma** is rare in children. It usually arises from the bones of the trunk or the upper ends of the humerus, femur or tibia. The clinical course is less rapid than that of osteosarcoma, and the prognosis, when amputation can be performed, is somewhat more favorable.

**Fibrosarcoma** may arise within the medullary cavity of a bone, commonly the lower end of the femur, or from the periosteum or adjoining connective tissue and erode the adjacent bone. It differs from osteosarcoma in that there is no tendency to formation of even atypical osteoid or bone. Roentgenographically the underlying bone may appear intact, or there may be areas of cortical destruction; the margins of the neoplasm are

usually poorly defined. *Treatment* consists in complete surgical resection or, if necessary, amputation; in general the prognosis is more favorable than is that of osteosarcoma.

**Multiple myelomas** are extremely rare in children. Roentgenographically they may simulate metastatic neuroblastoma, Ewing's tumor, acute leukemia, multiple eosinophilic granulomas, Hand-Schüller-Christian or Letterer-Siwe disease.

**Chordomas**, or tumors derived from remnants of the notochord, are rare in children. Although not strictly neoplasms of bone, they invade and destroy bone at their site of development, usually the sacrococcygeal region or base of the skull. They are locally invasive tumors which usually cannot be successfully removed; metastases are unusual. Some chordomas in children have been reported as responding to irradiation.

**Ameloblastomas (adamantinoma)**, which are epithelial tumors derived from remnants of the enamel organs, occur more frequently in the mandible than in the maxilla. Tumors arising in the maxilla may obliterate the antrum and bulge into the orbit, nasal cavity or mouth. Roentgenographically they are usually expansile, well circumscribed lesions, but they may penetrate into adjoining tissues. Recurrences following curettage are frequent, and rarely metastases may occur. Cranio-pharyngiomas (p. 1086) may have the histologic appearance of an ameloblastoma, and tumors of similar appearance have been reported in the tibia. Certain rare pigmented tumors occurring primarily in the maxilla of infants have been referred to as *melanoameloblastomas*; they may be derived from misplaced optic remnants (retinal anlage tumors).

**Odontoma.** See page 620.

JAMES B. AREY

## REFERENCES

### General

- Andersen, D. H.: Tumors of Infancy and Childhood. I. A Survey of Those Seen in the Pathology Laboratory of the Babies Hospital during the Years 1935-1950. *Cancer*, 4:890, 1951.
- Bodian, M., and White, L. L. R.: Neoplastic Diseases in Childhood. *Great Ormond St. J.*, 4:105, 1952.
- Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms. *Arch. Path.*, 30: 535, 1940.

### Tumors of the Nose, Pharynx, Ear and Mouth

- Lattes, R., and Waltner, J. G.: Nonchromaffin Paraganglioma of the Middle Ear. (Carotid-Body-Like

- Tumor; Glomus-Jugulare Tumor). *Cancer*, 2:447, 1949.
- Ringertz, N.: Pathology of Malignant Tumors Arising in the Nasal and Paranasal Cavities and Maxilla. *Acta Otolaryng.*, Suppl. 27, 1938.
- Sternberg, S. S.: Pathology of Juvenile Nasopharyngeal Angiofibroma—A Lesion of Adolescent Males. *Cancer*, 7:15, 1954.
- Tumors of Salivary Glands*
- Foote, F. W., Jr., and Frazell, E. L.: Tumors of the Major Salivary Glands. *Cancer*, 6:1065, 1953.
- Tumors of the Mediastinum*
- O'Gara, R. W., Horn, R. C., Jr., and Enterline, H. T.: Tumors of the Anterior Mediastinum. *Cancer*, 11:562, 1958.
- Tumors of the Heart*
- Prichard, R. W.: Tumors of the Heart. Review of the Subject and Report of One Hundred and Fifty Cases. *A.M.A. Arch. Path.*, 51:98, 1951.
- Tumors of the Gastrointestinal Tract*
- Mauro, J., and Prior, J. T.: Gastrointestinal Poly-poid Lesions in Childhood. *Cancer*, 10:131, 1957.
- Tumors of the Liver*
- Bigelow, N. H., and Wright, A. W.: Primary Carcinoma of the Liver in Infancy and Childhood. *Cancer*, 6:170, 1953.
- Edmondson, H. A.: Differential Diagnosis of Tumors and Tumor-Like Lesions of Liver in Infancy and Childhood. *A.M.A. Am. J. Dis. Child.*, 91:168, 1956.
- Tumors of the Kidney*
- Abeshouse, B. S.: The Management of Wilms' Tumor as Determined by National Survey and Review of the Literature. *J. Urol.*, 77:792, 1957.
- Gross, R. E., and Neuhauser, E. B. D.: Treatment of Mixed Tumors of the Kidney in Childhood. *Pediatrics*, 6:843, 1950.
- Ng, E., and Low-Beer, B. V. A.: The Treatment of Wilms' Tumor. *J. Pediat.*, 48:763, 1956.
- Tumors of the Adrenal*
- Hausman, C. F., and Girdany, B. R.: The Roentgenographic Findings Associated with Neuroblastoma. *J. Pediat.*, 51:621, 1957.
- Phillips, R.: Neuroblastoma; Hunterian Lecture. *Ann. Roy. Coll. Surg. England*, 12:29, 1953.
- Wittenborg, M. H.: Roentgen Therapy in Neuroblastoma. A Review of Seventy-Three Cases. *Radiology*, 54:679, 1950.
- Other Retroperitoneal Tumors*
- Arnheim, E. E.: Combined Pelvic and Retroperitoneal Teratomas in Infancy and Childhood. *Pediatrics*, 10:198, 1952.
- Tumors of the Testis*
- Dixon, F. J. and Moore, R. S.: Testicular Tumors. A Clinicopathological Study. *Cancer*, 6:427, 1953.
- Magner, D., Campbell, J. S. and Wiglesworth, F. W.: Testicular Adenocarcinoma with Clear Cells, Occurring in Infancy. *Cancer*, 9:165, 1956.
- Tumors of the Skin and Soft Tissues*
- Bivings, L.: Spontaneous Regression of Angiomas in Children. Twenty-Two Years' Observation Covering 236 Cases. *J. Pediat.*, 45:643, 1954.
- Christopherson, W. M., Foote, F. W., Jr., and Stewart, F. W.: Alveolar Soft-Part Sarcomas, Structurally Characteristic Tumors of Uncertain Histogenesis. *Cancer*, 5:100, 1952.
- Horn, R. C., Jr., and Enterline, H. T.: Rhabdomyosarcoma: A Clinicopathological Study and Classification of 39 Cases. *Cancer*, 11:181, 1958.
- Lever, W. F.: Histopathology of the Skin. 2nd ed. Philadelphia, J. B. Lippincott Company, 1954.
- McWhorter, H. E., and Woolner, L. B.: Pigmented Nevi, Juvenile Melanomas, and Malignant Melanomas in Children. *Cancer*, 7:564, 1954.
- Scherz, R. G., Louro, J. M., and Geppert, L. J.: Giant Hemangioendothelioma with Associated Thrombocytopenia. *J. Pediat.*, 52:212, 1958.
- Shnitka, T. K., Asp, D. M., and Horner, R. H.: Congenital Generalized Fibromatosis. *Cancer*, 11:627, 1958.
- Stout, A. P.: Juvenile Fibromatoses. *Cancer*, 7:953, 1954.
- Tumors of Bone*
- Aegerter, E., and Kirkpatrick, J. A.: Orthopedic Diseases. Physiology-Pathology-Radiology. Philadelphia, W. B. Saunders Company, 1958.
- Dahlin, D. C.: Chondromyxoid Fibroma of Bone, with Emphasis on Its Morphological Relationship to Benign Chondroblastoma. *Cancer*, 8:195, 1956.
- Dahlin, D. C.: Bone Tumors. Springfield, Ill., Charles C Thomas, 1958.
- Lichtenstein, L.: Benign Osteoblastoma. A Category of Osteoid- and Bone-Forming Tumors Other than Classical Osteoid Osteoma, Which May Be Mistaken for Giant-Cell Tumor or Osteogenic Sarcoma. *Cancer*, 9:1044, 1956.



# Radiation Injury

The roentgen ray, a form of ionizing radiation, is one of the components of atomic energy. Since in military, industrial and medical fields there is an increasing use of ionizing radiation, the possibility of untoward biologic effects is of special interest in relation to the child, for these effects may be most serious in growing tissues.

Ionizing radiation produces injury in the same manner regardless of the type of particle or ray emitted. The variation is quantitative rather than qualitative. The absorption of energy causes some of the molecules in the path of the radiations to become ionized. In attaining stability these molecules may form substances which alter, temporarily or perhaps permanently, biochemical processes within the cell or its environment. These effects upon cellular structures provide an explanation for the death of persons exposed to ionizing radiations, for the death of certain cancer cells treated with roentgen rays, for genetic mutations and for the production of cancer as a late effect of exposure to radiations.

Susceptibility of tissues to roentgen rays is, generally speaking, greater in the more rapidly mitosing and the more undifferentiated cells. Owing to an abundance of this type of tissue in the abdomen, a patient is more likely to have radiation sickness from roentgen therapy in this region than from comparable exposure of another part of the body.

**Dosage Factors.** Radiation absorption increases with the volume of the child's body exposed, with prolongation of exposure or with an increase in amperage or voltage. Absorption decreases in relation to the effectiveness of filters used and to an increase in distance between the patient and the roentgen tube.

Adverse acute effects of roentgen rays are diminished when the total dose is administered in several exposures separated by sufficient time for recovery from the subclinical effects of each. Repeated exposure to low doses of roentgen rays may produce pathologic

effects not manifest until years later. Some of the chemical changes produced in cells by roentgen rays are irreversible, and may lie dormant until aging, infection, hormonal alterations or further exposure to toxic agents makes them manifest.

The young infant may be more susceptible to the effects of roentgen rays than is the adult. However, even if there are no essential differences in susceptibility, his longer life span provides more time for such changes to develop.

Fluoroscopic dosages range from 1.5 to 40 roentgens per minute (mode—10 to 20). The dose required for a standard roentgenogram of the chest is 0.05 roentgen, whereas 15 roentgens is the average dose for a fluoroscopic examination of the same region, or 300 times that necessary to obtain the film.

Unfiltered machines in dental offices to secure roentgenograms of all the teeth (twenty-five to thirty exposures) may deliver as much as 315 roentgens to the head of the patient. Though not all these rays are de-

*Table 118. Customary Roentgen Ray Doses Used for Infants and Children, Measured in Air at the Point of Entry into the Patient's Body*

<i>Roentgen Procedure</i>	<i>Customary Roentgen Dose</i>
Fluoroscopy.....	10-20 r per minute
Chest film.....	0.05 r
Other common films.....	About 1.2 r each
Estimated dose to ovaries per examination of the abdomen.....	0.2 r
Intravenous pyelogram.....	7-8 r for a series of 6 plates
Barium enema studies, G-I series.....	10-20 r per minute for fluoroscopy and 1.2 r for each film
Dental film studies.....	1-15 r per film (average 5 r)
Diagnostic studies for congenital heart disease.....	140 r or more
Treatment of thymus.....	75-350 r
Treatment of acne.....	500-1000 r for a course of treatment

From R. W. Miller: *Pediatrics*, 11:294, 1953.

livered to the same portion of the patient's head, doses may be high in regions where the lines of radiation intersect.

Contrary to general opinion, roentgen rays in low doses do not have a stimulative action on cells.

**Early Effects of Irradiation.** Exposure of the entire body to 100 roentgens usually produces illness in man. A dose of 450 roentgens will cause death in 50 per cent of exposed persons. Higher doses can be tolerated if only a part of the body is exposed. Death results within hours to days when the entire body is exposed to the overwhelming dosage provided by an atomic bomb.

Symptoms of radiation sickness which vary with the exposure are malaise, fever, nausea, vomiting and diarrhea. Leukopenia develops rapidly, and in the more severe instances thrombocytopenia may appear within a week. When the initial symptoms are not severe, they are followed by a temporary period of well-being. Epilation begins about two weeks after the exposure. The leukopenia increases susceptibility to infection, and the low platelet count predisposes to hemorrhage. Death, if it occurs, might therefore be attributed to infection or hemorrhage. When an autopsy does not reveal the cause of death, it can only be assumed that the radiation injury was responsible for lethal "cytochemical changes." If the patient survives for six weeks, death is not likely from these effects of radiation.

Only a small percentage of deaths caused by an atomic explosion can be attributed to radiation effects alone; thermal and blast injuries account for most of them. Traumatic injuries do not heal effectively in persons with radiation sickness.

Therapy for radiation sickness resulting from exposure of the entire body is not very effective. Prophylactic administration of broad-spectrum antibiotics may diminish mortality. Transfusions of stored blood have not reduced the mortality in experimental animals or altered the bleeding diathesis. Transfusion of stored blood is therefore indicated only when the deficiency of red blood cells justifies it.

Dramamine and pyridoxine are partially effective in the relief of nausea, vomiting, headache and weakness from moderately severe radiation sickness.

**Late Effects of Irradiation.** Within the decade following the detonations of the atomic bombs in Japan there was a significant

rise in the incidence of leukemia in those who were within a radius of 1500 meters of the hypocenter (the spot on the ground immediately under the center of an air burst). The incidence of other hematologic abnormalities has not increased. Small lenticular opacities of the posterior capsule of the lens have developed in 85 per cent of those who epilated soon after the bomb explosion; the lesions are asymptomatic. Only ten of the thousands of survivors have grade III or IV radiation-induced cataracts. Microcephaly with mental retardation has occurred in infants exposed in utero to atomic radiation. The incidence of these defects was dependent on dosage and gestational age, susceptibility being greatest among those whose mothers had last menstruated seven to fifteen weeks before the detonation of the bomb. There is no doubt that genetic damage occurred, but it could not be demonstrated in the 80,000 first-generation offspring examined.

Radiation-induced premature aging, characterized by early senescence and death in middle age from diseases that ordinarily beset the elderly members of the species, has been described in animals, but has not been conclusively demonstrated in man.

That therapeutic doses of partial-body radiation may predispose to cancer is indicated by reports of a greater incidence of leukemia among adults treated for ankylosing spondylitis and of thyroid tumors among persons treated in early infancy for thymic enlargement. That repeated small doses of radiation to the entire body may predispose to leukemia is indicated by the increased incidence of this disease among radiologists.

Effects from exposure of part of the body include temporary sterility, dermatitis, bone and skin tumors and developmental defects in the teeth. There are several reports of arrest in bone growth in children who received cancericidal doses of roentgen rays.

**Radioisotopes.** Radioisotopes are providing new approaches to diagnosis, therapy and investigative studies. Hazards are comparable to those of roentgen rays, but the total amount of radiation is much less because of the small doses used. Biologic effects persist until the radioisotopes are excreted or until they disintegrate.

**Preventive Measures.** It is presently estimated that the allowable occupational radiation exposure (whole-body) for man is 0.1 roentgen per week. This dose is based on exposure of the gonads, because all doses re-



ceived by them are additive and presumably detrimental. The National Academy of Sciences has recommended for the *population at large* that the average cumulative gonadal exposure not exceed 10 roentgens per individual from conception to the age of thirty years; for the *individual* the cumulative dose should not exceed 50 roentgens.

The potentials for delayed somatic illnesses produced by partial-body radiation are not known, but it is thought that radiation changes within somatic cells are *incompletely* additive throughout life.

The child of today is likely to have repeated exposures to ionizing radiations, and there is a possibility that his tolerance may be dissipated. The pediatrician should limit as much as possible the exposure of his patients (and himself) to the emanations of roentgen ray machines and radioisotopes, but need not refrain from using them for essential diagnostic and therapeutic procedures. When a roentgen examination is needed, a film study should be obtained initially whenever possible, the exposure being far less than that for fluoroscopy. Subsequently fluoroscopic examination can be made if it is still required.

The duration of fluoroscopy can be shortened if no conversation is conducted during the examination. The machine should be operated only while the physician can use his eyes most effectively, i.e., after he has adapted to the dark and while he is thinking only of the picture before him—*not while he is trying to interpret the findings*. The field under study must be kept as small as possible by reducing the shutter opening to a minimum. The machine should be operated with the most effective filter available, with the roentgen-ray tube at the greatest possible distance from the patient, and with the lowest amperage and kilovoltage permitting adequate examination.

A pregnant mother should *not* enter a fluoroscopy or therapy room in the first trimester for fear of fetal injury.

Roentgen therapy should never be used except when the indications are unmistakable or the risk justified, as, for example, in the treatment of malignant tumors. Extreme care must be exercised to avoid unnecessary dam-

age to osseous growth centers, tooth buds and the various organs of the body.

Roentgen ray machines should be checked at least once a year for leakage which might be a hazard to personnel. The physician should wear his lead apron and gloves whenever the machine is in operation and should not expose unshielded parts of his body to the radiation beam.

A particular hazard for children is shoe-fitting by fluoroscopy. The machines are often poorly shielded and permit excessive leakage. The duration of the examination is prolonged by the interest of the child, and it is yet to be demonstrated that shoes cannot be equally well fitted by palpation.

ROBERT W. MILLER

## REFERENCES

- British Medical Research Council: The Hazards to Man of Nuclear and Allied Radiations. London, Her Majesty's Stationery Office, Cmd. 9780, June, 1956.
- Buschke, F., and Parker, H. M.: Possible Hazards of Repeated Fluoroscopies in Infants. *J. Pediat.*, 21: 524, 1942.
- Court-Brown, W. M., and Doll, R.: Leukemia and Aplastic Anemia in Patients Irradiated for Ankylosing Spondylitis. London, Medical Research Council, Special Report Series No. 295, Her Majesty's Stationery Office, 1957.
- March, H. C.: Leukemia in Radiologists in a 20 Year Period. *Am. J.M. Sc.*, 220:282, 1950.
- Miller, R. W.: Some Potential Hazards of the Widespread Use of Roentgen Rays in Pediatrics. *Pediatrics*, 11:294, 1953.
- Miller, R. W.: Delayed Effects Occurring within the First Decade after Exposure of Young Individuals to the Hiroshima Atomic Bomb. *Pediatrics*, 18:1, 1956.
- Neel, J. V., and Schull, W. J.: The Effect of Exposure to the Atomic Bombs on Pregnancy Termination in Hiroshima and Nagasaki. Washington, National Academy of Sciences, National Research Council Publication 461, 1957.
- Report of the Committee on Pathologic Effects of Atomic Radiation. Washington, National Academy of Sciences, National Research Council Publication 452, 1956.
- Simpson, C. L., and Hempelmann, L. H.: The Association of Tumors and Roentgen-Ray Treatment of the Thorax in Infancy. *Cancer*, 10:42, 1957.
- Summary Reports of the Committees on the Biological Effects of Atomic Radiation. Washington, National Academy of Sciences, National Research Council, 1956.

# Poisoning from Food, Metals, Chemicals and Drugs

## FOOD POISONING

So-called food poisoning may be produced by (1) contamination of food by chemical poisons, (2) contamination by bacteria, and (3) chemical or toxic substances natural to certain plants or animals.

Contamination of food may occur at the source from insecticides, such as lead arsenate, or from preservatives or fungicides, such as formaldehyde or copper sulfate. Lead arsenate may be on fruits and vegetables in sufficient quantity to produce symptoms of acute or chronic poisoning. Foods may become contaminated after packaging. The container or its lining may dissolve in the food or enter into a chemical reaction with it. At times foods have been placed in containers previously used for mixing arsenic sprays or lead paints. Insect powders have been added to foods by mistake for baking powder or flour. Silverware cleaned with cyanide polish has produced poisoning. Ingestion of the flesh of cattle and fowl that have fed on fruits and vegetables heavily contaminated with arsenic may also cause poisoning.

Bacterial contamination of foods usually takes place from the time of preparation to the time of consumption. Poisoning may be caused by the toxins elaborated, as in staphylococcal poisoning, or by actual bacterial invasion of the intestines, as in *Salmonella* infections. A large variety of organisms may produce poisoning. The bacteria may contain an endotoxin or produce an exotoxin.

### BOTULISM

Botulism is an often fatal intoxication due to the ingestion of food containing the *Clostridium botulinum*, an anaerobic spore-former. The source of the infection is chiefly home-canned foods, especially vegetables. Several powerful exotoxins are formed. Types

A, B and E being most often present. They are not heat stable and can be completely destroyed by thorough cooking (80° C. for ten minutes).

**Symptoms.** Symptoms develop in twelve to forty-eight hours and are due to the curare-like action of the poison on the motor nerves and on voluntary muscles. There may be anorexia, weakness, dizziness, diplopia, ptosis of the eyelids, strabismus, and difficulty in breathing, swallowing and talking. Death may occur in one to eight days.

**Treatment.** In addition to lavage and catharsis, specific antitoxin with large amounts of glucose should be given intravenously as early as possible. Parenteral fluid therapy should be continued during the acute phase.

### STAPHYLOCOCCAL POISONING

Some strains of staphylococci produce an exotoxin in pastry and other starchy foods, and other strains may develop a soluble exotoxin in other foods. Such foods as salads, chicken, ham and beef in hash or in gelatin, whipped cream and custards, especially when prepared in large quantities some time before consumption, are likely to become infected unless caution is taken in their preparation and refrigeration.

**Symptoms.** The symptoms of staphylococcal poisoning appear suddenly within one to six hours after the ingestion of contaminated food and consist in severe nausea and vomiting with retching, abdominal pain, acute prostration and diarrhea. There may be blood and mucus in the stools. The temperature may or may not be elevated. There is frequently sweating, hypotension and shock. The course of the poisoning is usually limited to twelve to twenty-four hours. Staphylococcal poisoning should always be suspected



when an entire family or a large group of people become ill about the same time.

**Treatment.** If the patient is seen within the first few hours, a saline cathartic may be given. Food should be withheld until the diarrhea is controlled. The important measures, however, are supportive ones. Fluids should be administered intravenously to combat dehydration and shock as well as any acidosis.

### STREPTOCOCCAL POISONING

Certain of the hemolytic streptococci of group A may produce an exotoxin and be a cause of food poisoning. Symptoms and treatment are similar to those of staphylococcal poisoning.

### SALMONELLA POISONING

(See also page 442.)

The Salmonella group of bacteria is pathogenic to man and animals and includes a number of organisms which are commonly associated with food poisoning in addition to those which characteristically produce typhoid-like fever. All these organisms are enterotoxic, but produce variable systemic reactions. Animals such as mice, birds and pigs may have the disease or may be carriers only. The excreta, flesh or products of such animals in food may be the source of infection. The contamination of foods, however, is most likely to occur from persons with active infection and from human carriers.

## LEAD POISONING

Lead poisoning is relatively common in infants and children. The residual effects of the toxic action of lead on the central nervous system are at times permanent and may even be progressive for years.

Infants and children may ingest lead in paint, particularly from repainted cribs, furniture and window sills and from fruit covered with insecticides, lead nipple shields, face powders, lead soldiers and toys, colored crayons and chalks and water from lead pipes. Lead may also be inhaled from fumes, as from the burning of storage batteries.

The likelihood of permanent damage to the central nervous system increases with the duration of exposure to lead. Pica is a common habit in infants and children with lead intoxication, and the child who has been treated for lead poisoning often continues to ingest lead if the opportunity is available. The physician should recommend a different environment or be certain that all sources of lead are eliminated from the home.

The incidence of lead poisoning appears to be increasing in certain metropolitan areas in the eastern United States. Failure to repaint woodwork and walls permits flaking of old lead-containing paint to which small children have easy access. Surveys of the lead concentration in the blood of infants and children disclose that many infants have toxic blood levels with few or no symptoms.

Lead enters the body through the gastrointestinal tract, skin or lungs. Except in acute poisoning, it is a slow-acting poison, and

symptoms may develop insidiously and at times be intermittent. A single ingestion may produce no symptoms, but the same quantity distributed over a long time may be toxic. The slow absorption and gradual accumulation of lead within the blood and soft tissues produce the clinical features of progressive poisoning. In the gastrointestinal tract soluble lead salts are formed which are absorbed. Lead salts contained in dust may be absorbed from the respiratory tract and also from the intestines from swallowed saliva containing dust. A large part of the absorbed lead enters the portal circulation and is excreted by the liver. Lead that reaches the systemic circulation is deposited in bone and in soft tissues, particularly in the liver, kidney, pancreas and brain. In the brain there is intense edema, widespread vascular damage, destruction of brain cells, and neuroglia disintegration. In the peripheral nerves the axon may be destroyed. Lead is slowly transferred from soft tissues to bone, where it is deposited as insoluble tertiary lead phosphate along with calcium. Factors which facilitate deposition of calcium favor the deposition of lead; decalcification is associated with release of lead from bone.

The occurrence of symptoms depends upon the amount of lead in soft tissues and in the blood. The amount of lead in the urine roughly parallels the amount in the blood and is thus an indication of the rate of transport to or from the tissues.

The urinary concentration of lead in nor-

mal children may vary from 0 to 400 micrograms per liter. In lead poisoning it may range from 35 to 720 micrograms. The total urinary excretion of lead during a twenty-four hour period is more significant than the amount in a single specimen. Excretion of 80 micrograms per twenty-four hours usually occurs in children with symptoms of severe lead poisoning; 50 to 80 micrograms per twenty-four hours may indicate lead poisoning or unusual exposure to lead. The excretion of less than 50 micrograms per twenty-four hours can be considered normal. Circulatory failure, renal ischemia and damage in severe lead poisoning may inhibit excretion of lead.

The concentration of lead in whole blood of children without a history of lead poisoning or pica has been found to range from 0.003 to 0.054 mg. per 100 ml.

An increase in urinary coproporphyrin is a constant and early sign of lead poisoning.

#### ACUTE LEAD POISONING

**Symptoms.** Acute lead poisoning is rare and occurs after the accidental ingestion of lead salts (lead acetate, lead carbonate) or the inhalation of lead fumes. Nausea, vomiting and abdominal pain follow. There may be acute paresthesia, pain and muscular weakness and occasionally a hemolytic crisis with anemia and hemoglobinuria. Renal damage is common. Death from shock may result in two to three days. Symptoms of chronic lead poisoning may follow recovery from acute poisoning.

**Treatment.** Gastric lavage followed by catharsis with magnesium sulfate, general supportive measures and treatment for shock are indicated. Absorbed lead should be mobilized into the bone as outlined under Chronic Lead Poisoning. Recovery is slow.

#### CHRONIC LEAD POISONING

**Symptoms.** The symptoms of chronic lead poisoning depend upon the rate and degree of transport of lead from intestine or bone to the soft tissues or blood. Symptoms may develop progressively from those of a mild nature to the severe characteristic manifestations; or there may be, for months or even years, a sequence in which periods of mild symptoms alternate with symptom-free periods. In the infant or young child, owing to the extreme vulnerability of the central nervous system, a relatively short period of exposure may be followed by severe symptoms of encephalitis, even before anemia, colic,

peripheral neuritis or other milder symptoms have developed. Encephalitis may also be precipitated in an otherwise quiescent case by release of lead from bones during an intercurrent acute infection or metabolic disturbance. Mild symptoms are weakness, irritability, loss of weight, vomiting, anemia, pallor out of proportion to the anemia, headache, abdominal pain or colic, loss of appetite (particularly for breakfast) and insomnia. Severe symptoms are muscular incoordination, peripheral motor paralysis of the most commonly used muscles (dorsiflexors of the feet or wrists), joint pains, hypertension, bradycardia or labile pulse rate, encephalopathy with separation of sutures, convulsions, and edema of the optic nerve. Encephalopathy is common in young children, whereas severe abdominal colic is more frequent in adults.

**Diagnosis.** The principal diagnostic features are basophilic stippling in the red blood cells, a lead line in the gums, roentgenographic evidence of increased densities at the ends of long bones (Fig. 426) and along margins of flat bones, an excessive concentration of lead in the urine or blood and excretion of coproporphyrin in the urine. Roentgenographic evidence is lacking in the presence of rickets. The presence of lead in the gums or bones does not necessarily mean that the clinical symptoms are due to lead toxicity, and, conversely, lead intoxication may be present in the absence of evidence of lead in the bones. Spectrographic examination of the blood may also be of value.

When there is encephalopathy, the cerebrospinal fluid is under increased pressure and may contain a large amount of protein and a few cells, usually less than 100 lymphocytes. Transient albuminuria, hematuria and glycosuria may also be present. The glycosuria is renal in origin and results from tubular damage.

**Differential Diagnosis.** Acute lead poisoning may simulate acute gastrointestinal disturbances with acute abdominal pain. Both the acute and chronic forms may simulate poliomyelitis, postdiphtheritic paralysis, localized neuritis or polyneuritis and rheumatic fever. In infants especially, lead encephalitis must be differentiated from other forms of encephalitis, brain tumor, brain abscess and meningitis, particularly tuberculous meningitis. The lead lines in the bones may be similar to those produced by bismuth and other heavy metals. When there is glycosuria associated with encephalopathy, the possibility of diabetic acidosis must be eliminated.



**Prognosis.** The prognosis is generally poor. Approximately half of affected infants and small children have encephalitic manifestations, and among these the mortality rate is about 25 per cent. Of those who recover from the active encephalitic phase, at least one third have permanent neurologic and/or mental sequels. It has been stated that children who have mild or latent forms of lead poisoning usually recover completely without residual defects if the source of the poison is removed, but one may doubt that this is invariably so. One long-term study has shown that of twenty children who had only mild evidences of lead poisoning during infancy, nineteen were mentally retarded or manifested some specific defect in mental development three to nine years later. Vascular nephrosclerosis as a residual of lead poisoning has been described.

**Treatment.** The primary aim of therapy is reduction of the concentration of lead in the blood and tissues by (1) prevention of continued absorption of lead from the intestines or other sources; (2) an increase in the excretion of lead primarily through the urine. A secondary consideration, particularly important in the presence of encephalopathy,

is the promotion of deposition of lead in the bones. Supportive treatment is of the utmost importance.

**Prevention of absorption.** All sources of lead must be removed from the environment. If oral fluids can be tolerated, relatively large amounts of milk should be given to form insoluble, poorly absorbed lead salts in the intestines.

**Increase in excretion.** Salts of ethylenediamine tetra-acetic acid (EDTA) form a non-ionized chelate with lead which is nontoxic and is excreted in the urine. Decrease in the concentration of lead in the blood occurs rapidly after its administration. EDTA is usually administered by intravenous infusion. A test dose of 0.2 gm. diluted with 200 ml. of 5 per cent glucose in distilled water is administered intravenously over a one-hour period. Observation for untoward reactions such as rash, vomiting, tetany, lethargy or shock should be continued for four hours after completion of the test dose. If none appears, then 1 gm. dissolved in 200 ml. of 5 per cent glucose in distilled water is given intravenously. The amount and rate of administration of this solution depend upon the total dose to be given. The maximum dose for children should not exceed 1 gm. per 15 kg. of body weight per day. This amount is usually administered daily by intravenous drip for five days. The presence of continued signs and symptoms of lead intoxication or a rise in the blood concentration of lead may necessitate a second course of therapy after an interval of at least two days. The administration of calcium EDTA orally may be effective, but its actions are delayed when given by this route. The use of EDTA by any route is contraindicated when lead is present in the intestines, since it facilitates absorption of lead, and encephalitic symptoms may be precipitated. A roentgenogram of the abdomen to detect the presence of lead in the intestines should precede therapy with EDTA.

BAL (p. 1381) will also cause an increase in the urinary excretion of lead. BAL apparently combines with lead in the red blood cells, but not effectively in tissues and so is of little value in lead poisoning.

**Increasing deposition of lead in the bones.** Lead appears to be absorbed, transported, deposited and excreted similarly to calcium. A relatively high intake of calcium, phosphorus and vitamin D diminishes the solubility of lead in the blood and hastens its deposition in bone.

Disturbances of electrolyte equilibrium,

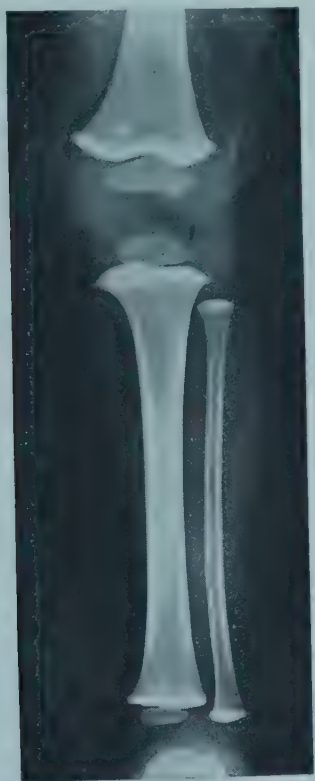


FIG. 426. Lead poisoning. Long bones of a child 20 months of age, showing an increase in the thickness and density of the zones of provisional calcification. The child chewed paint from her crib and presented with anemia and irritability.

often associated with acidosis, are common in lead poisoning. Correction of the disturbance is imperative, since the deposition of lead in the bones is inhibited in the presence of acidosis (see Parenteral Fluid Therapy, p. 191). Sodium citrate may be of value, not only in control of the acidosis, but also by its ability to form a soluble complex with lead which is excreted in the urine; the administration of 1 to 2 gm. three times a day has been associated with a decrease in the blood level of lead.

Infection also interferes with deposition of lead in the bones and consequently must be controlled.

**Treatment of lead colic.** Lead colic may be controlled by the use of antispasmodics, such as atropine, but on occasion opiates may be necessary. Lead colic is also often benefited by administration of calcium salts; 10 ml. of a 10 per cent solution of calcium gluconate or 10 ml. of a 5 per cent solution of calcium chloride may be given slowly by the intravenous route.

**Treatment of encephalopathy.** In addition to the therapeutic measures outlined above, the increased intracranial pressure and associated complications of encephalopathy require additional considerations. The most careful observation and the provision of constant nursing care are required.

Convulsions are best controlled by phenobarbital administered intramuscularly (p. 1122). Care must be taken to avoid further depression of the damaged brain by excessive sedation.

The increased intracranial pressure may necessitate repeated, carefully performed lumbar punctures using a small-bore needle. Only small amounts of fluid should be removed at one time, owing to the extreme

danger of brain-stem herniation; carefully performed, the procedure may be lifesaving. Surgical decompression by craniectomy may occasionally be necessary.

Oxygen should be administered for even mild evidences of respiratory depression.

Correction of fluid and electrolyte disturbances is imperative, but must be carried out with caution. Excessive administration of water and electrolytes may increase the cerebral edema, as may dextrose in an electrolyte-free solution. Dextrose in a hypotonic saline solution is the solution of choice; quantities of water and electrolytes are best gauged by the combination of clinical (hydration, adequate urinary output, blood pressure and evidences of increased intracranial pressure) and laboratory (carbon dioxide and/or pH, sodium, chloride and potassium) evaluation. Underhydration is safer than overhydration.

Urinary retention is common and may require intermittent or continuous catheterization.

Central nervous system stimulants are rarely indicated. The severity of the involvement of the brain makes their use ineffective, and they may cause further damage.

**Retreatment.** The initial course of therapy may eradicate the clinical manifestations of lead poisoning, even while lead remains in the bones. The residual lead is often liberated gradually and excreted without renewal of symptoms of toxicity, but the reverse may be the case, especially with intercurrent infection. The necessity for retreatment will depend upon a significant rise in the concentration of lead in the blood and the return of manifestations of toxicity. Close observation for long periods of time is essential for prevention of additional damage to the central nervous system.

## CHEMICAL AND DRUG POISONING

### GENERAL CONSIDERATIONS

In the United States accidents and poisonings account for the largest number of deaths in the pediatric age group, more than the next seven causes of fatalities combined.

Over 1400 fatal poisonings occur each year in persons of all ages; one third of these occur in children under the age of fifteen, and approximately four fifths are in children of one to four years. Nonfatal poisonings are estimated to be 100 to 150 times the number

of reported fatalities. Poisoning is more frequent in boys than in girls under the age of five years. The frequency and causes of poisoning vary in different sections of the country and between rural and metropolitan populations. Death from petroleum products is more frequent in the southern states and is six times more frequent in the nonwhite population than in white children; lye poisoning is four times more frequent in the southern states and three times more frequent in rural than in urban communities. Chronic



lead poisoning, which affects children primarily between the ages of one and four years, has been more prevalent in recent years in some metropolitan areas in the eastern half of the United States.

### PREVENTION OF POISONING

The majority of cases of accidental poisoning in childhood are preventable. The responsibility for prevention lies not only with the parents, but also with the child's physician.

In the home, parents have a primary responsibility to keep medicines and poisons out of the reach of the naturally curious child. Highly poisonous substances should be locked in cabinets, and all medicines and poisonous chemicals should be properly discarded when they are no longer needed. Poisons should never be stored with foods. All medicines and chemicals should be kept in their original containers, which should be properly labeled. The physician and the pharmacist by meticulous attention to accurate prescription writing and compounding may prevent many cases of poisoning. Prescriptions containing poisonous drugs should be written for small quantities sufficient only for the immediate medical need. Proprietary medicines should be properly labeled with instructions and precautions regarding administration to children. Particular attention to the dangers of candy medication is imperative, since it is responsible for as much as 87 per cent of the cases of aspirin poisoning.

Parents fail to realize that a number of common household substances are poisonous; legislation requiring manufacturers to declare the presence and the nature of the hazardous ingredients on the labels of household products is essential. Caution must be taken in the storage of many household products such as bleaches, polishes and insecticides which, as a group, account for nearly one third of accidental poisonings. These substances are often stored in cabinets under sinks and are easily accessible to the young infant.

Safety instructions to parents should become a routine part of pediatric care when the infant is about six months of age.

### DIAGNOSIS OF POISONING

Acute poisoning may simulate many acute diseases such as peritonitis, intestinal obstruction, appendicitis, acute diarrheal disease, tetany, meningitis or encephalitis. When adequate evidence cannot be found for the symptoms of an acutely ill child, poisoning should

be suspected, and gastric lavage should be considered. Symptoms occurring in several persons after ingestion of food from the same source are strongly suggestive of food poisoning.

*The action of many poisons may be characteristic.* Gastrointestinal disorders with vomiting, diarrhea and abdominal pain occur commonly in metallic, acid, alkali, veratrum and bacterial poisonings. Convulsions are characteristic of poisoning by central nervous system stimulants such as camphor, picrotoxin and strychnine and by poisons producing anoxia from methemoglobin formation. Central nervous system depressants, such as alcohol, atropine (initial effect is stimulation), chloral hydrate, barbiturates, opiates, chloroform and others causing anoxia may produce coma. Dilated pupils suggest poisoning from atropine, nicotine (late), cocaine and ephedrine. Pinpoint pupils may be due to opiates, physostigmine, muscarine and nicotine (initial). Caustic alkalis produce lesions of the mucous membranes of the mouth and skin. The odor of some poisons is characteristic—for example, turpentine and eucalyptol, which may impart an odor of violets to the urine.

Mercury poisoning tends to cause marked albuminuria; poisoning by other metals, boric acid and phenol derivatives, a moderate albuminuria. Intense cyanosis and dyspnea suggest poisoning by carbon monoxide, cyanide, strychnine, aniline derivatives or botulism. Cherry-red mucous membranes are associated with carbon monoxide poisoning.

**Methemoglobinemia.** This is caused by many poisons and deserves special attention, since the resulting anoxia may lead to death or serious disturbance of vital functions: Nitrites, aniline derivatives, acetanilid, pyridium, dinitrophenol and potassium chlorate are the poisons which most commonly produce methemoglobinemia. Relatively small amounts of methemoglobin (15 per cent of the total hemoglobin) may produce recognizable cyanosis, which is usually more gray than blue and often not associated with dyspnea. When methemoglobinemia is suspected, a drop of blood should be placed on a slide beside a drop of normal blood; normal reduced hemoglobin becomes a bright red, whereas methemoglobin or sulfhemoglobin shows no change. Spectroscopy reveals a dark band at 618 millimicrons which does not change on addition of potassium cyanide to the blood.

The symptoms of methemoglobinemia are

those of anoxia and are related to the concentration of methemoglobin in the blood. A concentration of 15 per cent produces only cyanosis, particularly acrocyanosis; up to 20 per cent it causes mild fatigue and cyanosis, and 30 to 40 per cent may produce weakness, fatigue, tachycardia, nausea and generalized pains. Over 40 per cent concentration causes weakness, fatigue, tachycardia, confusion and coma, and death may occur.

**Identification of the Poisonous Agent.** Attempts should be made to identify the poison in every instance. If it is known that the child has ingested some household substance or drug, knowledge of its use may be of value in diagnosis. If the specific contents are not listed on the label, the container or bottle should be obtained and information concerning its contents sought from the prescribing druggist, poison control center or manufacturer. If this information is not available, the residual gastric contents should be analyzed. Emergency treatment should not be delayed until an analysis can be done, but identification of the poison may determine later aspects of treatment and ultimate prognosis. The first emesis or initial lavage specimen and a specimen of urine should be saved for analysis. Analysis and the clinical picture may be complicated by the fact that many household products and prescriptions contain several potentially poisonous ingredients. Approximately 50 per cent of poisonings are due to such medications as salicylates, especially aspirin, laxatives, sedatives and cough preparations; cleaning, polishing and sanitizing agents such as bleaches, lyes, furniture polishes and cleaning fluids are responsible for at least 25 per cent, and petroleum products, including kerosene, produce 10 to 20 per cent.

#### GENERAL TREATMENT OF POISONING

The treatment of acute poisoning is always an emergency. Time cannot be taken initially to analyze the poison ingested, and most emergency treatment is, of necessity, symptomatic. Procedures to be followed are (1) removal of the poison, (2) administration of an antidote, and (3) general or specific supportive and symptomatic treatment. At times it is necessary to give a specific antidote before removal of the poison is attempted.

**Removal of the Poison.** Poisons on the external surface of the body and in the nasal and oral cavities should be removed by copious irrigation with water. Acids should be

neutralized with weak bases, and alkalis with weak acids. If toxic oils are present, organic solvents should be applied, and removed with a mild soap solution. Orally ingested poisons may be removed by inducing emesis or gastric lavage. Immediate induction of vomiting may be lifesaving and can be carried out by the parents before the doctor's arrival. Emesis may be induced by administering a strong salt solution or powdered mustard in lukewarm water followed by stimulation of the posterior pharynx with the finger. The child should be held with his head dependent to avoid aspiration. Drug emetics are usually ineffective and may intensify the depressing action of some poisons. Emesis should never be induced in a comatose patient or after ingestion of caustic alkali or kerosene. Lavage is also not without danger. In corrosive poisoning the esophagus may be perforated; in strychnine ingestion the stimulation of a lavage tube may induce a fatal convulsion, and in kerosene poisoning, lavage, improperly done, may cause aspiration and pneumonia.

Gastric aspiration should be performed with caution. The child should be properly restrained, with his head slightly dependent and his face turned to one side. The gastric contents should be removed with a well lubricated, large-bore (28 French or larger) catheter, using an Ewald aspirating bulb. Small amounts of lavage solution (150 to 200 ml.) should be injected and aspirated as many times as necessary to remove all traces of the poison. Two to 4 liters of solution should be used. Water, weak salt and sodium bicarbonate solutions may be used until a more suitable solution is available. Activated charcoal mixed with water will absorb large amounts of alkaloids such as strychnine, morphine and atropine as well as mercuric and arsenic compounds. Tannic acid also precipitates alkaloid and metallic poisons, and strong tea may be used. Magnesium oxide suspensions are of value in mineral acid poisoning. Potassium permanganate 1:5000 solution will oxidize various organic poisons.

**Administration of an Antidote.** Antidotes for poisons are of two types—chemical and physiologic. A chemical antidote renders the poison innocuous or unabsorbable by direct chemical combination, absorption, adsorption or covering of the poisonous particles with a protective coating. Physiologic antidotes combat the effects of poisons after absorption. Unfortunately, specific chemical and physiologic antidotes are not available for all poisons.



The *universal antidote* for unknown poisons consists of 2 parts of pulverized charcoal, 1 part magnesium oxide, 1 part tannic acid; the dose is 4 ml. in a small glass of warm water. Milk and egg white are more or less specific chemical antidotes for metallic poisons. Strong tea, tannic acid and dilute iodine solutions are effective against alkaloids. Sodium formaldehyde sulfoxalate, if given immediately, is effective in the treatment of mercury poisoning. Nitrites and sodium thiosulfate have a specific action in cyanide poisoning. Methylene blue is indicated in methemoglobinemia, and ascorbic acid given intravenously may also be effective. Methylene blue is of questionable value in sulfhemoglobinemia and in large doses may produce further methemoglobin. Epinephrine, strychnine, picrotoxin and inhalations of oxygen and carbon dioxide may be indicated when anoxia and central nervous system depression are present. Stimulant and convulsive poisons demand sedation.

Gastric lavage may be followed by a large dose of a saline cathartic to hasten removal of poisons from the gastrointestinal tract. Catharsis is contraindicated, however, in severe phosphorus poisoning when bloody diarrhea and desquamation of the intestinal mucosa are present. Magnesium sulfate may produce severe central nervous system depression because the rate of absorption of magnesium from the bowel may exceed the rate of excretion, particularly if there is oliguria or renal damage.

*British anti-lewisite* (BAL, 2,3-dimercaptopropanol) deserves special mention, owing to its remarkable effect on some metallic poisons. The action of the metallic ions, particularly mercury and arsenic, is thought to be due to their chemical combination with important tissue sulfhydryl groups. As a result, essential enzyme systems requiring free SH groups are inactivated. The administration of BAL can reverse the inhibiting action of antimony, bismuth, chromium, nickel, copper and zinc on the sulhydryl enzymes. BAL is ineffective in poisoning caused by tellurium, thallium or vanadium. Under certain conditions it may augment the toxic effects of lead and may actually hasten death in poisoning due to cadmium and selenium.

Undesirable side effects are common with administration of BAL. These are lacrimation, salivation, nausea, vomiting, headache, pain in teeth, a burning sensation of the lips, mouth, throat and eyes, sweating, generalized muscular aching with burning and

tingling of the extremities, a sense of constriction in the chest, tachycardia, fever and agitation. Toxic symptoms begin within ten to fifteen minutes after injection and gradually subside within one to two hours. (For dosage schedule of BAL see Treatment of Arsenic and Mercury Poisoning.)

Certain metallic poisonings, particularly lead, mercury and iron, have responded to treatment with ethylenediamine tetra-acetic acid (EDTA), a synthetic polyamino acid. Various soluble salts of this compound such as calcium disodium versenate have the property of forming virtually nonionized metal complexes (chelates) with divalent and trivalent metal ions. The chelate is less toxic than the ionized metal and is excreted in the urine. Increase in the excretion of lead and mercury results without increase in toxicity. Toxic reactions of these chelating compounds have not been clearly defined.

Experience is being accumulated to show that performance of an exchange transfusion may be of value in accidental poisoning. Exchange transfusions should be considered for poisoning with methyl salicylate, boric acid, paranitraniline, chlorinated hydrocarbons, benzene, chlorate and bromate, copper sulfate, cyanide, dicoumarin, ferrous sulfate, naphthalene, phenol and thiocyanates.

**Supportive Therapy.** Excessive manipulation of the child must be avoided at all times, and medications, particularly stimulants and sedatives, should be administered with caution. Overtreatment may cause more damage than the poison itself. General supportive therapy is frequently more effective than removal of the poison or administration of specific antidotes. The type of supportive therapy required is dependent upon the actions of the poison involved. All organ systems of the body may be affected by poisons, and toxicity of one system may seriously affect other vital functions; e.g., respiratory depression may be secondary to central nervous system intoxication.

The nervous system is exceptionally vulnerable to the toxic action of poisons, but the symptomatology is variable. Evidence of stimulation or depression is usually noted. Stimulation results in convulsions, restlessness, confusion, and delirium. Sedation is frequently indicated, but must be administered with caution to avoid depression. Sedation also masks many signs and symptoms, making evaluation of the patient's condition difficult. Depression of the central nervous system is the most dangerous complication of

poisoning. It is manifested by lethargy, stupor and coma. Central nervous system depression commonly affects the cardiovascular, renal and respiratory systems. Prompt, intensive therapy is mandatory and is directed toward stimulation of the central nervous system and support of other systems affected.

The respiratory system is affected by many poisons, and the patient must be observed for evidence of respiratory depression, obstruction, pulmonary edema and pneumonia. Tachypnea may result from central nervous system stimulation and produce respiratory alkalosis. Artificial respiration, administration of oxygen and maintenance of a patent airway may be imperative.

Involvement of the cardiovascular system is frequent. Peripheral circulatory collapse may occur and must be combated by intravenous administration of saline and glucose solution, plasma or blood and possibly sympathomimetic vasoconstricting agents. Cardiac failure may occur initially or later, and disturbances of the heart rate and rhythm require emergency treatment.

Some poisons cause intense gastrointestinal irritation with severe vomiting and diarrhea. Replacement of the water and electrolyte loss by parenteral fluid therapy is imperative. Nausea, pain and abdominal distention may be severe.

Poisons affect the kidney either by direct toxic action or by the production of shock with renal ischemia. The most important aspect of therapy is administration of the correct amounts of fluids and electrolytes which will maintain homeostasis of the intracellular and extracellular fluid compartments. The extent of renal damage varies from mild involvement to acute tubular necrosis. If metabolic equilibrium is maintained by the judicious use of fluids containing electrolytes, glucose and protein, severe renal damage may be reversible. Hypertension from renal or peripheral vascular involvement is frequent. Urinary retention may also result from bladder atony or vesical neck spasm, and repeated catheterizations or the insertion of an indwelling catheter may be necessary.

There is a wide variation in the extent of liver involvement in poisoning, from minimal damage to severe necrosis. Supportive therapy is primarily the provision of a diet high in protein and carbohydrate and low in fat content, with vitamin supplementation. The extent of recovery is variable, but considerable regeneration of poisoned liver cells does occur. A serious secondary manifestation of hepatic

toxicity is depletion of prothrombin, and vitamin K administration is indicated prophylactically.

Disturbance of fluid and electrolyte balance is associated with many poisonings. The types, amounts and methods of administration of fluids and electrolyte-containing solutions must be selected for the individual case. The following are general considerations:

1. Administration of total fluids in amounts adequate to meet the daily body requirements.
2. Avoidance of water intoxication, hyper-electrolytemia or hyponatremia resulting from administration of inadequate or excessive amounts of water and/or electrolyte-containing solutions.
3. Correction of any potassium and/or calcium imbalances.
4. Maintenance of an adequate caloric and vitamin intake. Oral feedings are preferable for children if they can be retained.

The control of body temperature is frequently impaired, and avoidance of extreme hyperthermia or hypothermia is important. In barbitol and opiate poisonings the depressant action of these drugs is intensified by hypothermia.

The child who is poisoned may be susceptible to infection, and use of antimicrobial agents should be considered, but not instituted routinely. Antibiotic therapy is indicated for the prevention of secondary bacterial infection in poisoning by kerosene and other hydrocarbons which produce chemical pneumonitis.

The child may often be in severe pain, which must be alleviated. In planning the management of the child who has been poisoned the provision of competent, continuous nursing care must never be overlooked.

## CHEMICAL POISONING

Treatment of poisoning consists in general supportive care when the toxic substance is unknown, and specific when the substance is identified and definitive therapy for it is established. In each instance efforts should be made to identify the toxic agent. The chemical constituents of many medicinal, household and chemical products are recorded on the labels, and this practice must become increasingly common. If the chemical composition is not recorded, it may be obtained from the manufacturer, textbooks of toxicology, poison control centers or municipal or state toxicologists.

It is impossible to include in a pediatric textbook all known toxic chemical substances.



In the following sections a number of potentially toxic chemical compounds are listed. This chapter includes general classes of chemicals (alphabetically arranged) with associated signs and symptoms of toxicity and recommended therapy. The List of Chemicals (p. 1394) includes individual chemical compounds. Many chemicals are now assigned commercial or trade names, and, in general, these are used rather than the chemical nomenclature. Synonyms are also listed.

1. **Abrin.** The toxic albumin found in jequirity beans. Ricin is a related toxic albumin found in castor beans. One bean thoroughly chewed may cause fatal poisoning. Toxic material causes hemolysis of red blood cells at extreme dilutions. In acute poisoning, vomiting, diarrhea and circulatory collapse may occur. Symptoms may be delayed one to three days. Hemolysis, hemorrhages and edema of the gastrointestinal tract occur.

**Treatment.** Gastric lavage followed by catharsis and treatment for shock are indicated.

2. **Acids, Corrosive, and Acid-Like Substances.** Corrosive acids produce irritation, blistering and destruction of mucous membranes within a few moments after ingestion. Lesions may be brown or black except with nitric and picric acids, which produce yellow stains. Severe burning pain in the mouth, pharynx and abdomen followed by bloody vomiting and diarrhea may occur. Shock followed quickly by death occurs in approximately half of the cases. Esophageal stricture occurs in the majority of patients who recover.

**Treatment.** Water, milk or beaten eggs should be given immediately and repeated to dilute any free acid. Gastric lavage is not without danger at any stage and probably should not be performed later than one-half hour after ingestion. Later, perforation of the esophagus may occur. For more detailed treatment see page 643.

3. **Alcohols and Glycols. Methyl alcohol.** Ingestion of 3 to 8 ounces may be fatal. The metabolic products, formic acids or formaldehyde, inhibit cellular metabolism. Toxic and degenerative changes in the liver, kidneys, heart and brain occur. Optic atrophy may follow recovery from acute poisoning. Ethyl alcohol may competitively block metabolism of methyl alcohol.

**Treatment.** Gastric lavage and immediate intravenous administration of large amounts of alkali to combat severe acidosis. Potassium should be administered to correct the hypokalemia.

**Ethyl alcohol.** Signs and symptoms are primarily those of central nervous system depression. Fatalities occur at blood alcohol concentrations above 0.3 to 0.5 per cent.

	Blood concentration
Mild intoxication . . . . .	0.05–0.15 %
Moderate intoxication . . . . .	0.15–0.3 %
Severe intoxication . . . . .	0.3 –0.5 %
Coma . . . . .	Above 0.5 %

Blood  
Fatal dose for an adult . . . . 300–400 ml.

**Treatment** is supportive.

**Ethylene glycol, diethylene glycol.** These substances are metabolized to oxalic acid (see oxalates and oxalic acid). Central nervous system depression, shock and anuria may occur within a few hours, and respiratory failure and pulmonary edema occur within twenty-four hours.

**Treatment.** Lavage, catharsis and calcium gluconate.

4. **Aluminum and Zinc Salts.** Aluminum and zinc salts are used as astringents, deodorants and antiseptics. Symptoms consist of burning pain in the mouth and throat, vomiting, watery or bloody diarrhea, anuria, hepatic damage, collapse and convulsions.

**Treatment.** Immediate dilution with water or milk followed by repeated gastric lavage (see No. 2 and No. 49).

5. **Amphetamine, Privine, Ephedrine and Related Drugs.** Acute poisoning from ingestion, inhalation, injection or application to mucous membranes produces nausea, vomiting, chills, cyanosis, nervousness, irritability and fever. Blurred vision, mydriasis, altered ocular reflexes, spasms, convulsions, coma and respiratory failure may follow.

**Treatment.** Lavage and catharsis are indicated. Administration of barbiturates may be followed by severe depression.

6. **Aniline, Dimethylaniline, Nitroaniline, Toluidine and Nitrobenzene, Acetophenetidin, Acetanilid.** These dyes are used in paints, paint removers, printing inks and cloth marking inks and as solvents. Aniline poisoning of infants may occur from dye materials recently stamped on diapers or shirts. Paranitraniline is found in some yellow and orange wax crayons. A roentgenogram of the abdomen may show the opaque pieces of crayon in the intestine. Intense methemoglobinemia is produced by all these compounds. Symptoms include cyanosis, headache, shallow respiration, dizziness, hypotension, convulsions and coma. Hemolytic anemia may occur later. Five to 20 gm. of acetanilid may be fatal; a single dose of 0.5 to 5.0 gm. produces sweating, chills, gastric irritation, tinnitus, hypotension and circulatory collapse.

**Treatment.** Removal of poison from skin, repeated gastric lavage followed by catharsis. Oxygen, transfusion, exchange transfusion and methylene blue are of value.

7. **Antimony.** After ingestion, nausea, vomiting and severe diarrhea occur. Anemia, eosinophilia, hemoglobinuria and hematuria may be present.

**Treatment.** See No. 9.

8. **ANTU.** Antu produces massive pulmonary edema and pleural effusion in experimental animals by its action on the pulmonary capillaries and by increasing lymph flow. It is thought to be relatively nonpoisonous to man; more than one pound of a 20 per cent mixture has been ingested without producing symptoms.

9. **Arsenic.** Arsenic poisoning may be acute, subacute or chronic. Arsenic compounds may be absorbed from the gastrointestinal tract, lungs and skin. Arsenic inactivates sulfhydryl-containing enzymes and inhibits cellular respiration. It is stored in the tissues for a long time and is excreted slowly in the urine and feces. The more soluble salts may produce death quickly. In *acute poisoning*, symptoms usually occur within one-half to one hour after ingestion. If arsenic is ingested with a meal, there

may be delay as long as twelve hours. Constriction of the throat with dysphagia, intense gastric pain, persistent and projectile vomiting of large amounts of "rice water" occur; a severe watery diarrhea, becoming bloody, is common. The loss of fluids leads to severe dehydration, oliguria, hematuria and albuminuria. Eventually shock develops with cardiovascular and respiratory failure, terminating in coma and convulsions.

**Subacute or chronic poisoning.** If the patient survives the acute phase, there may be residual symptoms such as multiple neuritis, myelitis and hypoplastic anemia. Alopecia, dermatitis, macular erythema and pigmentation of the skin may also occur. In chronic arsenic poisoning due to ingestion of small amounts of arsenic over a period of time the development of symptoms is insidious with weakness, languor, anorexia, occasional nausea and vomiting, and constipation or diarrhea. Later, coryza, nasal and conjunctival congestion, edema of the lower eyelids, stomatitis, salivation and a garlic-like odor to the breath are present. The early symptoms may be followed by or be associated with any of the residual signs of involvement of the nervous system, the liver or the hematopoietic and epithelial tissues that occur in patients surviving acute poisoning. Pigmentation, hyperkeratosis of the soles and palms and exfoliative dermatitis are sometimes striking.

**Treatment.** Even though symptoms of acute arsenic poisoning are present, intensive and repeated lavage is indicated. If the patient is seen early, repeated lavage with a freshly prepared mixture of ferric hydroxide and magnesium oxide is said to be of value. Intensive intravenous hydration therapy is necessary. Sedation and morphine for pain are advisable.

BAL should be given promptly. The recommended intramuscular dose is 2.5 to 5 mg. per kilogram every four hours; the larger amount is approximately half of the toxic dose, so that undesirable side effects are frequent (see p. 1381 for toxic reactions). For mild arsenic reactions each injection should provide 2.5 mg. of BAL per kilogram of body weight. Four injections are given on each of the first and the second days; two on the third day, and one injection on each of the following ten days, or until recovery. For severe arsenic reactions, each injection should provide 3 mg. per kilogram. On the first and second days six injections are given each day at intervals of four hours; on the third day four injections are given, and subsequently, until recovery, two injections are given daily. Dosage schedules are essentially the same for reactions to gold.

Treatment should also be directed toward support of the damaged nerve, liver and kidney tissues.

**10. Aspidium, Male Fern.** The oleoresin, used as a vermifuge, produces progressive vomiting, diarrhea, abdominal pain, headache, colored or blurred vision, tremors, collapse, convulsions and death in respiratory failure. If recovery occurs, jaundice and blindness may persist for weeks.

**Treatment.** Gastric lavage followed by catharsis and general supportive measures. Castor oil and other oily cathartics should be avoided.

**11. Asterol.** A commercial fungicidal agent used against tinea infections. It has been reported to pro-

duce generalized muscular contractions. The sensorium is clear. There may be rotatory nystagmus and mydriasis.

**Treatment** is supportive.

**12. Atropine.** Active alkaloid of a number of the Solanaceae, which include *Datura stramonium* (Jimson weed, thorn apple), *Hyoscyamus niger* (henbane), *Datura arborea* (angel's trumpet), *Solanum nigrum* (black or deadly nightshade), *Solanum pseudocapsicum* (Jerusalem cherry), *Solanum dulcamara* (true bittersweet) and *Duboisia* (cork woods in New South Wales and Queensland). Severe poisoning may occur in children from the therapeutic use of atropine, homatropine and scopolamine. Symptoms develop promptly after ingestion. Dryness and burning of the mouth, thirst and difficulty in swallowing and talking occur. The vision is blurred, and photophobia is prominent. The skin is dry, hot and flushed. A rash occurs over the face, neck and upper part of the trunk, and desquamation may follow. In infants and small children the temperature may rise to as high as 107° F. The pupils are widely dilated; the pulse becomes weak and rapid, although no change may occur in infants; the blood pressure is elevated, and there may be palpitation, urinary urgency and difficult micturition. There may also be restlessness, excitability, confusion, weakness, muscular incoordination, giddiness and mild delirium, suggesting an acute psychosis. In infants the outstanding manifestations may be extreme abdominal distention, rapid respirations and distinct discomfort. Symptoms may persist for several hours or days, and the initial phase of excitement be followed by depression with circulatory collapse, respiratory failure and death. Diagnosis is often difficult; the rash, fever, tachycardia and delirium may suggest the onset of scarlet fever. The subcutaneous injection of 3 to 10 mg. of acetyl-beta methyl choline (Mechoyl) may be of diagnostic value. If salivation, sweating, lacrimation and intestinal hyperactivity do not occur after its injection, atropine poisoning may be present.

**Treatment.** Administration of water, milk or universal antidote should be followed by repeated gastric lavage and measures to reduce high fever. Short-acting barbiturates may control excitement and delirium.

**13. Barbiturates.** Five to six times the average hypnotic doses are toxic. The depressant action of barbiturates is due to an inhibition of the pyruvic-oxidase system. Symptomatology varies with the rapidity of action and the duration of the effect of the various compounds. Symptoms are somnolence, stupor, contracted pupils, coma, fall in blood pressure, respiratory and circulatory depression and occasionally pulmonary edema. In some instances there is hyperexcitability and confusion.

**Treatment.** The intensity of therapy should be adjusted to the degree of depression. Careful evaluation of the reflex responses and the cardiocirculatory and respiratory states should be made before institution of therapy. Short-acting barbiturates may produce death within an hour. Long-acting barbiturates may have depressing effects for four or five days. Lavage is indicated in all cases. Saline catharsis and stimulants may be indicated. Small repeated doses of caffeine, ephedrine, Coramine, Metrazol or strychnine may be of value. The repeated adminis-



tration of picrotoxin intravenously in the comatose patient may avoid further respiratory failure and lessen the depth of coma. The use of ephedrine and strychnine combined has been recommended. Intravenous glucose and saline solutions facilitate excretion of the drug and aid the liver in its detoxification. However, owing to the low ventilatory exchange, administration of large amounts of fluids too rapidly may lead to pulmonary edema. Maintenance of body temperature is of great importance. Blood transfusions, oxygen, carbon dioxide and artificial respiration may be necessary.

**14. Barium Salts.** The carbonate, hydroxide and chloride salts are used as pesticides; the sulfide, in depilatories. The barium ion produces stimulation of all muscle cells. After ingestion, tightness of the muscles of the face and neck, vomiting and diarrhea, muscular tremors, weakness, difficulty in breathing, cardiac irregularity, convulsions and death, from cardiac or respiratory failure, occur.

**Treatment.** Ten milliliters of 10 per cent sodium sulfate should be injected slowly intravenously every fifteen minutes until symptoms subside. Thirty grams of sodium sulfate in 250 ml. of water should be administered orally and repeated in one hour.

**15. Benzene Derivatives. Benzene.** Ingestion or inhalation of benzene fumes produces central nervous system depression. Principal clinical findings are coma and anemia. In mild poisoning dizziness, weakness, euphoria, headache, nausea, vomiting, tightness in the chest and staggering occur. In severe poisoning, visual blurring, tremors, shallow rapid respiration, paralysis, unconsciousness and convulsions ensue. Violent excitement or delirium may precede unconsciousness. Chronic poisoning from inhalation produces headache, anorexia, drowsiness, nervousness, pallor, anemia, petechiae and abnormal bleeding.

**TREATMENT.** Gastric lavage followed by catharsis. Great care should be taken to avoid aspiration. Epinephrine and ephedrine may induce ventricular fibrillation and should not be given.

**Naphthalene.** Common ingredient of moth repellents. Naphthalene produces hemolysis of red blood cells resulting in hemoglobinuria and hematuria. Liver necrosis may occur. Symptoms from acute poisoning following ingestion or inhalation are nausea, vomiting, diarrhea, oliguria, anemia, jaundice and pain on urination. Excitement, coma and convulsions may occur. Mental confusion and visual disturbances may occur after inhalation of fumes. Hemoglobinuria, albuminuria and casts may be present (pp. 264, 953).

**TREATMENT.** Gastric lavage followed by catharsis. Blood transfusions for anemia and exchange transfusion may be of value.

**Turpentine.** One-half ounce may cause fatal poisoning. Turpentine produces severe abdominal burning, nausea and vomiting. Diarrhea, pain on urination, unconsciousness, shallow respiration, bronchopneumonia and convulsions occur. Anemia, hemoglobinuria, hematuria, albuminuria and glycosuria may be present.

**TREATMENT.** Lavage should be performed carefully to avoid aspiration. Mineral oil may allay gastric irritation. General supportive measures and exchange transfusion are indicated.

**16. Bismuth.** Poisoning from injectible bismuth compounds is rare.

**Treatment.** See No. 9.

**17. Boric Acid and Borate Salts.** Boric acid may produce toxic symptoms when ingested or used as a wet dressing or as an ointment on large areas of injured skin, as in burns, diaper rashes or eczema. The mortality rate in infants is about 70 per cent. Excretion of boric acid from the body is slow, and cumulative action may occur. Symptoms of nausea, vomiting, abdominal pain and diarrhea occur. A maculopapular, urticarial or scarlatiniform rash occurs; the soles and palms are red. Desquamation follows in a few days. The mucous membranes are intensely congested. In infants signs of meningeal irritation may occur. Convulsions, delirium and coma follow. Albuminuria and azotemia may occur.

**Treatment** is symptomatic. Exchange transfusion may be lifesaving.

**18. Bromate.** Potassium bromate is used as a neutralizer in "cold wave" for the hair. Ingestion results in release of hydrogen bromate. Three ounces of the 3 per cent neutralizer solution may be fatal. Vomiting, diarrhea, abdominal pain, oliguria, lethargy, coma, convulsions and shock may occur.

**Treatment.** Gastric lavage followed by catharsis. One to 5 gm. of a 10 per cent solution of sodium thiosulfate intravenously is of value.

**19. Bromides.** Bromides are depressant to the central nervous system. Delirium and hallucinations may occur.

**Treatment.** The chloride ion, particularly ammonium chloride, may expedite elimination of bromide; 5 to 8 gm. per day in divided doses are recommended for adults. Intake of fluids should be generous.

**20. Cadmium.** Cadmium may be dissolved from plated pitchers and ice trays by such acid-containing foods as citrus fruit juices. Symptoms are manifest within approximately one-half hour and include nausea, vomiting, cramps and occasionally diarrhea, accompanied by general weakness. Recovery is usually rapid, within less than twenty-four hours.

**Treatment.** General supportive and sedative therapy is indicated. BAL will increase the concentration of cadmium in the urine, producing destructive tubular changes, and should not be used.

**21. Carbon Disulfide.** Inhalation of fumes or ingestion of the liquid produces central nervous system depression, with coma and terminal convulsions. Recovery may be followed by permanent damage to the central nervous system or the peripheral nerves.

**Treatment** is supportive.

**22. Carbon Monoxide.** The symptomatology of carbon monoxide is predominantly that of anoxia of varying degrees, with severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, collapse, coma, intermittent convulsions and failing respiration. The symptoms are dependent upon the concentration of methemoglobin in the blood (see p. 1379). A cherry-red color is particularly noticeable on the lips and fingernails. Permanent residual damage to the central nervous system may occur if the anoxia is profound or prolonged.

**Treatment.** Carbon monoxide can be removed almost completely from the blood in thirty minutes if oxygen in high concentration with carbon dioxide

is administered. Artificial respiration should be continued until normal breathing is resumed.

23. **Chenopodium (Wormseed Oil).** Ten to twelve drops of oil of chenopodium may produce toxic symptoms and death. The symptoms are dizziness, tinnitus, impaired vision, vomiting, profound depression and unconsciousness and, in more severe cases, diarrhea, muscular twitchings and convulsions. Glycosuria has been observed. If the patient survives the acute symptoms, deafness may be present for a few days to a month. Damage to the liver is manifested by jaundice; injury to the kidney by hematuria and albuminuria.

**Treatment.** Saline catharsis, stimulants, oxygen and copious amounts of oral and parenteral fluids are required.

24. **Chlorobenzene Derivatives.** A large number of chlorobenzene derivatives are found in household solvents, insecticides, fungicides, sprays, waxes, and paint solvents and cleansers. The volatile halogenated hydrocarbons are very toxic. Chlorinated insecticides are less toxic and are usually only so by ingestion. However, they are fat soluble and often are marketed in a hydrocarbon vehicle.

25. **Chlorinated Insecticides.** These consist of the *chlorobenzene derivatives*: DDT, TDE, DFDT, Methoxychlor, Dimite, DMC, Neotran, Ovotran, Dilan; the *chlorinated camphenes* such as toxaphene; and the *indan derivatives*, Chlordane, heptachlor, Aldrin, Dieldrin, Endrin, and Diendrin. These are fat-soluble, highly stable insecticides used as dusts, wetting powders and solutions in organic solvents. Most toxic is Aldrin. Skin absorption of indan derivatives in organic solvents may be fatal within one hour. One to 3 gm. of these derivatives produces severe symptoms and may be fatal. Symptoms are stimulation of the central nervous system such as hyperexcitability, tremors, ataxia, and convulsions beginning within thirty minutes to six hours. Central nervous system depression with respiratory failure ensues. Recovery is more likely if convulsions are delayed.

**Treatment.** Gastric lavage with large volumes of water followed by catharsis. The skin should be scrubbed with soap and water to remove contamination. Convulsions may be controlled with barbiturates, intramuscularly or intravenously. Stimulants should be avoided, and epinephrine is contraindicated.

26. **Chromates.** Chromate salts are highly irritating and destructive to tissues. After ingestion, dizziness, intense thirst, abdominal pain, vomiting, shock and oliguria or anuria occur. Chronic poisoning produces an eczematous dermatitis.

**Treatment.** Gastric lavage followed by catharsis and supportive fluid therapy.

27. **Cleaning Solutions.** Chemical constituents of various types: *Automobile paint cleaners* (free alkali, alkali salts, detergents, soap); *brush cleaners* (aromatics, halogenated hydrocarbons, alcohols, paraffins); *carbon cleaners* (aromatics, halogenated hydrocarbons, alcohols, paraffins); *dry cleaners for clothes* (halogenated hydrocarbons, alcohols, paraffins); *glass and furniture cleaners* (ammonium hydroxide, methyl alcohol, sodium hydroxide, detergents, soap); *grease removers (degreasers)* (usually contain only paraffins such as kerosene, hydrocarbons, gasoline or free alkali, alkali and salts, deter-

gents, soap); *gun cleaners* (nitranilines); *metal cleaners* (nitric acid, sulfuric acid, cyanides); *silver polish* (silver nitrate, free alkali, alkali salts); *radiator (automobile) cleaning compounds* (free alkali, alkali salts, detergents, soap); *straw hat cleaners* (oxalic acid); *toilet and drain cleaners* (hydrochloric acid, sulfuric acid, sodium sulfate, sodium hydroxide, sodium carbonate); *typewriter cleaners* (aromatics, halogenated hydrocarbons, and paraffins).

28. **Cocaine (Butocaine, Tutocaine, Methycaine, Nupercaine, etc.).** Toxicity develops quickly after oral ingestion, hypodermic injection or local application of cocaine or its derivatives to mucous membranes. Symptoms are excitability, restlessness, confusion, delirium, hyperactive reflexes, rapid pulse, elevated blood pressure, widely dilated pupils and exophthalmos. Nausea and vomiting are due to central stimulation. Death is preceded by Cheyne-Stokes respiration and convulsions.

**Treatment.** See No. 72. The patient should be catheterized to prevent reabsorption of cocaine from the bladder.

29. **Coniine.** Toxic component of the parsley family. These include poison hemlock (*Conium maculatum*) and water hemlock (*Cicuta maculata* and other *Cicuta* species). Coniine produces peripheral muscular paralysis similar to that of curare. Increasing muscular weakness, paralysis and respiratory failure occur.

**Treatment.** Gastric lavage followed by catharsis, artificial respiration and oxygen.

30. **Cosmetics. Deodorants** (aluminum salts); *depilatories* (barium or sodium sulfide); *freckle removers* (bichloride of mercury, bismuth, ammoniated mercury); *skin foods and creams* (mercury, salicylic acid); *hair sprays* (synthetic and natural resins). Inhalation produces diffuse pulmonary granulomatous lesions.

31. **Cough Medicines,** commonly contained agents of: antibiotics, antihistamines, chloroform, codeine, ephedrine sulfate and related compounds, opium derivatives, barbitol derivatives.

32. **Cyanide.** Acute cyanide poisoning from ingestion of the salt or inhalation of hydrocyanic acid produces symptoms of giddiness, hyperpnea, headache, palpitation, cyanosis, unconsciousness and asphyxial convulsions resulting in death within a few seconds to minutes. Death may be delayed as long as three hours. The odor of oil of bitter almonds on the breath is diagnostic. Symptoms may be confused with those of nitrobenzene poisoning, which produces methemoglobinemia with cyanosis.

**Treatment.** Specific, prompt treatment is sometimes successful. Poisoning following inhalation of cyanide gas should be treated with amyl nitrite inhalation immediately and repeated every five minutes unless blood pressure falls. Clothing should be removed and the skin washed with soap and water. Artificial respiration and oxygen should be given. Ten milliliters of 3 per cent sodium nitrite solution should be administered intravenously at a rate of 2.5 to 5 ml. per minute; if the systolic blood pressure falls below 80 mm. of mercury, it should be stopped. After administration of sodium nitrite, 50 ml. of a 25 per cent solution of sodium thiosulfate should be given intravenously at a rate of 2.5 to 5 ml. per minute. The sodium nitrite produces methemo-



globin, which can combine with the cyanide ion to form cyanmethemoglobin. The sodium thiosulfate is injected slowly to convert the cyanide released by dissociation of cyanmethemoglobin to thiocyanate. One per cent solution of methylene blue intravenously may be of some value.

33. **Daphne (Daphnin).** In bright red berries and all parts of the plants. Ingestion of the plant produces abdominal pain, vomiting, bloody diarrhea, weakness, convulsions and renal damage.

34. **Darnel.** The seeds contain temuline. Flour may be contaminated with darnel, and bread made with such flour may produce vertigo, staggering, vomiting, visual disturbances, burning pain in the mouth and prostration.

35. **Detergents.** *Cationic:* Phemerol (benzethonium chloride), Zephiran (benzalkonium chloride), Diaparene (benzethonium chloride) and Ceepryn chloride (cetyl pyridinium chloride) destroy bacteria and are used as skin cleansers, on surgical instruments, cooking equipment, sick room supplies and diapers. Ingestion of 1 to 3 gm. may be fatal. Symptoms are vomiting, collapse and coma with death within a few hours.

**Treatment.** Gastric lavage should be done immediately and thoroughly, using ordinary soap solutions.

36. **Digitalis.** Poisoning occurs most commonly from medicinal preparations. Digitalis glucosides, however, are contained in a large number of plants. Symptoms of poisoning occur within one-half to six hours after ingestion of large doses and are usually initiated by nausea and vomiting of reflex origin. Arrhythmias and bradycardia may be present. Headache, drowsiness and coma have been described. Death occurs from ventricular fibrillation. Electrocardiographic changes are present in about 66 per cent of overt poisonings. Overdosage of digitalis during therapeutic administration of the drug is evident initially by the appearance of anorexia, soon followed by nausea and vomiting. These symptoms may become manifest over a period of several days; if large doses have been given, the vomiting may occur without preceding episodes of nausea. Excessive salivation and diarrhea, often accompanied by abdominal discomfort and pain, may be present. Cardiac arrhythmias, particularly extrasystoles of ventricular origin, and paroxysmal tachycardia may also occur. Bradycardia resulting from the direct action of digitalis on the sinoatrial pacemaker or the atrioventricular conduction system may follow. Death may occur from ventricular fibrillation. Headaches, fatigue, malaise, blurred vision, drowsiness and mental symptoms of confusion, disorientation and even convulsions may occur.

**Treatment.** When poisoning is due to accidental ingestion, prompt gastric lavage is indicated, but when it results from continued overdosage, lavage will not be helpful. Adequate fluids should be given to facilitate excretion, but diuretics may be dangerous, owing to excessive extraction of digitalis from the tissues. Absolute bed rest should be enforced until clinical and electrocardiographic evidence of toxicity to the heart has disappeared. Nothing more is indicated if the pulse is slow or even if there is a heart block, but when there is ventricular tachycardia, emergency treatment is required to avoid ventricular fibrillation. Five to 10 ml. of a 10 per

cent solution of magnesium sulfate should be administered intravenously for an immediate effect and should be followed by oral administration of quinidine sulfate. One to 2 grains should be given every two to three hours throughout the twenty-four hour-period for two or three days. If the child is vomiting, intramuscular injection of quinidine is required.

37. **Dinitro-ortho-cresol.** These derivatives of phenol and cresol are used as insecticides and herbicides. They inhibit phosphate synthesis which results in increased cellular respiration. *Acute poisoning* from skin contamination, ingestion or inhalation produces fever, prostration, thirst, nausea and vomiting, excessive perspiration and difficulty in breathing. Later anoxia, cyanosis, muscular tremors and coma occur. *Chronic poisoning* produces skin eruption, neuritis, hepatic and renal damage and injury to the bone marrow.

**Treatment.** Thorough lavage with saturated bicarbonate solution should be done, followed by catharsis. Control of body temperature, oxygen and support of respiration are required. Intravenous glucose to support increased metabolic activity is advisable.

38. **Ergot.** Ergot is present in certain proprietary mixtures used as abortifacients. Rye flour may be contaminated with ergot fungus. Acute poisoning from ingestion, injection or application to mucous membranes produces vomiting, diarrhea, dizziness, unstable blood pressure, weak pulse, dyspnea, convulsions and loss of consciousness. The dose required to produce an abortion may cause death.

**Treatment.** Absorption may be delayed by giving water, milk or universal antidote; gastric lavage should follow. Saline catharsis is indicated. Sedation should be prescribed for convulsions.

39. **Esters, Aldehydes and Ethers.** *Dimethylsulfate* is caustic to mucous membranes of the eyes, nose, throat and lungs. Inhalation produces pulmonary edema. Symptoms of intense irritation and erythema of the eyes, severe lacrimation, and chemosis occur after inhalation, skin absorption or ingestion. Cough and edema of the tongue, lips, larynx and lungs follow. The corrosive action is similar to that of sulfuric acid; dimethylsulfate in the presence of water hydrolyzes to methyl alcohol and sulfuric acid.

**TREATMENT.** Copious washing of contaminated mucous membranes and skin surfaces.

*Tri-ortho-cresyl-phosphate.* The ortho form is toxic. The agent is used as a lubricant, fireproofing and plasticizer in coating plastics. Food may become contaminated. Symptoms are due to inhibition of cholinesterase, producing weakness and paralysis of distal muscles. Death from respiratory paralysis may occur. Symptoms may be delayed several weeks, and degenerative changes in the muscles and spinal cord may be observed at autopsy.

**TREATMENT.** Gastric lavage followed by saline cathartics and support of respiration are necessary.

*Acetaldehyde, metaldehyde, and paraldehyde.* Paraldehyde and metaldehyde are thought to degrade to acetaldehyde in the body. Toxicity is related to limited oxidation of acetaldehyde. Acetaldehyde vapors cause severe irritation of mucous membranes, cough, pulmonary edema and narcosis. Ingestion causes nausea, vomiting, diarrhea, narcosis and re-



spiratory failure. Paraldehyde produces deep and prolonged sleep, and metaldehyde causes nausea, severe vomiting, abdominal pain, muscular rigidity, convulsions, and death from respiratory failure.

**Treatment.** Copious washing of material from mucous membranes and gastric lavage, followed by saline catharsis. Artificial respiration is necessary.

40. **Favism.** Ingestion of *Vicia fava* (broad beans, horsebean) or inhalation of the dust of such beans may produce, particularly in children, symptoms of poisoning. The mechanism by which hemolysis is brought about is related to a defect in the glucose-6-phosphate dehydrogenase system of the erythrocytes (pp. 264, 953).

**Treatment.** Severe hemolytic anemia may require transfusions. A corticosteroid should be given.

41. **Fish Poisoning.** Several varieties of fish contain poisons within their bodies throughout the year. Others are poisonous only during the spawning season. Fish may also become contaminated with pathogenic or saprophytic organisms (*Salmonella*, typhoid, staphylococci). Fish poisoning (ichthyotoxism) may be due to eating of Tetraodontidae (puffers) or of the Diodontidae (porcupine fish). The Clupeidae (herring family), particularly *Clupea thrissa* and *venonosa*, and the Scarus (parrot fish) may also contain poisons. An alkaloid-like substance, fugin, present in puffers and certain other fish produces headaches, restlessness, salivation, vomiting, paralysis, cyanosis, and dilatation of the pupils. Death occurs from dyspnea and anoxia. Some varieties of sturgeon (*Acipenseridae*), pike (*Esocidae*) and barbel (species of *Barbus*) have poisons in their reproductive organs during their spawning season.

42. **Fluoride.** Fluoride salts and compounds are rapidly absorbed and slowly excreted. They are protoplasmic poisons inhibiting cellular enzyme action. Fluoride poisoning produces severe nausea and vomiting, diarrhea and collapse within a few hours. If patients are ill over a longer time, there are excessive salivation, dilated pupils, steady pulse, shallow unlabored respirations and weak heart tones. Cyanosis due to fluoromethemoglobinemia is not uncommon. Occasionally there is paralysis of the muscles of deglutition, carpopedal spasm and muscular spasm of the extremities.

**Treatment.** Immediate lavage with calcium chloride prevents absorption by forming insoluble calcium fluoride; if calcium chloride is not available, copious quantities of milk may be given after lavage with warm water. Intravenous calcium chloride or calcium gluconate may also be of value. Treatment is largely symptomatic and supportive. Exchange transfusion may be indicated.

43. **Fluoroacetate.** Fluoroacetate blocks aerobic metabolism at the citric acid level of the Krebs' cycle. Very small doses may be fatal for children, and 300 mg. may be fatal for an adult. Symptoms are prompt vomiting, apprehension, stupor and generalized convulsions occurring within six hours. Carpopedal spasm may be present. Respiratory and cardiac irregularity and failure may occur.

**Treatment.** Lavage and catharsis are indicated. Cardiac and central nervous system symptoms may be modified by administration of 0.1 to 0.5 ml. per kilogram of acetate such as glycerol monoacetate

injected intramuscularly at hourly intervals. An overdose of monoacetate may lead to nervous system depression and death. Calcium may be of value for tetanic manifestations. Digitalization for cardiac irregularities is of little value. Fluid therapy should be cautious because of cardiac and respiratory stress.

44. **Formaldehyde.** Formaldehyde is a general protoplasmic poison. It is a protein precipitant which preserves and hardens tissues. The gas is now infrequently used as a fumigant. Exposure to the gas produces intense conjunctivitis and irritation of the respiratory tract, often with resulting coryza, bronchitis and pneumonia. Ingestion of formaldehyde is followed by severe irritation of the mucosa of the mouth, throat and intestinal tract, intense abdominal pain, vomiting and diarrhea. Formaldehyde depresses the central nervous system, producing vertigo, depression and coma. Convulsions are rare. Oxidation of formaldehyde by the body produces formic acid and a resultant acidosis.

**Treatment.** Lavage should be carried out with dilute ammonia water (0.2 per cent) or egg albumen in water. The acidosis and impending shock must be treated, and respiratory stimulants may be indicated.

45. **Hydrocarbons (Kerosene, Solvent Distillate and Gasoline).** Ingestion of more than 10 ml. of these petroleum distillates increases the toxicity tremendously. These agents produce over 200 deaths a year in children in the United States. Within fifteen minutes to one hour after ingestion of most hydrocarbons, symptoms of nausea, vomiting, cough and central nervous system stimulation may occur. Kerosene produces a gastroenteritis; gasoline usually does not. The hydrocarbons are readily absorbed and are excreted by the lungs. Vertigo, fever, drowsiness and confusion result. Methemoglobin formation is common. Bronchitis or pneumonia from aspiration of hydrocarbons may develop within the first twenty-four hours or be delayed. Inhalation of gasoline produces an intense burning sensation in the throat and lungs within a few minutes after exposure, and bronchopneumonia may develop rapidly.

**Treatment.** It is advisable not to induce vomiting in hydrocarbon poisoning, since the frequency of pulmonary complications is thought to be greater. Lavage carefully done is advisable, extreme caution being taken to avoid aspiration. When only small amounts have been taken, saline cathartics are indicated, and lavage is usually not necessary. General supportive measures, oxygen, transfusion for methemoglobinemia, and carbon dioxide stimulation may prevent development of secondary bacterial pneumonia.

46. **Hydrocarbons (Halogenated).** *Carbon tetrachloride.* A nonflammable volatile solvent, used as a cleaner in floor waxes and in fire extinguishers. Ingestion of 3 to 5 ml. may be fatal. Symptoms occur quickly after inhalation or ingestion or from skin absorption. Signs of central nervous system depression, such as dizziness, confusion and unconsciousness, occur. Respiratory and cardiac irregularity and collapse occur. Recovery may be followed in a few days or up to two weeks by evidence of liver or kidney damage.

**Treatment.** General supportive measures, artificial respiration and gastric lavage followed by



catharsis. A high carbohydrate intake is advisable. Epinephrine and ephedrine are contraindicated because they may induce ventricular fibrillation.

**Methyl bromate, methyl chloride.** These gases are used as refrigerants and fumigants. They may be present with carbon tetrachloride in fire extinguishers. Toxic tissue effects are similar to those of carbon tetrachloride except that bronchopneumonia and pulmonary edema are more common. The substances are metabolized to methyl alcohol and hydrobromic or hydrochloric acids in the body. Acute poisoning from inhalation, ingestion or skin absorption produces nausea, vomiting, vertigo, weakness, oliguria, drowsiness, hypotension, coma and convulsions. Pulmonary edema develops and progresses for several hours. In mild poisoning the symptoms may not develop for several hours. Vesiculation of the skin may be present where contact has occurred.

**TREATMENT** as for carbon tetrachloride with special measures for pulmonary edema.

**Trichloroethane.** This solvent may be present in rug, wall and clothing cleaners. Symptoms are those of severe depression of the central nervous system followed by evidence of myocardial, hepatic and renal injury. Recovery may be rapid after removal of the poison; late jaundice is uncommon.

**TREATMENT** as for carbon tetrachloride.

**Tetrachloroethane.** Occasionally present in household cleaners, it is the most poisonous of the halogenated hydrocarbons. Death from acute poisoning may occur quickly and leave evidence of congestion of the lungs, kidneys, brain and gastrointestinal tract. Symptoms of acute poisoning are intense irritation of the eyes and nose, headache, nausea, cyanosis and central nervous system depression appearing over a period of one to four hours. After recovery, evidence of jaundice, anuria and uremia may be present.

**TREATMENT** as for carbon tetrachloride.

**Ethylene chlorohydrin.** Used as a cleaning solvent and also to speed the germination of seeds and potatoes. Ingestion results in pulmonary edema, vascular damage, direct toxic action on cardiac muscle and depression of the nervous system followed by damage to the liver and kidneys. Symptoms are those of respiratory and circulatory failure.

**Chlorinated naphthalene and chlorinated diphenyl** (Halowax, Arochlor). These substances are used as high temperature dielectrics for electrical equipment. Chronic poisoning produces acneiform lesions, drowsiness, hepatic injury and coma.

**TREATMENT** as for carbon tetrachloride.

47. **Iodine.** The toxic effects of iodine are due largely to its corrosive action on the gastrointestinal tract. Iodine is highly reactive and combines readily with starch, proteins and fats in the digestive tract. Ingestion is followed by reflex vomiting, burning abdominal pain and bloody diarrhea. Shock may result from fluid loss, and death may occur in one to forty-eight hours. The diagnosis is obvious from the brownish staining of the mucous membrane and the blue color of the vomitus or lavaged material.

**Treatment.** Lavage with soluble starch solutions or a combination of sodium thiosulfate (5 per cent) and albumen (egg white). Intravenous fluid is indicated to avert dehydration and shock.

48. **Iron Salts (Ferrous Sulfate).** As few as ten to fifteen ferrous sulfate candy-coated tablets (5

grains) may be fatal. Symptoms may occur thirty to sixty minutes after ingestion. Danger may exist for at least twenty-four hours. Acute gastroenteritis, vomiting, diarrhea, dehydration, collapse, and coma ending in death may occur. A severe acidosis may also be present. The diarrhea may be initially watery, becoming bloody and then tarry. Approximately 50 per cent of the reported cases have been fatal.

**Treatment.** Lavage with sodium bicarbonate to produce insoluble ferrous carbonate. Sodium bicarbonate should be left in the stomach along with magnesium sulfate for catharsis. BAL is probably of little value. Management of the dehydration, acidosis and shock is imperative.

49. **Lye and Corrosive Alkalis.** Potassium hydroxide, sodium hydroxide, potassium carbonate, sodium carbonate, sodium phosphate and sodium silicate are corrosive alkalis. Ammonia and ammonia hydroxide may also produce corrosive tissue actions. These substances produce intense local irritation of the mouth, pharynx, esophagus and stomach. Perforation of the esophageal or gastric wall may occur within relatively few hours. Recovery is invariably associated with scarring of the esophagus and with stenosis unless proper precautions are taken. Ingestion of alkali produces severe pain, vomiting, diarrhea and collapse.

**Treatment.** Lavage with copious volumes of dilute vinegar, lemon juice or weak acids. Instillation of several ounces of olive oil or flour paste after lavage may be of value. Vomiting should not be induced in corrosive alkali poisoning. If an hour or more has elapsed since ingestion, lavage should be avoided, and only aspiration of the thick accumulated secretions from the pharynx should be performed. Small quantities of olive oil should be given at frequent intervals. A liquid diet and parenteral fluids are necessary, owing to the dysphagia. Stricture of the esophagus may at times be avoided by early dilation (see p. 643).

50. **Meadow Saffron (Colchicum Autumnale).** Colchicine is present in the leaves and seeds, which may be eaten in salad. Symptoms occur three to six hours after ingestion, with abdominal discomfort and violent, uncontrollable vomiting and purging. Bloody diarrhea and collapse from exhaustion and dehydration follow.

**Treatment.** Lavage followed by saline catharsis. Dehydration and shock must be treated.

51. **Mercury.** Mercury, usually ingested by children in the form of mercury bichloride tablets, is a protein precipitant (see also Acrodynia, p. 1398). Mercury produces severe, painful lesions of an ashen-gray color on the mucous membranes of the mouth, throat, stomach and intestines. In the stomach it causes intense gastric pain and vomiting within a short time. The prognosis is improved if the interval between ingestion and vomiting is short and if there is extensive vomiting. If mercury reaches the small intestine, a severe, profuse, bloody diarrhea occurs. Mucosal shreds may be passed. Profound shock due to circulatory collapse soon follows. If the patient survives the acute phase, severe symptoms of systemic toxicity appear within a few hours and last for many days. Damage to the renal capillaries and tubules is responsible for the albuminuria, hematuria and excretion of casts. Diuresis sometimes



occurs initially, owing to the faulty reabsorption of water by damaged renal tubules, but eventually there is oliguria and anuria. Widespread capillary hemorrhages and transudation of protein and fluid from the blood stream result in circulatory failure and shock.

**Treatment.** Immediate and repeated lavage with raw white of egg or milk provides protein for precipitation by the mercury. BAL is particularly effective. It should be given intramuscularly as promptly as possible, since experimentally it is less effective after extensive tissue damage has occurred. The initial dose should be 5 mg. per kilogram, followed in one or two hours by a dose of 2.5 mg. per kilogram. After two to four hours the latter dose should be repeated, and in severe cases a fourth one should be administered within the first twelve hours after the first injection. On the second day two injections may be given, each of 2.5 mg. per kilogram. On the third day only one dose of 2.5 mg. per kilogram is necessary.

Sodium formaldehyde sulfoxalate is said to reduce soluble mercuric salts to the insoluble monovalent (mercurous) form; the stomach is lavaged with 250 ml. of a 5 per cent solution. From 100 to 250 ml., depending upon the age of the child, are then left in the stomach. This procedure is followed by intravenous administration of 50 to 200 ml. of a 10 per cent solution. Lavage with 10 ml. of 10 per cent sodium hypophosphite containing 2.5 ml. of hydrogen peroxide and diluted to 100 ml. is also of value. Sodium hyposulfite, chalk, freshly precipitated ferrous hydroxide, milk of magnesia or starch paste may also be used. After lavage, attention should be given to maintenance of a normal composition of the body fluids; one-half isotonic Ringer's or polyionic solutions should be given parenterally to maintain body fluids and to produce a copious diuresis in order to protect the kidneys from high concentrations of mercury. Such therapy should be continued unless edema and oliguria develop. Prognosis depends upon the amount of mercury taken, the interval between ingestion and lavage, and the degree and duration of kidney damage. Too much stress cannot be placed upon the importance of the immediate removal of ingested mercury, since absorption is rapid.

52. **Milk sickness**, or "trembles," occurs in animals from eating the rayless goldenrod (*Tremetol*) or the white snakeroot which contain toxic substances. In man the ingestion of milk products or the flesh of poisoned animals produces nausea, vomiting and constipation. The tongue becomes dark red and tremulous; the cheeks are flushed and the lips red. Abdominal pain and muscular weakness may occur. Deaths have been reported.

53. **Monk's Hood Root (Wolfsbane) and Larkspur.** The fresh leaves and roots of these plants contain aconite. Absorption occurs readily and may result in instantaneous death, probably from paralysis of the heart. Symptoms are tingling in the mouth, stomach and skin (most important diagnostic feature), excessive salivation, nausea, vomiting and diarrhea. The pulse is slow and feeble, and there are dyspnea, weakness, impaired speech, unconsciousness and convulsions. Death usually follows in two to six hours.

**Treatment.** Prompt lavage with potassium per

manganate, 1:1000, should be followed by saline catharsis; artificial respiration, oxygen and cardiac and respiratory stimulants should be used when indicated.

54. **Mountain Laurel (Andromedotoxin).** Ingestion of young shoots and leaves produces salivation, lacrimation and nasal discharge. Vomiting, convulsions, slowing of pulse, lowering of blood pressure, and paralysis may occur.

**Treatment.** See No. 76.

55. **Mushroom Amanita Muscaria (Mycetismus Nervosus, Fly Amanita).** This plant contains muscarine and produces severe gastrointestinal symptoms soon after ingestion, followed shortly by profuse perspiration, salivation, miosis, delirium, hallucinations, convulsions and coma. The pharmacologic action of muscarine on smooth muscle and glands is similar to that of acetylcholine. Mild degrees of intoxication occur, and there may be individual susceptibility.

**TREATMENT.** Lavage followed by saline catharsis is imperative. Atropine given hypodermically is of value.

**Amanita phalloides (Mycetismus choleriformis, death cup, destroying angel).** This plant, which is extremely toxic, contains several toxins not completely identified; the mortality in human poisoning is 60 to 100 per cent. Symptoms may be delayed six to fifteen hours after ingestion, when there are sudden severe abdominal cramps followed by vomiting and diarrhea, with mucous and bloody stools. The intoxication is prolonged, and jaundice develops in two to three days, indicating severe degenerative changes in the liver. The kidney is involved, and direct toxic action of the heart may result in cardiac failure and death within five to eight days.

**TREATMENT.** Immediate lavage, enemas and saline catharsis are indicated. Dehydration and shock must be treated. The degree of toxic tissue changes may be ameliorated by large amounts of glucose, plasma and blood intravenously.

56. **Nicotine.** The toxicity and rapidity of action of nicotine are comparable to those of cyanide. The local caustic action produces nausea, salivation, abdominal pain, vomiting and diarrhea. After absorption there are headache, dizziness, visual and hearing disturbances, mental confusion and intense weakness, and death may follow within a few minutes. Respiratory stimulation, elevated blood pressure and slow pulse are also early manifestations. Later there are pinpoint pupils and a curare-like action of the skeletal and respiratory muscles. Respiratory and circulatory failure is followed by convulsions and death.

**Treatment.** Lavage with tannic acid, strong coffee or tea for ingested poison. Nicotine on the skin should be thoroughly washed off. Owing to the rapid destruction of nicotine in the body, death can be averted if primary attention is directed toward prevention of respiratory failure. Artificial respiration and oxygen should be continued until normal breathing is resumed or the heart has stopped. Epinephrine, caffeine and Coramine are not ordinarily indicated unless respiratory failure develops.

57. **Nitrites.** Medications, such as bismuth subnitrite, amyl nitrite, sodium nitrite or spirit of glyceryl trinitrate, may be taken accidentally by children. Therapeutic use of bismuth subnitrite may



result in formation of nitrites by bacterial decomposition in the intestines. Cyanosis in infants due to poisoning with water containing nitrates has been described. Water seeping from barnyards heavily laden with bacteria and dissolved nitrogenous materials may become increasingly purified by passage through the soil. However, certain soil bacteria oxidize the ammonia and other nitrogenous compounds to nitrates. The solution of nitrates, free of coli organisms, may enter subsurface channels leading directly into wells used for drinking purposes. Ingestion of such water in milk formulas may result in conversion of the nitrates to nitrites by gastrointestinal organisms. Flushing of the skin, fall in blood pressure, severe methemoglobinemia, cyanosis and dyspnea develop. Syncope and respiratory failure may occur.

**Treatment.** Lavage should be followed by saline catharsis, particularly in bismuth subnitrite poisoning. When syncope occurs, epinephrine and other vasopressor agents should be avoided. A deep Trendelenburg position of the body and passive movements of extremities may facilitate return of venous blood to the heart. Transfusions and oxygen are indicated for the methemoglobinemia, and methylene blue is of value.

58. **Nutmeg.** One teaspoonful of powdered nutmeg may produce severe toxic symptoms. Narcosis with periods of delirium and excitability may occur within one to six hours.

59. **Oils.** Most of the nonvolatile hydrocarbon oils are nontoxic. Ingestion, however, may be associated with vomiting and aspiration into the lungs. Pulmonary complications are more intense with vegetable and animal oils.

**Treatment.** Emetics should not be given. Lavage should be done with care, avoiding emesis.

60. **Opiates.** Several natural alkaloids of opium, particularly morphine and codeine, and some synthetic narcotics cause toxic effects in infants and children. Poisoning occurs as a result of excessive therapeutic administration or from accidental ingestion. It has been stated that infants and children are more susceptible to the actions of the opiates, but there is reason to doubt this statement. Manifestations of opiate poisoning are those of central nervous system depression. Somnolence, coma and respiratory depression, often severe, may be noted. Pinpoint pupils, although observed, are not diagnostic of opiate poisoning.

**Treatment.** Prompt, vigorous treatment is mandatory and should be directed to the prevention of anoxia and further respiratory depression. Oxygen and artificial respiration may be indicated, and the airway must be kept patent.

Two specific opiate antagonists are available: N-allylnormorphine (Nalline) and L-3-hydroxy-N-allylmorphinan tartrate (Lorfan). Both drugs have specific antagonistic actions against all opiates, natural and synthetic. They are ineffective against other central nervous system depressants such as phenobarbital, and, in fact, will produce the toxic effects of opiates if used in situations other than opiate poisoning. The drugs should be administered intravenously as rapidly as possible. The recommended intravenous dose of Nalline is 0.025 mg. per kilogram; the dose of Lorfan is approximately one twentieth of the above. The same dose of either

drug may be repeated once or twice as needed at intervals of twenty minutes, the approximate duration of effect of each drug.

61. **Oxalates and Oxalic Acid.** Local irritation is produced by ingested oxalic acid. Both the acid and its salts are rapidly absorbed, and death occurs quickly. Absorbed oxalate combines with the ionized calcium of the blood, producing hypocalcemia leading to muscular twitchings, laryngospasm, tetany and convulsions. The heart stops beating in diastole.

**Treatment.** Lavage with 0.1 per cent potassium permanganate should be followed by a 5 per cent calcium chloride, chalk or lime solution. Calcium gluconate or calcium chloride intravenously is of value if signs of tetany are present.

62. **Phenols (Carbolic Acid, Cresol, Creosote, Creolin, Lysol, Resorcinol and Pyrogallol).** Phenol may produce symptoms leading to death within a few minutes, dependent upon the surface from which the substance is absorbed. Death (lethal dose is 8 to 15 gm.) usually occurs within twenty-four hours from respiratory failure. Initial symptoms are severe, painful local corrosion of mucous membranes and severe vomiting. Widespread capillary damage, medullary depression and shock occur quickly. Fleeting excitement may occur, followed by unconsciousness. Other symptoms are low blood pressure, cold sweat, hypothermia, oliguria, albuminuria and hemoglobinuria.

**Treatment.** The drug must be removed promptly before absorption occurs. Lavage with olive oil or other vegetable oils provides a solvent for the phenol. Neither alcohol nor mineral oil should be used; alcohol facilitates absorption, and mineral oil is a poor solvent for phenol. After lavage several ounces of olive oil should be left in the stomach. Copious parenteral fluid administration should be instituted to protect the kidneys. The acidosis responds promptly to intravenous administration of sodium bicarbonate or sixth-normal sodium lactate. Artificial respiration should be performed when respiratory failure occurs.

63. **Phenolphthalein.** Phenolphthalein is present in many candy cathartics (Analax, Ex-lax, Phenolax and cathartic chewing gum). Children have been known to eat more than a box of the tablets. Apparently, large amounts of phenolphthalein can be ingested without serious results. The range of toxic doses is not known. Severe toxic actions may be manifest in hypersusceptible persons. A violent cathartic action results several hours later. A bright red skin eruption and swelling of the eyelids may occur. High fever, meningismus, hemiplegia, albuminuria, oliguria, and respiratory and cardiac failure have been attributed to phenolphthalein poisoning.

**Treatment.** General supportive treatment is indicated. If violent catharsis is present, and dehydration and acidosis ensue, parenteral fluid therapy should be administered. Diagnosis may be established easily by the development of a pink color in lavaged material, stool or urine on the addition of alkali.

64. **Phosphorus, Inorganic.** Red phosphorus is nonabsorbable and therefore nonpoisonous. Yellow phosphorus is highly poisonous, producing severe tissue destruction. Yellow or white phosphorus is used in rodent and insect poisons, in fireworks and



in the manufacture of fertilizer. Zinc phosphide used in rat poisons releases phosphine on contact with water. Symptoms of acute poisoning occur within one to two hours. Nausea, vomiting, diarrhea, and a garlic odor of the breath and excreta may be noted. Coma may occur within twenty-four to forty-eight hours. If recovery from the acute phase occurs, symptoms may return in one to two days with nausea, vomiting, diarrhea, large tender liver, jaundice, shock, oliguria and multiple hemorrhages. Phosphorus causes second- to third-degree burns on contact with the skin.

**Treatment.** Acute poisoning should be treated by gastric lavage with large amounts of 0.2 per cent copper sulfate. Potassium permanganate, 1:1000, or 2 per cent hydrogen peroxide tends to convert elemental phosphorus to harmless oxidation products. Phosphorus is soluble in mineral oil; therefore the instillation of 100 to 200 cc. of mineral oil after lavage may facilitate its elimination. Supportive measures include treatment for dehydration, acidosis and shock, and subsequently a high carbohydrate diet and amino acids, orally or parenterally to protect the liver from serious injury. When there has been liver damage, such treatment should be continued until there is evidence that function has returned.

**65. Phosphorus, Organic.** Phosphate ester insecticides should never be used in homes. All are anticholinesterase compounds. There are three major types of organic phosphate insecticides: the nitrophenyl thiophosphates, the alkyl pyrophosphates, and the phosphoramides. They vary in distribution of tissue and in duration of action. The phosphoramide compounds have no cerebral action, acting entirely by peripheral inhibition of cholinesterase. The alkyl pyrophosphates are rapidly hydrolyzed in the body to nontoxic metabolites. The thiophosphates are more stable and are detoxified slowly. Most of these compounds are several times more toxic than nicotine. One drop of parathion in the eye may be fatal. Malathion is probably the least toxic. One gram, however, may be fatal. Symptoms are prompt within thirty minutes, and may continue for twenty-four to forty-eight hours. They consist of increased secretions (such as sweat, saliva, tears and bronchial fluids), nausea, vomiting, diarrhea, miosis, blurred vision, bronchiolar spasms and pulmonary edema. Ataxia, vertigo, tremors, muscular weakness, fibrillation, fasciculation, finger and mouth twitching, muscular paralysis, cyanosis, dyspnea, chest constriction, stupor, coma and convulsions may also occur.

**Treatment.** Artificial respiration to maintain ventilatory exchange is indicated. Wash all insecticide off the skin and mucous membranes. Atropine in effective doses should be given hourly if necessary. Pupillary dilatation and decreasing secretions are a measure of atropine effect. Magnesium sulfate intravenously may be of value. Morphine, barbiturates and respiratory depressants should be avoided.

**66. Rotenone (Derris Root, Cubeb).** An insecticide frequently mixed with pyrethrum powder. The lethal dose is probably large. Solutions or powder may be absorbed from the lungs or gastrointestinal tract. Symptoms are predominantly respiratory. There is an acceleration in the respiratory rate followed by a decrease; death occurs from respiratory failure. Evidences of gastric irritation such as nausea

and vomiting may occur. Symptoms occur promptly within a few minutes to an hour.

**Treatment.** Lavage, catharsis and supportive measures.

**67. Salicylates (Methyl Salicylate, Salicylic Acid, Sodium Salicylate, Acetyl Salicylic Acid and a Variety of Proprietary Ointments and Medications Containing either Salicylic Acid or Salicylates).** Prolonged excessive or accidental ingestion of salicylates may result in severe poisoning. Absorption may occur from the mouth, gastrointestinal tract and the skin. The peak action occurs about four hours after a single toxic dose and may last longer than eighteen hours. Rarely, effects of poisoning may persist for ten days. Methyl salicylate and salicylic acid produce symptoms rapidly. Both cause severe gastrointestinal irritation with nausea and vomiting. Local painful lesions are caused by the caustic action of the acid. Intoxication may occur from the use of salicylic acid powder or ointment on large, open, weeping skin lesions. The toxic dose is usually in excess of 0.15 gm. per kilogram of body weight.

Initial symptoms in man, as well as those produced in experimental animals, are respiratory. Respiratory stimulation occurs via the vagus. There is an increase in the respiratory minute volume without necessarily an increase in rate, leading to a decrease in the  $p\text{CO}_2$ . Thus a respiratory alkalosis (increase in blood serum pH) leads to cerebral vasodilatation with symptoms of apathy, confusion, coma and an increase in cerebrospinal fluid pressure. Renal compensation follows, producing an increase in bicarbonate in the urine, a decrease in urine chloride, with corresponding rise in plasma chloride and a decrease in serum base. Renal compensation thus leads to loss of base from the body, predominantly as a result of the increased sodium excretion in the urine. In addition, salicylates appear to disturb the metabolism of carbohydrate. An unusually striking and persistent ketosis is associated with or soon follows early symptoms of toxicity. The ketoacidosis produces further base depletion via the kidney, and a true metabolic acidosis may be superimposed upon the respiratory alkalosis. Thus diagnosis of the electrolyte disorder cannot be made merely by determination of the carbon dioxide content of the blood. Measurement of the pH of the blood is of great value when correlated with other findings. Salicylates have an inhibiting effect on the formation of prothrombin by the liver, leading to purpuric manifestations. Dehydration in uncomplicated salicylate poisoning in a well child is usually not striking; however, salicylate poisoning often occurs in children who are ill, and the dehydration produced may be moderate to severe. Vertigo, tinnitus, deafness, visual blurring, anorexia, vomiting, sweating, pallor or flushing, cyanosis, tetany, numbness and tingling of the face, lips and extremities, and bleeding from any area of the body may occur. Laboratory findings of value are acetoneuria and a falsely positive test for diacetic acid with ferric chloride. Diacetic acid produces a burgundy color with ferric chloride, whereas salicylates in the urine produce a violet to a deep purple color. Boiling of acidified urine will volatilize the diacetic acid, producing a negative ferric chloride test in the absence of salicylate. Late evidences of toxicity may



consist of erythematous, scarlatiniform, pruritic, eczematous or desquamative skin lesions.

**Treatment.** See page 196.

68. **Santonin.** The high solubility of santonin in a bile and alkaline solution causes rapid absorption from the upper intestine and leads to rapid development of toxic symptoms. An unknown product is formed which, when excreted, is an aid in diagnosis, since it produces a yellow color in acid urine and a pink color in alkaline urine. Toxic symptoms are manifest initially by a transitory blue vision and later by yellow vision. Other symptoms include headache, vomiting and confusion; with large doses there may be abdominal pain, diarrhea and bloody urine. The skin is cold and clammy and covered with perspiration. A fall in body temperature, a skin rash, tremors, cardiac and respiratory depression and convulsions develop.

**Treatment.** Immediate lavage should be followed by saline catharsis. Intramuscularly administered barbiturates may be used for convulsions.

69. **Shellfish.** Most shellfish poisoning in the United States is due to contamination by staphylococci or to allergic sensitivity. In some localities during certain seasons (summer and fall) mussels and clams may contain powerful neurotoxins. The origin of the poison is thought to be a dinoflagellate in the bodies of the clams. The poison is not destroyed by heating. Three general types of involvement occur: (1) gastroenteritis with nausea, vomiting and diarrhea; (2) nervous symptoms, diffuse erythema, urticaria, angina and dyspnea; and (3) a paralytic form in which symptoms simulate those of curare poisoning with respiratory paralysis.

70. **Sodium Hypochlorite.** Bleaching solutions contain sodium hypochlorite, 3 to 6 per cent in water. Their action is similar to that of sodium hydroxide in high concentrations. Acid secretions in the stomach release irritating hypochlorous acid. Fifteen to 30 ml. orally may be fatal for children. Inhalation of hypochlorous acid fumes produces pulmonary irritation, coughing and choking, and pulmonary edema. Ingestion causes irritation and corrosion of mucous membranes. Edema of the pharynx and larynx may be intense.

**Treatment.** Lavage with sodium bicarbonate solution repeatedly. Administration of a saline cathartic is advisable. Acid antidotes should never be used.

71. **Solanine (Solanism).** Symptoms of poisoning may follow ingestion of sprouted potatoes containing an alkaloid solanine, found in or near the peel. Species of *Solanum* (black night shade, bittersweet) also contain the poison. Vomiting, diarrhea, colicky pains, headaches, depression, pain in the rectum, suppression of urine, and collapse occur within a few hours. Hallucinations and coma are sometimes present.

72. **Strychnine.** Strychnine is a powerful central nervous system stimulant. It produces little local gastrointestinal reaction, and the first symptoms are those of nervous system stimulation. At first a stiffness of the face and neck muscles occurs, followed by hyperactive reflexes of all muscles, and later by muscular twitchings and spinal convulsions. A characteristic position of the body occurs due to the action of the stronger groups of muscles. The back is arched in a position of opisthotonos; the legs are adducted and extended, and the feet turned in; the

fists are clenched and the facial muscles are tightly contracted, producing risus sardonicus; and there is exophthalmos and mydriasis. Involvement of the muscles of respiration produces respiratory arrest with resultant cyanosis. The patient usually remains conscious and is in severe pain. After such a convulsion, which lasts a minute or more, there is a period of relaxation with depression and, in some instances, unconsciousness due to apnea and anoxemia. In ten to fifteen minutes another spinal convulsion occurs. Medullary paralysis, due to excessive stimulation or anoxemia, follows the second to fifth convulsion.

**Treatment.** Lavage should not be done during convulsive attacks. Recurrence of convulsions must be prevented. Large doses of short-acting barbiturates should be given intravenously and repeated if necessary; sodium phenobarbital and amytal are effective. The dose should be sufficient to prevent or stop convulsions and keep the patient asleep, but not to depress respiration or blood pressure. Anesthesia may be temporarily necessary until a barbiturate can be given. All types of stimuli should be avoided. Lavage with 2 per cent tannic acid or strong tea may be performed when the patient is asleep.

73. **Thallium.** Thallium acetate has been administered orally to produce depilation in the treatment of ringworm of the scalp and locally as a depilatory for cosmetic purposes, but owing to the danger of serious toxic effects such use is to be condemned. The initial acute gastrointestinal symptoms, which usually result from accidental ingestion, occur twelve to twenty-four hours after ingestion. There is severe, paroxysmal abdominal pain with vomiting and diarrhea. Hemorrhage, desquamation of the mucosa, and eosinophilia may be present. The late effects of acute or chronic poisoning are predominantly on the nervous system. Peripheral neuritis with paralysis, optic atrophy and cerebral symptoms occur. Alopecia, attributed to a toxic effect on the sympathetic nervous system, is common.

**Treatment.** Essentially the same as for arsenic (9), but BAL is of limited value.

74. **Thiocyanate Insecticides.** These agents induce coma, cyanosis, dyspnea and tonic convulsions. Respiratory difficulty may occur.

**Treatment.** Skin contamination should be removed by scrubbing with soap and water. Gastric lavage with tap water and saline catharsis are advisable. Renal and hepatic injury may occur later.

75. **Veratrine.** An alkaloid obtained from *V. cecadilla* (Sabadilla), a false hellebore plant. Cevadine is crystallized veratrine. Sabadilla dusts and spray and extracts of Sabadilla are used as insecticides and pediculicides. Ingestion produces violent vomiting and diarrhea, intense burning and generalized muscular weakness. Muscular and autonomic nervous system reactions are similar to those from pyrethrum and nicotine.

**Treatment.** See No. 56.

76. **Veratrum.** *Veratrum* and *Zygadenus* are found in Hellebore (*Veratrum album*, *viride* or *californicum*). *Zygadenus venenosus*, the death camass, contains similar nitrogenous compounds. Ingestion of these plants produces nausea, severe vomiting, diarrhea, muscular weakness, visual disturbances, bradycardia and low blood pressure. Very large doses may produce hypertension.

**Treatment.** Gastric lavage followed by saline catharsis. Atropine is of value to block the reflex fall of blood pressure and the bradycardia.

77. **Warfarin (Dicoumarin)** (3- $\alpha$ -acetylbenzyl-4-hydroxycoumarin). A rodenticide found in Dethmor, Rax Powder, D-con and other products. Available in 1:200 concentration in cornstarch and used as a rat bait in 1:400 concentration in corn meal. The dicoumarol action inhibits prothrombin formation, but it is forty times more potent than dicoumarol. Absorption is slow and irregular; twenty-four to forty-eight hours may elapse before any effect is noted. Elimination is slow. The action is chiefly on the synthesis of prothrombin with a gradual depression of prothrombin levels in the blood leading to spontaneous hemorrhages. The action may persist for ten days.

**Treatment.** Gastric lavage and catharsis should be instituted. Vitamin K in large doses should be given intravenously. Whole blood transfusions may also be needed.

78. **Zinc Stearate Powder.** A severe irritation of the respiratory mucous membranes is produced by aspiration with resulting congestion, hyperemia, edema, and obstruction of bronchioles with mucus. Bronchopneumonia is common in infants who survive the first day or two. Choking, coughing, cyanosis and signs of suffocation tend to develop immediately.

**Treatment.** Aspiration of the powder and accumulated secretions by bronchoscopy is worthy of trial, but it is not likely to be effective because of the adhesive quality of the powder. Administration of oxygen is important, and there may be an added advantage in giving it in combination with helium. Powders containing zinc stearate should *never* be used for infants and small children.

### LIST OF CHEMICALS

The following list includes individual chemical compounds, alphabetically arranged, with an appended numeral referring to the class (see p. 1383) with which they are associated; e.g., Chloroethane (46) is referred to Hydrocarbons (Halogenated).

Abrin, 1  
Acetaldehyde (ethyl aldehyde), 39  
Acetanilid (N-phenylacetamide), 6  
Acetic acid, concentrated, 2  
Acetoarsenite (Paris green), 9  
Acetone, 3  
Acetophenetidin (phenacetin), 6  
Acetylene tetrachloride (tetrachloroethane), 46  
Acetyl salicylic acid (Aspirin), 67  
Acid. See particular acid.  
Acid-like substances, 2  
Aconite (aconitine), 53  
Alcohol, 3  
Alcohol, ethyl (ethanol, grain alcohol, neutral spirits), 3  
Aldehydes, 39  
Aldrin (Compound 118), 25  
Alkalis, corrosive, 49  
Allethrin (Allyn cinerin), 56  
Allyl-isopropylacetyl-carbamide (Sedormid), 13

Allyn cinerin (Allethrin), 56  
Aluminum salts, 4  
Amanita, 55  
p-Aminophenol, 6  
Aminopyrine (Amidopyrine), 6  
Ammonia (ammonium hydroxide), 49  
Ammoniated mercury, 51  
Ammonium hydroxide (ammonia), 49  
Amobarbital (Amytal), 13  
Amphetamine, 5  
Amyl nitrite, 57  
Amytal (Amobarbital), 13  
Andromedotoxin, 54  
Aniline (phenylamine), 6  
Antihistaminics, 13  
Antimony, 7  
Antipyrene, 6  
ANTU, 8  
Arochlor, 46  
Arsenates and arsenites, 9  
Arsenic trioxide (white arsenic), 9  
Aspidium, 10  
Aspirin (acetyl salicylic acid), 67  
Asterol, 11  
Atropine, 12  
Barbital (Veronal), 13  
Barbiturates, 13  
Barium salts, 14  
Benadryl, 13  
Benzalkonium chloride (Zephiran), 35  
Benzene (Benzol), 15  
Benzene hexachloride (hexachlorocyclohexane), 25  
Benzethonium chloride (Phemorol), 35  
Benzine, 45  
Benzol (Benzene), 15  
Beta-naphthol ( $\beta$  naphthol), 62  
Bichloride of mercury (mercuric chloride, corrosive sublimate), 51  
Bismuth, 16  
Bismuth subnitrate, 57  
Boracic acid (boric acid), 17  
Borate salts, 17  
Borax (sodium tetraborate), 17  
Boric acid (boracic acid), 17  
Boron, 17  
Bromate, methyl, 46  
Bromate salts, 18  
Bromides, 19  
Brown Mixture (contains tartar emetic), 7  
Butcaine, 28  
Cadmium salts, 20  
Calcium hypochlorite (chlorinated lime), 70  
Calomel (mercurous chloride), 51  
Campho-phenique, 62  
Camphor (gum camphor), 62  
Camphor tar (naphthalene, naphthene), 15  
Carbitol, 3  
Carbolic acid (phenol, hydroxybenzene), 62  
Carbon bisulfide (carbon disulfide), 21  
Carbon monoxide, 22  
Carbon tetrachloride (perchloromethane), 46  
Castrix, 72  
Catechol (Pyrocatechol), 62  
Caustic potash (potassium hydroxide), 49  
Caustic soda (sodium hydroxide), 49  
Ceepryn chloride (cetyl pyridinium chloride), 35  
Cetyl pyridinium chloride (Ceepryn chloride), 35  
Chenopodium oil (wormseed oil), 23



- Chloral hydrate, 13  
Chlordane (Compound 1068), 25  
Chloride, methyl, 46  
Chlorinated camphene (Toxaphene, Compound 3956, octachlorocamphene), 25  
Chlorinated diphenyl, 46  
Chlorinated insecticides, 25  
Chlorinated lime (calcium hypochlorite), 70  
Chlorinated naphthalene, 46  
Chlorine water, 49  
Chloroacetic acid, 43  
Chloroaniline, 6  
Chlorobenzene, 24  
Chlorobutanol, 13  
Chloroethane (ethyl chloride), 46  
Chloroform (trichloromethane), 46  
Chlorohydrin, ethylene, 46  
Chloronitrobenzene, 6  
Chromate salts, 26  
Chromic acid, 2  
Cicutoxin, 72  
Cleaning solutions, 27  
Clorox, 70  
Cobalt salts, 2  
Cocaine, 28  
Codeine, 60  
Colchicum autumnale, 50  
Compound 42 (Warfarin), 77  
Compound 118 (Aldrin), 25  
Compound 1068 (Chlordane), 25  
Compound 1080 (sodium fluoroacetate), 43  
Compound 1836 (diethyl 2-chloro-vinyl phosphate), 65  
Compound 3956 (Toxaphene, chlorinated camphene, octachlorocamphene), 25  
Coniine, 29  
Copper acetoarsenite (Paris green), 9  
Copper arsenate, 9  
Copper salts, 2  
Corrosive acids, 2  
Corrosive alkalis, 49  
Corrosive sublimate (mercuric chloride, bichloride of mercury), 51  
Cosmetics, 30  
Cough medicines, 31  
Coumachlor (Tomorin), 77  
Creolin, 62  
Creosol, 62  
Creosote, 62  
Cresol (methylphenol, Tricresol), 62  
Cubeb, 66  
Cumene, 15  
Cyanates, 32  
Cyanides, 32  
Dactin (DDH), 70  
Daphne, 33  
Daphnin, 33  
Darnel, 34  
Daturine (hyoscyamine), 12  
DDD (Dichloro diphenyl dichloroethane, D-3), 25  
DDH (Dactin), 70  
DDT (dichloro diphenyl trichloroethane), 25  
Death cup, 55  
Demerol (Meperidine), 60  
Derris root, 66  
Destroying angel, 55  
Detergents, 35  
Dexedrine, 5  
DFDT (difluoro diphenyl trichloroethane), 25  
Diazinon, 65  
O-Dichlorobenzene (Ortho-dichlorobenzene), 46  
Dichloro diphenyl dichloroethane (DDD, D-3), 25  
Dichloro diphenyl trichloroethane (DDT), 25  
Dichloropropane (propylene dichloride), 46  
Dicoumarin, 77  
Dieldrin, 25  
Diethyl 2-chloro-vinyl phosphate (Compound 1836), 65  
Diethylene glycol, 3  
Diethyl-p-nitrophenol thiophosphate (Parathion, DNTP, E-605), 65  
Diethyl paranitro phenyl phosphate (Para-oxon, E-600), 65  
Difluoro diphenyl trichloroethane (DFDT), 25  
Digitalis, 36  
Dihydrorothenone, 66  
Dimethylaniline, 6  
Dimethylsulfate, 39  
Dinitrobenzene, 6  
Dinitro-ortho-cresol, 37, 62  
Dinitrophenol, 62  
Diphenyl, chlorinated, 46  
Distillate, solvent, 45  
DMDT (Methoxychlor), 25  
DNPT (diethyl-p-nitrophenol thiophosphate, Parathion, E-605), 65  
Dowicides, 62  
E-600 (Para-oxon, diethyl paranitro phenyl phosphate), 65  
E-605 (Parathion, diethyl-p-nitrophenol thiophosphate, DNTP), 65  
EDC (ethylene dichloride), 46  
EMP (ethyl mercury phosphate), 51  
Endrin (hexachloro octahydroendo, endodimethanonaphthalene), 25  
Ephedrine, 5  
Ergot, 38  
Esters, 39  
Ethandiol (ethylene glycol), 3  
Ethanol (ethyl alcohol), 3  
Ethers, 39  
Ethyl alcohol (ethanol, grain alcohol, neutral spirits), 3  
Ethyl aldehyde (acetaldehyde), 39  
Ethyl chloride (Chloroethane), 46  
Ethyl mercury chloride, 51  
Ethyl mercury phosphate (EMP), 51  
Ethylene chlorobromide, 46  
Ethylene chlorohydrin, 46  
Ethylene dibromide, 46  
Ethylene dichloride (EDC), 46  
Ethylene glycol (Ethandiol), 3  
Ethylene tetrachloride (tetrachloroethylene), 46  
Eucalyptol, 15  
Favism, 40  
Fern, male, 10  
Ferrous and ferric (iron) salts, 48  
Fish poisoning, 41  
Fly amanita, 55  
Fluoaluminat, sodium, 42  
Fluoride salts, 42  
Fluoroacetate salts, 43  
Formaldehyde, 44  
Formalin, 44  
Fowler's solution, 9  
Furfural (Furfuraldehyde-2), 44

- Gasoline, 45
- Glycols, 3
- Grain alcohol (ethyl alcohol, Ethanol, neutral spirits), 3
- Guaiacol, 62
- Gum camphor (camphor), 62
- Halogenated hydrocarbons, 46
- Halowax, 46
- Heptachlor, 25
- HETP (hexaethyl tetraphosphate), 65
- Hexaethyl tetraphosphate (HETP), 65
- Hexachlorocyclohexane (Benzene hexachloride), 25
- Hexachloroethane (Perchloroethane), 46
- Hexachloro octahydroendo, endodimethanonaphthalene (Endrin), 25
- Hexamethylenetetramine (Methenamine), 44
- Hydrocarbons, 45
- Hydrocarbons, halogenated, 46
- Hydrochloric acid, 2
- Hydrocyanic acid (hydrogen cyanide), 32
- Hydrofluoric acid (hydrogen fluoride), 42
- Hydrogen cyanide (hydrocyanic acid), 32
- Hydrogen fluoride (hydrofluoric acid), 42
- Hydroquinone, 6, 62
- Hydroxybenzene (phenol, carboic acid), 62
- Hydroxylamine, 57
- Hydroxymercurichlorophenol, 51
- Hydroxymercurinitrophenol, 51
- Hyoscine (Scopolamine), 12
- Hyoscyamine (Daturine), 12
- Hypochlorite salts, 70
- Insecticides, chlorinated, 25
- Insecticides, thiocyanate, 74
- Iodine, 47
- Iron salts (ferrous and ferric), 48
- Isodrin, 25
- Isopestox, 65
- Isopropyl cresol, 62
- Jimson weed, 12
- Kerosene, 45
- Kilphos, 65
- Larkspur, 53
- Laudanum (tincture of opium), 60
- Laurel, mountain, 54
- Lead arsenate, 9
- Lethane 60, Lethane 384, 74
- Lindane, 25
- Lobeline, 56
- Lye, 49
- Lysol, 62
- Malathion, 65
- Male fern, 10
- Meadow saffron, 50
- Menthol, 15
- Meperidine (Demerol), 60
- Mercuric chloride (bichloride of mercury, corrosive sublimate), 51
- Mercurous chloride (calomel), 51
- Mercury, 51
- Metaldehyde, 39
- Methanol (wood alcohol, methyl alcohol), 3
- Methenamine (hexamethylenetetramine), 44
- Methoxychlor (DMDT), 25
- Methoxyethylmercuriacetate, 51
- Methycaine, 28
- Methyl alcohol (methanol, wood alcohol), 3
- Methyl benzene (Toluene), 45
- Methyl bromate, 46
- Methyl chloride (monochloromethane), 3, 46
- Methyl phenol (Cresol, Tricresol), 62
- Methyl salicylate (oil of wintergreen), 67
- Milk sickness, 52
- Mineral spirits, 45
- Mirbane (nitrobenzene), 6
- Monochloromethane (methyl chloride), 3
- Monk's hood root, 53
- Morphine, 60
- Mountain laurel, 54
- Muscarine, 55
- Mushrooms, poisonous, 55
- Mycetismus, 55
- Naphazoline (Privine), 5
- Naphtha (petroleum naphtha, petroleum ether), 45
- Naphthalene (Naphthene, camphor tar), 15
- Naphthalene, chlorinated, 46
- Naphthol (beta-naphthol), 62
- Neo-Antergan maleate (Pyrilamine maleate), 13
- Neutral spirits (ethyl alcohol, Ethanol, grain alcohol), 3
- Nicotine, 56
- Nitrites, 57
- Nitroaniline (nitraniline), 6
- Nitrobenzene (Mirbane), 6
- Nitrochlorobenzene, 6
- Nitroglycerin (glyceryl trinitrate), 57
- p-Nitrophenol (paranitrophenol), 6, 62
- Nitroprusside salts, 57
- Nupercaine, 28
- Nutmeg, 58
- Octachlorocamphene (Toxaphene, chlorinated camphene, Compound 3956), 25
- Octamethyl pyrophosphoramidate (Schraddon), 65
- Oil of bitter almonds, 32
- Oil of Mirbane, 6
- Oil of wintergreen (methyl salicylate), 67
- Oil, wormseed, 23
- Oils, 59
- Opiates, 60
- Opium, 60
- Orthodichlorobenzene (O-dichlorobenzene), 46
- Oxalate salts, 61
- Oxalic acid, 61
- P-40 (sodium selenate), 9
- Pantopon, 60
- Parachlorometacresol (PCMC), 62
- Parachlorometaxylenol (PCMX), 62
- Paradichlorobenzene (PDB), 46
- Paraldehyde, 39
- Paranitrophenol (p-nitrophenol), 6, 62
- Para-oxon (diethyl paranitro phenyl phosphate, E-600), 65
- Parathion (diethyl-p-nitrophenol thiophosphate, DNTP, E-605), 65
- Paris green (copper acetoarsenite), 9
- PCMC (parachlorometacresol), 62
- PCMX (parachlorometaxylenol), 62
- PCP (pentachlorophenol), 6, 37
- PDB (paradichlorobenzene), 46
- Pentachloroethane, 46
- Pentachlorophenol (PCP), 6, 37
- Perchloroethane (hexachloroethane), 46
- Perchloromethane (carbon tetrachloride), 46
- Permanent wave neutralizer, 18
- Petroleum ether (petroleum naphtha, naphtha), 45
- Phemerol (Benzethonium chloride), 35
- Phenacetin (acetophenetidin), 6



- Phenol (carbolic acid, hydroxybenzene), 62  
 Phenol mercuric chloride, 51  
 Phenolphthalein, 63  
 N-Phenylacetamide (Acetanilid), 6  
 Phenylamine (aniline), 6  
 Phenylenediamine, 6  
 Phenylmercuric acetate (PMA), 51  
 Phenyl salicylate (Salol), 62  
 Phosphoric acid, 2  
 Phosphorus, inorganic, 64  
 Phosphorus, organic, 65  
 Picric acid (2,4,6-Trinitrophenol), 62  
 Pival, 77  
 PMA (phenylmercuric acetate), 51  
 Potash (potassium hydroxide, caustic potash), 49  
 Potassium chlorate, 18  
 Potassium chromate, 2  
 Potassium cyanide, 32  
 Potassium hydroxide (caustic potash), 49  
 Potassium thiocyanate, 74  
 Privine (Naphazoline), 5  
 Propylene dichloride (dichloropropane), 46  
 Propylene glycols, 3  
 Prussic acid, 32  
 Pyrenone, 56  
 Pyrethrin, 56  
 Pyrethrum, 56  
 Pyribenzamine hydrochloride (Tripeleminamine hydrochloride), 13  
 Pyrilamine maleate (Neo-antergan maleate), 13  
 Pyrocatechol (catechol), 62  
 Pyrogallol (1,2,3-trihydroxybenzene), 6, 62  
 Quicklime, 49  
 Quinine, 67  
 Red squill, 36  
 Reserpine, 13  
 Resorcinol, 62  
 Rotenone, 66  
 Saffron, meadow, 50  
 Salicylanilide, 6, 67  
 Salicylates, 67  
 Salicylic acid, 67  
 Salol (phenyl salicylate), 62  
 Santonin, 68  
 Schraden (octamethylpyrophosphoramidate), 65  
 Scopolamine (Hyoscine), 12  
 Sedormid, 13  
 Selenium compounds, 9  
 Shellfish, 69  
 Silicofluoride salts, 42  
 Silver salts, 2  
 Sodium arsenate, 9  
 Sodium cyanide, 32  
 Sodium fluoracetate (Compound 1080), 43  
 Sodium fluoride, 42  
 Sodium hydroxide (caustic soda), 49  
 Sodium hypochlorite, 70  
 Sodium nitrite, 57  
 Sodium oxalate, 61  
 Sodium perborate, 17  
 Sodium salicylate, 67  
 Sodium selenate (P-40), 9  
 Sodium tetraborate (borax), 17  
 Solanine, 71  
 Solvent distillate, 45  
 Squill, red, 36  
 Stramonium, 12  
 Strophanthin, 36  
 Strychnine, 72  
 Sulfotepp, 65  
 Systox, 65  
 Tartar emetic, 7  
 TEP (tetraethylpyrophosphate), 65  
 Terpin hydrate, 15  
 Tetrachloroethane (acetylene tetrachloride), 46  
 Tetrachloroethylene (ethylene tetrachloride), 46  
 Tetraethylpyrophosphate (TEP), 65  
 Thallium salts, 73  
 Thiocyanates, 74  
 Thymol, 62  
 Tincture of opium (laudanum), 60  
 Toadstools, 55  
 Toluene (methyl benzene), 45  
 Toluidine, 6  
 Tomorin (Coumachlor), 77  
 Toxaphene (chlorinated camphene, octachlorocamphene, Compound 3956), 25  
 Trembles, 52  
 Trialkyl thiophosphate, 65  
 Trichloroacetic acid, 2  
 Trichloroacetonitrile, 32  
 Trichloroethane, 46  
 Trichloroethylene, 46  
 Trichloromethane (chloroform), 46  
 Trichlorophenols, 62  
 Trichlorophenoxypropionic acid, 25  
 Tricresol (methyl phenol, Cresol), 62  
 Triethylene glycol, 3  
 1,2,3-Trihydroxybenzene (Pyrogallol), 6  
 Trinitrobenzene, 6  
 2,4,6-Trinitrophenol (picric acid), 62  
 Tri-ortho-cresyl-phosphate, 39  
 Tripeleminamine hydrochloride (Pyribenzamine hydrochloride), 13  
 Triphenyl phosphate, 65  
 Turpentine, 15  
 Tutocaine, 28  
 Veratrine, 75  
 Veratrum, 76  
 Veronal (barbital), 13  
 Vinyl chloride, 46  
 Vinyl cyanide, 32  
 Warfarin (Compound 42), 77  
 White arsenic (arsenic trioxide), 9  
 Wolfsbane, 53  
 Wood alcohol (methyl alcohol), 3  
 Wormseed oil (chenopodium oil), 23  
 Xylene (xylol), 15  
 Xylol (Xylene), 15  
 Zephiran (benzalkonium chloride), 35  
 Zinc arsenate and arsenite, 9  
 Zinc cyanide, 32  
 Zinc salts, 4  
 Zinc stearate, 78

JOHN A. ANDERSON

## REFERENCES

- Aub, J. C.: Biochemical Behavior of Lead in the Body. *J.A.M.A.*, 104:87, 1935.  
 Bain, K.: Death Due to Accidental Poisoning in Young Children. *J. Pediat.*, 44:616, 1954.  
 Blatt, M. L., and Steigman, F.: Phenolphthalein Tolerance in Childhood. *J. Pediat.*, 22:719, 1943.

- Boggs, T. R., Jr., and Anrode, H. G.: Boric Acid Poisoning Treated by Exchange Transfusion. Report of Case. *Pediatrics*, 16:109, 1955.
- Byers, R. K., and Lord, E. E.: Late Effects of Lead Poisoning on Mental Development. *Am. J. Dis. Child.*, 66:471, 1943.
- Dean, G. E., and others: The Use of BAL in the Treatment of Acute Lead Encephalopathy. *J. Pediat.*, 42:409, 1953.
- Eckenhoff, J. E., Hoffman, G. I., and Dripps, R. D.: N-allylnormorphine: An Antagonist to the Opiates. *Anesthesiology*, 13:242, 1952.
- Frear, D. E. H.: *Pesticide Handbook*. State College, Pa., College Science Publishers, Current Annual Edition.
- Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*. New York, Macmillan Company, 1955.
- Robinson, M. J., Karpinski, F. E., and Brieger, H.: Lead in Plasma, Whole Blood and Erythrocytes. *Pediatrics*, 21:793, 1958.

## ACRODYNIA

(PINK DISEASE, SWIFT'S DISEASE, FEER'S DISEASE, ERYTHREDEMA, DERMATO-POLYNEURITIS)

Acrodynia (the term, derived from the Greek, denotes painful extremities) is a syndrome consisting of many unusual symptoms which form a characteristic clinical pattern. A relatively large number (at least eleven) of etiologic possibilities have been suggested, but only one has substantial support. Warkany and Hubbard assembled convincing data that most, if not all, instances of acrodynia are the result of an unusual sensitivity or idiosyncrasy to mercury.

The diagnosis is based on the clinical appearance and the course of the disease, which in the well established case are so distinctive that there is practically no differential diagnosis. The characteristic clinical manifestations which make up this unusual syndrome are extreme irritability and restlessness alternating with periods of apathy; insomnia; anorexia; profuse perspiration; pink hands and feet and scarlet tip of nose and cheeks; inconstant and variable generalized skin rashes; desquamation; itching, which causes the child to rub the body and especially the extremities against the bed or other objects, initiating trophic ulcers; photophobia; alopecia; salivation; loss of teeth and nails and, rarely, of phalanges; pain in the extremities; hypotonia; rapid pulse rate; and increased blood pressure. The great discomfort causes the child to be extremely restless, and the hypotonia permits him to assume many different and bizarre positions. There are few clinical conditions

in which extreme and persistent misery is such a prominent part of the clinical picture.

**History.** As early as 1903 Selter of Solingen, in an address which attracted little attention, described this disease and called it a trophodermatosis. Feer of Zurich, whose name is attached to the disease in Europe, did not know that such a clinical entity existed until the early 1920's, when he described his interpretation of it as "Vegetative Neurose des Kleinkindes." The condition had been recognized in Australia as early as 1890 as "pink disease"; but it was not until 1914 that Swift's paper brought it into focus as a distinct clinical entity under the name "erythredema." His article was published in the transactions of an Australian society which were not widely distributed. The disease had been observed and commented upon as early as 1915 in Oregon, but there was nothing in British or American literature on the condition until two physicians in the United States independently published articles describing it in 1920.

**Etiology.** Acrodynia is principally a disease of infancy and early childhood. In the United States it has become uncommon except in the southeastern states, where the incidence is apparently also decreasing. The highest incidence seems to be in Australia, with relatively large numbers of cases observed in France, Switzerland and England.

Acrodynia has been ascribed to avitaminosis, chronic infections, a combination of dietary deficiency and infection, poisoning with a variety of substances, including the fungus of maize and rye, and a number of different chemicals, especially arsenic and mercury, and to unspecified viral agents. Feer, impressed with such clinical manifestations as hypertension, tachycardia and excessive sweating, concluded that the syndrome resulted from an overactivity of the sympathetic nervous system.

On the basis of the similarity of some of the clinical manifestations of acrodynia to poisoning with mercury or arsenic, Warkany and Hubbard (1945) made a systematic search for heavy metals in the urine of an infant with acrodynia. The only one detected was mercury. Since this observation, mercury has been demonstrated in the urine of a large number of infants with the syndrome; Warkany and Hubbard in twenty-five of twenty-eight patients, Fanconi and Botsztein in Switzerland in nineteen of twenty, and Holzel and James in England in sixty-one of ninety-four. Mercury has been demonstrated in the urine of persons ingesting it who had no manifestations of acrodynia. Such observations, however, are uncommon, and in general the amounts demonstrated in the urine



of patients with acrodynia have been considerably greater than in that of apparently healthy persons.

The incidence of mercury in urine would seem to be highest in geographic areas where mercurial medications are or have recently been widely prescribed. In the southern United States and in England, where mercurial teething powders and lotions have been used extensively, the peak incidence is under one year of age, whereas in France and Switzerland, where mercurial vermifuges are more widely used, the peak incidence is between two and four years of age. Other reported sources of mercury include calomel, mercurial ointments, diaper rinses and protiodide of mercury in the form of pills. The possibility of accidental ingestion, of course, exists.

If mercury, or less frequently other chemicals such as arsenic, gold and thallium, should be the etiologic agent or agents of acrodynia, the question must be answered: Why do only relatively few of the persons who come in contact with them acquire the disease? At present there is no better answer than that the clinical pattern represents an unusual sensitivity or idiosyncrasy to heavy metal. It should be recognized, however, that mercury is not universally accepted as the etiologic factor in acrodynia.

**Pathology.** No consistent or characteristic pathologic changes have been observed. Many of the observations can be explained on the basis of a chronic disease in association with a state of semistarvation with resultant degeneration of nervous tissue. A patient of the author's with extremely severe symptoms of acrodynia was thoroughly studied by means of many sections of the entire nervous system (brain, cord, peripheral nerves and the sympathetic ganglia and their nerves). No information was obtained which could contribute to an understanding of the disease.

**Clinical Manifestations.** There are all grades of severity. The child becomes listless; he is no longer interested in play and is restless and irritable. There may be an associated upper respiratory tract infection. Generalized, inconstant rashes which are protean recur from time to time. Early the tips of the fingers and toes acquire a pinkish color, and later the hands and feet become a dusky pink which shades off at the wrists and ankles; they are cold and clammy. These changes in the extremities are the most distinctive features of the syndrome, being different from those of any other disease occurring in children, and

are responsible for the term "pink disease." Frequently the cheeks and the tip of the nose acquire a scarlet color.

As the disease becomes established, the sweat glands are enormously dilated and enlarged, causing perspiration to become profuse; at times the infant may actually be drenched, necessitating frequent changes of clothing. A severe pyoderma may develop. There is desquamation of the soles and palms, which, though usually superficial, may be marked and may disappear and recur during the course of the disease. The fingers and toes appear edematous; the swelling is due to hyperplasia and hyperkeratosis of the skin. Fever is usually not present unless there is some complication as pyuria or bronchopneumonia. An outstanding symptom is excruciating pain in the hands and feet. Children will rub their hands together for hours, and older children will complain of a severe burning sensation. In more than 60 per cent of the cases there is a photophobia without evidence of local inflammation of the eyes. The children shield their eyes or bury their faces in their pillows. The lax ligaments and hypotonia permit the children to assume unusual positions (Fig. 427), and they often lie for hours with their heads between their legs. The so-called salaam position is frequently assumed, often with constant rubbing motions of the hands and feet, owing to the pain and itching.

One of the most dramatic occurrences is the loss of a nondecayed tooth. In extreme cases all the teeth may be lost; necrosis of the jaw bones frequently follows. Initially the gums appear normal except for a slightly deeper red color; later they become markedly inflamed and swollen. Salivation then becomes pronounced, and the saliva often flows from the mouth in a constant stream. The nails become darker and frequently drop off. Occasionally gangrene of the toes and fingers develops, and trophic ulcers may result from the constant rubbing of the hands and feet. The hair tends to fall out and is often pulled out by the child. Anorexia is marked, but because of the excessive perspiration large quantities of water are consumed. There may be diarrhea, and prolapse of the rectum is a frequent complication. The blood pressure and pulse rate even in infants may be increased.

The nervous symptoms are an important part of the syndrome. Whether they are due to specific lesions cannot be stated. Early in the disease the tendon reflexes may be normal



FIG. 427. Extreme hypotonia and photophobia in an infant with acrodynia. This bizarre position may be maintained for hours.

or increased, but later they disappear. There is not a true motor paralysis, but because of the soft, flabby musculature the child has no desire to walk. Many of the symptoms and signs suggest involvement of the vasomotor mechanism. The severe pain prevents normal sleep. There is no time when a child with acrodynia appears happy or comfortable; he does not play or smile, but appears dejected and melancholic, a picture of abject misery.

**Laboratory Data.** There are no characteristic morphologic changes of the blood or significant changes in the cerebrospinal fluid. There may be albuminuria, but there are no characteristic urinary findings other than the presence of mercury.

**Prophylaxis.** There is little need for mercurial medications in pediatric practice, and they should be avoided whenever possible. Perhaps it is most important at the moment to be alert for possible contacts with mercury in various household and industrial preparations.

**Treatment.** In 1948 Bivings and Lewis treated acrodynia in an infant whose urine contained mercury, with BAL (British anti-lewisite; 2, 3-dimercaptopropanol) with apparently good effect. In general, subsequent results have been favorable, especially when administration was begun early in the disease. The recommended plan of treatment is 3 mg. per kilogram of body weight of BAL every four hours for forty-eight hours, then every six hours for twenty-four hours, followed by administration at intervals of twelve hours for seven days. The drug is administered intramuscularly in a 10 per cent solution. Toxic effects of BAL have been observed (p. 1381).

The natural course of acrodynia is prolonged, extending from several months to a

year. There is probably no more difficult therapeutic problem in pediatrics than the management of an infant with severe acrodynia. The extreme restlessness, irritability and pain are not readily allayed. In view of the long duration of the disease opiates should not be given, except for temporary emergencies, to avoid the danger of habit formation. Barbiturates are usually not as effective as paraldehyde administered rectally in olive oil (5 to 10 cc.). Symptomatic relief has also been reported from the use of Priscoline in doses of 12.5 mg. at intervals of four to six hours.

The diet should contain generous amounts of proteins, minerals and vitamins. Frequently anorexia is so great that feeding must be by gavage.

Owing to the profuse sweating, thirsting is usually prominent, and, in contrast to the frequent refusal to eat, the child will usually take relatively large quantities of fluids. Any deficits of sodium, chloride or potassium should be taken into account in the planning of emergency parenteral fluid therapy. So far as possible fluid intake should be oral rather than parenteral. If milk is not taken well, it can be supplemented with fruit juices, glucose in Ringer's solution, and water.

The child should be kept as clean as possible to minimize the chances of secondary pyogenic skin infections. Frequent alcohol rubs may aid in this respect in addition to being soothing for the child. The clothing should be light, preferably of cotton, and should be changed frequently when perspiration is profuse.

Mortality rates have been significantly higher in hospitalized patients than in those treated at home because of their susceptibility



to cross infections. It is obvious that the family must be made aware of the nature of the illness and of its prolonged course if they are to be expected to play their part successfully.

J. B. BILDERBACK

#### REFERENCES

- Bilderback, J. B.: Group of Cases of Unknown Etiology and Diagnosis. *Northwest Med.*, 19:263, 1920.
- Bivings, L.: Acrodynia: A Summary of BAL Therapy Reports and a Case Report of Calomel Disease. *J. Pediat.*, 34:322, 1949.
- and Lewis, G.: Acrodynia: New Treatment with BAL. *J. Pediat.*, 32:63, 1948.
- Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children: Report of Cases. *Am. J. Dis. Child.*, 20:347, 1920.
- Fanconi, G., and Botsztejn, A.: Die Feersche Krankheit (Akrodynia) und Quecksilbermedikation. *Helvet. paediat. Acta*, 3:264, 1948.
- Feer, E.: Eine eigenartige Neurose des vegetativen Systems beim Kleinkinde. *Ergebn. d. inn. med. u. Kinderh.*, 24:100, 1923.
- : Die spezifische vegetative Neuropathie des Kleinkindes (kindliche Akrodynia). *Schweiz. med. Wchnschr.*, 65:977, 1935.
- Gillespie, A.: Acrodynia Treated with Priscoline. *Canad. M.A.J.*, 67:418-21, 1952.
- Peterson, J. C., and Laughmiller, R.: Acrodynia: Treatment with Adrenolytic Drugs. *Acta pediat.*, 43:517, 1954.
- Warkany, J., and Hubbard, D. M.: Adverse Mercurial Reactions in Form of Acrodynia and Related Conditions. *Lancet*, 1:829-30, 1948.

# Appendix

## NORMAL BLOOD VALUES

Table 119. Chemical Constituents and Physical Properties of the Blood

Acid-Base Constituents		
Base, total fixed (Na + K + Ca + Mg) . . . . . (serum)	150-155	mEq./liter
By methods of Hald and Sunderman, normal values tend to be lower . . . . . (serum)	315-330	mg./100 ml.
Sodium . . . . . (serum)	143-150	mEq./liter
Potassium . . . . . (serum)	133-143	mEq./liter
Calcium . . . . . (serum)	307-330	mg./100 ml.
Calcium, diffusible (ionized Ca) . . . . . (serum)	4.1-5.6	mEq./liter
Magnesium . . . . . (serum)	16-22	mg./100 ml.
Chlorides, expressed as Cl . . . . . (serum)	5-6	mEq./liter
At birth and during early infancy the plasma (serum) chloride is 6-10 mEq./liter higher than that of older infants and children	10-12	mg./100 ml.
expressed as NaCl . . . . . (serum)	5-5.5	mg./100 ml.
The chloride concentration of whole blood depends largely on the cell volume, since the cells contain approximately half as much chloride as serum	1.65-2.5	mEq./liter
Phosphorus, inorganic, as P . . . . . (serum)	2-3	mg./100 ml.
HPO <sub>4</sub> <sup>-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> (average valence 1.8 at pH 7.4). Slightly higher in newborn infants, then decreasing during childhood	100-106	mEq. liter
Sulfates, inorganic, as SO <sub>4</sub> <sup>-</sup> . . . . . (serum)	355-376	mg./100 ml.
Sulfates, ethereal . . . . . (serum)	100-106	mEq./liter
Sulfur, neutral . . . . . (serum)	585-620	mg./100 ml.
Lactic acid . . . . . (serum)	1.45-1.77	mM./liter
Serum protein-base binding power . . . . . (serum)	4.5-5.5	mg./100 ml.
Bicarbonate bound base . . . . . (serum)	2.6-3.2	mEq. liter
pH at 38° C . . . . . (blood, plasma or serum)	0.5-1.0	mEq./liter
Arterial blood in a resting person is about 0.03 pH unit higher than venous blood	2.5-5.0	mg./100 ml.
pH at 38° C . . . . . (serum from arterial blood)	0.1-1.0	mg./100 ml.
(Data from Cassels and Morse)	1.7-3.5	mg./100 ml.
1-5-3.4 years . . . . .	10-20	mg./100 ml.
3.5-5.4 years . . . . .	1.1-2.2	mEq./liter
5.5-12.4 years . . . . .	15.5-18.0	mEq. liter
12.5-17.4 years . . . . .	19-30	mEq. liter
	7.3-7.45	
	7.35-7.41	



Table 119 (Continued)

Water.....	(whole blood)	79-81	gm./100 ml.
	(serum)	91-92	gm./100 ml.
	(red blood cells)	64-65	gm./100 ml.
Carbon dioxide content.....	(serum from venous blood)	45-70	vol. per cent
		20.3-31.5	mM./liter
The CO <sub>2</sub> content is lower at birth and rises slightly during the first four days of life			
Carbon dioxide content.....	(whole venous blood)	40-60	vol. per cent
		18.0-27.0	mM./liter
Carbon dioxide content.....	(arterial blood)		
(Data from Cassels and Morse)			
1.5- 3.4 years.....		34.5-45.7	vol. per cent
Carbon dioxide content			
3.5- 6.4 years.....		41.7-47.1	vol. per cent
6.5-11.4 years.....		43.0-48.0	vol. per cent
11.5-14.4 years.....		44.3-49.4	vol. per cent
14.7-17.4 years.....		45.4-49.6	vol. per cent
Carbon dioxide tension.....	(arterial blood)		
(Data from Cassels and Morse)			
1.5- 6.4 years.....		33.5-41.1	mm. Hg
6.5-12.4 years.....		35.4-40.6	mm. Hg
12.5-17.4 years.....		38.3-44.4	mm. Hg
Oxygen capacity*.....	(whole blood)	19-22	vol. per cent
Oxygen saturation.....	(whole venous blood)	60-85 per cent	
Hemoglobin*			
At birth.....	(whole blood)	17-20	gm./100 ml.
3 months.....	(whole blood)	10.5-12	gm./100 ml.
1 year.....	(whole blood)	11-12.5	gm./100 ml.
5 years.....	(whole blood)	12-13	gm./100 ml.
10 years.....	(whole blood)	13-14	gm./100 ml.
Above 10 years.....	(whole blood)	14-16	gm./100 ml.
Methemoglobin.....	(whole blood)	0.0-0.3	gm./100 ml.
Premature infants at higher level.....		(0.4)	

*Carbohydrates, Lipids and Pigments*

Sugar, fasting arterial blood.....		80-120	mg./100 ml.
fasting venous blood.....		70-100	mg./100 ml.
fasting venous blood (Folin-Wu procedure).....		85-120	mg./100 ml.
Pyruvic acid, fasting whole blood.....		0.7-1.2	mg./100 ml.
Total lipids (fats).....	(serum)	500-700	mg./100 ml.
Total cholesterol.....	(serum)	170-250	mg./100 ml.
Total cholesterol, infant.....		80-125	mg./100 ml.
At birth serum cholesterol averages 75 mg./100 ml.			
Cholesterol esters.....	(serum)	125-180	mg./100 ml.
Bilirubin.....	(serum)	0.2-0.8	mg./100 ml.
Higher in newborn infants.....		1 or more	mg./100 ml.
Icterus index.....	(serum)	4-6	

*Proteins†*

Total protein.....	(serum)	6.5-7.5	gm./100 ml.
At birth the protein level is slightly lower			
Albumin (fractionation by Na <sub>2</sub> SO <sub>4</sub> [22 per cent] precipitation of globulin).....	(serum)	4.5-5.5	gm./100 ml.

\* The oxygen capacity and iron content of blood are directly related to the hemoglobin content of blood.

† The total protein as determined from electrophoretic measurements is slightly lower than the values above (6.0-6.7). By electrophoretic fractionation the albumin is about 55 per cent of the total protein; alpha 1 globulin, 5 per cent; alpha 2 globulin, 9 per cent; beta globulin, 13 per cent; gamma globulin, 11 per cent; fibrinogen, 7 per cent.

When globulins are precipitated with 26.8% Na<sub>2</sub>SO<sub>4</sub> or with a mixture containing 20.8% Na<sub>2</sub>SO<sub>4</sub> and 7.0% Na<sub>2</sub>SO<sub>3</sub>, albumin values are obtained which match those obtained by electrophoretic measurements.

Table 119 (Continued)

Globulin (by difference).....(serum)	1.7-3.0	gm./100 ml.
Protein values vary slightly with age. The following values for plasma are adapted from the paper of Metcalf and Stare (New England J. Med., 1947)		
Total protein (plasma)		
Premature infant.....	4.55 $\pm$ 0.59	gm./100 ml.
Full term infant.....	5.11-5.70	gm./100 ml.
Birth to 1 year.....	6.10 $\pm$ 0.29	gm./100 ml.
1-4 years.....	6.94 $\pm$ 0.47	gm./100 ml.
5-12 years.....	7.30 $\pm$ 0.59	gm./100 ml.
12 years and above.....	7.16	gm./100 ml.
Albumin (plasma)		
Premature infant.....	3.55 $\pm$ 0.65	gm./100 ml.
Full term infant.....	3.76-3.79	gm./100 ml.
Birth to 1 year.....	4.97 $\pm$ 0.73	gm./100 ml.
1-4 years.....	4.59-4.83	gm./100 ml.
5-12 years.....	5.0 $\pm$ 0.78	gm./100 ml.
12-15 years.....	4.72	gm./100 ml.
Globulin (plasma)		
Premature infant.....	1.01 $\pm$ 0.45	gm./100 ml.
Full term infant.....	1.34-1.66	gm./100 ml.
Birth to 1 year.....	1.38 $\pm$ 0.68	gm./100 ml.
1-4 years.....	2.03 $\pm$ 0.34	gm./100 ml.
5-12 years.....	2.4 $\pm$ 0.74	gm./100 ml.
12-15 years.....	2.49	gm./100 ml.
Fibrinogen (plasma).....	0.2-0.4	gm./100 ml.
Gamma globulin.....	10-15	% of total protein
	0.7-1.2	gm./100 ml.

At birth values approximate adult levels, owing to passive transfer from the mother; during the ensuing weeks there is a decrease, the "low point" being reached between the second and fourth months. After this there is a gradual increase to the "adult level" by about the second year of life.

## Nitrogen Constituents

Nonprotein nitrogen.....(whole blood)	25-40	mg./100 ml.
Urea nitrogen.....(plasma)	18-30	mg./100 ml.
.....(whole blood)	7-15	mg./100 ml.
Creatine + creatinine.....(plasma)	10-17	mg./100 ml.
.....(whole blood)	5-8	mg./100 ml.
Creatine in low concentration in plasma		
Creatinine.....(whole blood)	0.5-2	mg./100 ml.
.....(plasma)	0.6-1.2	mg./100 ml.
Uric acid.....(whole blood)	2.5-3.5	mg./100 ml.
At birth the uric acid concentration of the infant's blood is identical with that of the mother		
Ammonia.....(whole blood)	0.1-0.3	mg./100 ml.
Amino acid nitrogen.....(plasma)	3.5-5.5	mg./100 ml.
Plasma rather than serum is recommended for the amino acid nitrogen, since serum gives slightly lower values		

## Miscellaneous

Phosphatase, infants.....(serum)	5-10	Bodansky units
children 2-15 years.....	3-13	Bodansky units
infants.....(serum)	0.5-1.14	Kay units
children.....	0.17-0.34	Kay units
infants.....(serum)	156-241	Lundsteen and
children.....	43-147	Vermehren units
children.....(serum)	3.4-11.0	Lundsteen and
children.....(serum)	15-20	Vermehren units
children.....(serum)	35-40	Jenner-Kay units
		King-Armstrong units
		Cayla units



Table 119 (Continued)

Amylase.....	(plasma)	80-150	Somogyi units
Ascorbic acid.....	(serum)	0.4-1.5	mg./100 ml.
Iron (above 10 years).....	(whole blood)	47-55	mg./100 ml.
See note under Oxygen Capacity			
Iron.....	(serum)	0.04-0.18	mg./100 ml.
Copper.....	(serum)	0.08-0.13	mg./100 ml.
Lead.....	(serum)	0.001-0.003	mg./100 ml.
Iodine, organic (protein-bound).....	(serum)	0.003-0.008	mg./100 ml.
Plasma volume (Metcoff and Stare), Evans blue method			
Neonatal.....		144-164	ml.
Under 1 year.....		144-270	ml.
1-4 years.....		483-653	ml.
5-12 years.....		891-1590	ml.
13-16 years.....		2030-2610	ml.
Physical Measurements			
<hr/>			
Specific gravity.....	(whole blood)	1.048-1.050	
Newborn infants: falls rapidly during first two weeks and continues to decrease until second or third year	(whole blood)	1.060-1.085	
	(plasma)	1.025-1.030	
Prothrombin time (Quick).....	(plasma)	12-15	seconds
This determination should always be controlled by a determination on a normal blood, since the activity of the thromboplastin preparations may vary markedly			
Bleeding time.....		1-3	minutes
Coagulation time (test tube method).....		3-9	minutes
Viscosity, compared to water as unity.....	(whole blood)	4.5-5.5	
	(serum)	1.7-2.1	
Corrected sedimentation rate (Rourke-Ernstene).....		0.1-0.35	mm./min.
Cutler method.....		2-10	mm./hr.
The rate is slower in the neonatal period			
Freezing point depression.....	(serum)	-0.535°-(-0.555°) C.	
Refractive index, 20° C.....		1.3485-1.3505	

NORMAL CEREBROSPINAL FLUID VALUES

Amount in the newborn.....		up to 5 ml.
Increases with age to adult figure.....	100-150	ml.
Initial pressure.....	70-200	mm. of water
Cell count		
Under 1 year.....		up to 10 cells/c. mm.
1-4 years.....		up to 8 cells/c. mm.
5 years to puberty.....		0-5 cells/c. mm.
Specific gravity.....		1.005-1.009
Viscosity.....		1.0424-1.0489
Freezing point depression.....		-0.56-(-0.60)° C.
Refractive index at 20° C.....		1.33554
pH 38° C. (protected against loss of CO <sub>2</sub> ).....	7.33-7.42	
Fluid exposed to air becomes alkaline		
Carbon dioxide-combining power.....	40-70	vol. per cent
Chloride, as NaCl		
7 days-3 months.....	636-716	mg./100 ml.
	108.8-122.5	mEq./liter
	659-742	mg./100 ml.
4-12 months.....	112.7-128.5	mEq. liter
	683-763	mg./100 ml.
13 months-12 years.....	116.8-130.5	mEq./liter

Cholesterol	trace-0.22	mg./100 ml.
Glucose, 6 months-10 years	71-90	mg./100 ml.
over 10 years	50-80	mg./100 ml.
Total base	about 155	mEq. liter
Sodium	300-380	mg./100 ml.
Potassium	11-16	mg./100 ml.
Calcium	4.5-5.5	mg./100 ml.
Magnesium	2.8-3.3	mg./100 ml.
Phosphorus, inorganic	1.0-2.0	mg./100 ml.
3 mg. first day of life		
Lactic acid		Trace
Fluid on standing may increase in concentration with disappearance of glucose		
Protein	15-40	mg./100 ml.
The ventricular fluid contains much less protein than does lumbar fluid		
Fluid from the cisterna magna contains more protein than that from the ventricle and less than that from lumbar region		
Albumin		80% of total protein
Globulin		20% of total protein
Fibrinogen		none
Pandy reaction		no precipitate
Urea nitrogen	7-15	mg./100 ml.
Nonprotein nitrogen	8.5-20	mg./100 ml.
Creatinine	0.45-1.90	mg./100 ml.
Uric acid	0.3-1.5	mg./100 ml.
Amino acid nitrogen	1.5-3	mg./100 ml.
Bilirubin		none
Iodine		trace
Colloidal gold number (Wuth and Faupel)		0000000000
Dilutions 1:10 to 1:5120 with 0.4% NaCl solution.		

METHOD FOR CONVERSION OF  
MILLIGRAMS TO MILIEQUIVALENTS PER LITER

mg. = milligrams                      ml. = milliliter  
gm. = grams                          1 ml. = 1.000027 cc.  
mEq./liter (milliequivalents per liter) =  $\frac{\text{mg. per liter}}{\text{equivalent weight}}$

equivalent weight =  $\frac{\text{atomic weight}}{\text{valence of element}}$

For example: A sample of blood serum contains 10 mg. of Ca in 100 ml. The valence of Ca is 2, and the atomic weight is 40. The equivalent weight of Ca is therefore  $40 \div 2$ , or 20. The milliequivalents of Ca per liter is  $10 \times 10 \div 20$ , or 5 milliequivalents per liter.

mM./liter (millimols per liter) =  $\frac{\text{mg./liter}}{\text{molecular weight}}$

vol. % (volumes per cent) = mM./liter  $\times 2.24$  for a gas whose properties approach that of an ideal gas, such as oxygen or nitrogen.

For carbon dioxide the factor is 2.226.

Table 120. Factors for Conversion of Concentrations Expressed in Milliequivalents per Liter to Milligrams per 100 Milliliters, and vice versa, for Common Ions That Occur in Physiologic Solutions

Element or Radical	mEq. per Liter	Mg. per 100 ML.	Mg. per 100 ML.	mEq. per Liter
Sodium	1	2.30	1	0.4348
Potassium	1	3.91	1	0.2558
Calcium	1	2.005	1	0.4988
Magnesium	1	1.215	1	0.8230
Chloride	1	3.55	1	0.2817
Bicarbonate (HCO <sub>3</sub> )	1	6.1	1	0.1639
Phosphorus valence 1	1	3.10	1	0.3226
Phosphorus valence 1.8	1	1.72	1	0.5814
Sulfur valence 2	1	1.60	1	0.625

Example: To convert milliequivalents of magnesium per liter to milligrams per 100 milliliters, multiply by the factor 1.215.

To convert milligrams of potassium per 100 milliliters to milliequivalents per liter, multiply by the factor 0.2558.



Table 121. Milliequivalents and Milligrams of Cations and Anions Present in a Millimol of Salts Commonly Used in Physiologic Solutions

Salt	mM. per Liter	Mg. per Liter	Cation	Anion	mEq. Cation per Liter	Mg. Cation per Liter	mEq. Anion per Liter	Mg. Anion per Liter
Sodium chloride (NaCl)	1	58.5	Na <sup>+</sup>	Cl <sup>-</sup>	1	23.0	1	35.5
Potassium chloride (KCl)	1	74.6	K <sup>+</sup>	Cl <sup>-</sup>	1	39.1	1	35.5
Sodium bicarbonate (NaHCO <sub>3</sub> )	1	84.0	Na <sup>+</sup>	HCO <sub>3</sub> <sup>-</sup>	1	23.0	1	61.0
Sodium lactate (CH <sub>3</sub> CH(OH)COONa)	1	112.0	Na <sup>+</sup>	Lactate <sup>-</sup>	1	23.0	1	89.0
Potassium phosphate (K <sub>2</sub> HPO <sub>4</sub> ) dibasic	1	174.2	K <sup>+</sup>	HPO <sub>4</sub> <sup>-</sup>	2	78.2	1	96.0
Potassium phosphate (KH <sub>2</sub> PO <sub>4</sub> ) monobasic	1	136.1	K <sup>+</sup>	H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	1	39.1	1	97.0
Calcium chloride anhydrous (CaCl <sub>2</sub> )	1	111.0	Ca <sup>++</sup>	Cl <sup>-</sup>	2	40.0	2	71.0
Calcium chloride dihydrate (CaCl <sub>2</sub> ·2H <sub>2</sub> O)	1	147.0	Ca <sup>++</sup>	Cl <sup>-</sup>	2	40.0	2	71.0
Magnesium chloride anhy- drous (MgCl <sub>2</sub> )	1	95.2	Mg <sup>++</sup>	Cl <sup>-</sup>	2	24.3	2	71.0
Magnesium chloride hexahy- drate (MgCl <sub>2</sub> ·6H <sub>2</sub> O)	1	203.3	Mg <sup>++</sup>	Cl <sup>-</sup>	2	24.3	2	71.0
Ammonium chloride (NH <sub>4</sub> Cl)	1	53.5	NH <sub>4</sub> <sup>+</sup>	Cl <sup>-</sup>	1	18.0	1	35.5

MILLIOSMOLAR SOLUTION: In studying osmotic pressure relationships in solution it is useful to express the concentration in terms of ionic concentrations. The term "milliosmolar" is used instead of millimolar to show the additive osmotic effect of the ions.

For example: A millimolar solution of glucose (180 mg. per liter) is also a milliosmolar solution (1 milliosmol per liter), because there is no increase in the number of active particles through ionization. A millimolar solution of sodium chloride (58.5 mg. per liter) contains one chemical milliequivalent of sodium ions and one chemical milliequivalent of chloride ions. The milliosmolar concentration is 2 milliosmols per liter, because one chemical milliequivalent of sodium or chloride ions is equal to 1 milliosmol of sodium or chloride ions, respectively. This is true for all univalent ions. The chemical milliequivalence of a divalent ion is twice the milliosmolar value. In a millimolar solution of calcium chloride (CaCl<sub>2</sub>) there are two chemical milliequivalents of calcium ions, but only 1 milliosmol of calcium ions. The millimolar solution of calcium chloride contains two chemical milliequivalents of chloride ions or 2 milliosmols of chloride ions per liter. A millimolar solution of calcium chloride contains 3 milliosmols per liter, because it ionizes into one calcium ion and two chloride ions.

In blood serum containing 10 mg. of calcium per 100 ml., there are 5 chemical milliequivalents of calcium per liter, but only 2.5 milliosmols of calcium per liter. The average normal total ionic concentra-

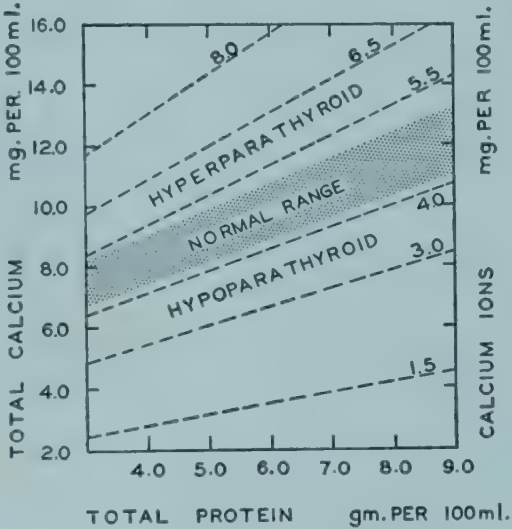


FIG. 428. Nomogram for estimation of serum ionized calcium from total calcium and total protein values. Modified by Lytt I. Gardner from the McLean-Hastings data. (J. Biol. Chem., Vol. 108.)

tion of blood serum is 290 milliosmols; cation concentration 151, anion concentration 139. The osmotic pressure of the blood serum of infants and children is comparable to that of adults.

HOWARD W. ROBINSON

# SODIUM AND POTASSIUM CONTENTS OF ORAL FLUIDS\*

Fluid	mEq./1000 gm.	
	Na	K
Apple juice (sweet cider, bottled).....	1.7	26
Coca-cola.....	0.4	13
Ginger ale.....	3.5	0.15
Grape juice (concord, sweetened, bottled).....	0.4	31
Grapefruit juice (sweetened, canned)...	0.2	38.5
Milk, whole.....	21.7	36
Orange juice (unsweetened, canned)...	0.2	48.8
Pepsi-cola.....	6.5	0.77
Pineapple juice (unsweetened, canned)...	0.2	36
Root beer.....	3.5	0.13
Tomato juice (canned, salt added)....	100	59
Water (New Haven, Conn.).....	0.13	0.03

\* Calculated from C. E. Bills, F. G. McDonald, W. Niedermeier and M. G. Schwartz: Sodium and Potassium in Foods and Waters. Determination by the Flame Photometer. *J. Am. Dietetic A.*, 25: 304, 1949. Prepared by R. E. Cooke.

## FOOD VALUES

Table 122. Percentage Composition and Caloric Equivalents of Various Foods

Food Material	Protein per cent	Fat per cent	Carbo- hydrate per cent	Ash per cent	Calories per Avoird- upois Oz.	Calories per Kilogram or Liter
Milk foods						
Cow's milk (average).....	3.3	4.0	5.0	0.7	20	719
Skimmed milk, commercial fat-free.....	3.4	0.3	5.1	0.7	11	375
Skimmed milk, after removal of gravity cream.....	3.3	1.0	5.0	0.7	13	429
Buttermilk.....	3.0	0.5	4.8	0.7	10	364
Whey.....	1.0	0.3	5.0	0.7	8	276
Butter.....	1.0	85.0	....	3.0	225	7949
Meats						
Beef, lean ribs.....	19.6	12.0	....	1.0	54	1918
Beef, lean round.....	21.3	7.9	....	1.1	46	1609
Beef, roasted.....	22.3	28.6	....	1.3	101	3572
Beefsteak, round, cooked, fat removed.....	27.6	7.7	....	1.8	53	1852
Beefsteak, loin, broiled.....	23.5	20.4	....	1.2	81	2866
Beef juice.....	4.9	0.6	....	1.5	7	254
Beef liver.....	20.4	4.5	1.7	1.6	38	1334
Mutton, leg, lean.....	19.8	12.4	....	1.1	56	1962
Lamb chop, broiled.....	21.7	29.9	....	1.3	104	3671
Fish, halibut.....	18.6	5.2	....	1.0	35	1246
Fish, mackerel.....	18.7	7.1	....	1.2	40	1422
Bacon, smoked, lean.....	15.5	42.6	....	11.0	130	4597
Fowl.....	19.3	16.3	....	1.0	65	2304
Capon, cooked.....	27.0	11.5	....	1.3	61	2172
Turkey.....	21.1	22.9	....	1.0	85	2998
Turkey, roast.....	27.8	18.4	....	1.2	81	2855
Eggs						
Eggs, white boiled.....	12.3	0.2	....	0.6	16	551
Eggs, yolk boiled.....	15.7	33.3	....	1.1	107	3759
Sugar and starch						
Cane sugar, granulated.....	....	....	100.0	....	116	4101
Milk sugar.....	....	....	....	....	116	4101
Arrowroot.....	....	....	97.5	0.2	113	4002
Cornstarch.....	....	....	90.0	....	105	3693
Sago.....	9.0	0.4	78.1	0.3	102	3605
Tapioca.....	0.4	0.1	88.0	0.1	103	3638
Cereals						
Barley, pearled.....	8.5	1.1	77.8	0.1	103	3638
Barley flour.....	10.5	2.2	72.8	2.6	103	3616
Oatmeal.....	16.1	7.2	67.5	1.9	116	4101
Oats, various preparations.....	16.8	7.3	66.8	1.7	116	4090
Rice.....	8.0	0.3	79.0	0.4	102	3394
Wheat, cracked.....	11.1	1.7	75.5	1.6	105	3715
Wheat flour (average).....	11.4	1.0	75.1	0.5	103	3638
Wheat, whole, flour.....	13.8	1.9	71.9	0.9	105	3693



Table 122. (Continued)

Food Material	Protein per cent	Fat per cent	Carbo- hydrate per cent	Ash per cent	Calories per Avoird- upois Oz.	Calories per Kilogram or Liter
Wheat, farina.....	11.0	1.4	76.3	0.4	105	3715
Wheat, macaroni.....	13.4	0.9	74.1	1.3	104	3671
Wheat bread, average.....	9.2	1.3	53.1	1.1	76	2679
Whole-wheat bread.....	9.7	0.9	49.7	1.3	71	2513
Bread, graham.....	8.9	1.8	52.1	1.5	76	2668
Wheat bread, toast.....	11.5	1.6	61.2	1.7	89	3131
Zwieback.....	9.8	9.9	73.5	1.0	123	4343
Rolls (average).....	8.9	4.1	56.7	1.1	87	3075
Cornmeal.....	8.4	4.7	74.0	1.3	108	3814
Cornbread.....	7.9	4.7	46.3	2.2	75	2657
Corn hominy.....	8.3	0.6	79.0	0.3	103	3638
Crackers.....	10.7	8.8	71.9	1.8	119	4200
Vegetables						
Asparagus.....	1.8	0.2	3.3	0.7	7	231
Beans, lima.....	7.1	0.7	22.0	1.7	36	1257
Beans, string.....	2.3	0.3	7.4	0.8	12	430
Beets.....	1.6	0.1	9.7	1.1	13	474
Carrots.....	1.1	0.4	9.3	1.0	13	463
Celery.....	1.11	0.1	3.3	1.0	5	187
Lettuce.....	1.2	0.3	2.9	0.9	6	198
Onions.....	1.6	0.3	9.9	0.6	14	496
Peas.....	7.0	0.5	16.9	1.0	29	1025
Potatoes.....	2.2	0.1	18.4	1.0	24	848
Potatoes, sweet.....	1.8	0.7	27.4	1.1	36	1257
Spinach.....	2.1	0.3	3.2	2.1	7	243
Squash.....	1.4	0.5	9.0	0.8	13	474
Fruits						
Apples.....	0.4	0.5	14.2	0.3	18	639
Blackberries.....	1.3	1.0	10.9	0.5	17	595
Dates, pressed.....	2.1	2.8	78.4	1.3	101	3561
Figs, pressed.....	4.3	0.3	74.2	2.4	92	3252
Grapes.....	1.3	1.6	19.2	0.5	28	992
Oranges.....	0.8	0.2	11.6	0.5	15	529
Peaches.....	0.7	0.1	9.4	0.4	12	419
Pears.....	0.6	0.5	14.1	0.4	18	650
Prunes, dried.....	2.1	.....	73.3	2.3	88	3087
Raspberries, red.....	1.0	.....	12.6	0.6	16	562

To convert requirements per kilogram of body weight to requirements per pound of body weight, divide the value per kilogram by 2 and subtract 10 per cent of the product.

METHOD FOR DIET CALCULATION\*

The following is a convenient method for calculation of diabetic and other quantitative diets which can be used by the average practitioner. It is sufficiently accurate for clinical use. The principle is based on the classification of foods on the basis of the approximate equality of their carbohydrate, protein and fat contents, so-called food equivalents (see Tables 123 and 124).

The steps for determining the diet for a given child are as follows:

- 1. Determine dietary prescription.  
(For diabetic diet, see p. 1209)  
(For obesity diet, see p. 356)  
Example below based on diabetic diet of C, 200; P, 70; F, 80.
- 2. List number of servings from each list of food exchanges in Table 124, which are considered essential for the basic needs of the child; tabulate

Example:

List	Food	No. of Servings	Carbo- hydrate Gm.	Pro- tein Gm.	Fat Gm.
1.....	Milk	4 cups (1 qt.)	48	32	40
2a....	Vegetables	As desired	0	0	0
2b....	Vegetables	4	28	8	0
3.....	Fruit	3	30	0	0
4.....	Bread	4	60	8	0
5.....	Meat	3	0	21	15
6.....	Fat	4	0	0	20
			166	69	75

amounts of carbohydrate, protein and fat for each list and total each element separately.

3. Subtract amounts of carbohydrate, protein and fat in (2) from amount of each specified for the prescribed diet.

	Carbohydrate Gm.	Protein Gm.	Fat Gm.
Prescribed diet.....	200	70	80
Basic diet.....	166	69	75
Deficit.....	34	1	5

4. Make up deficits of carbohydrate, protein and fat in preliminary diet list (step 2) by adding appropriate number of servings from any of the lists of food exchanges (Table 124), based on child's dietary habits and desires.

Example:

List	Serving	Carbohydrate Gm.	Protein Gm.	Fat Gm.
3.....	3	30	0	0
4.....	1	5	2	0
6.....	1	0	0	5
		35	2	5
Basic Diet.....		166	69	75
Final prescription....		201	71	80

\* Adapted from E. K. Caso and F. J. Stare: Simplified Method for Calculating Diabetic Diets. J.A.M.A., 133: 169, 1947.

Table 123. Food Exchanges

## LIST 1. MILK EXCHANGES (carbohydrate, 12 gm.; protein, 8 gm.; fat, 10 gm.; calories, 170)

	Measure	Gm.
Milk, whole*	1 cup	240
Milk, evaporated	1½ cup	120
Milk, powdered*	¼ cup	35
Buttermilk*	1 cup	240

\* Add 2 fat exchanges if fat-free.

## LIST 2. VEGETABLE EXCHANGES

A. These vegetables may be used as desired in ordinary amounts. Carbohydrates and calories negligible.

Asparagus	Lettuce
Broccoli	Mushrooms
Brussels sprouts	Beet greens
Cabbage	Chard
Cauliflower	Collard
Celery	Dandelion
Chicory	Kale
Cucumbers	Mustard
Escarole	Spinach
Eggplant	Turnip greens
	Tomatoes

B. Vegetables: 1 serving equals ½ cup equals 100 gm. (carbohydrate, 7 gm.; protein, 2 gm.; calories, 36)

Beets	Peas, green	Squash, winter
Carrots	Pumpkin	Turnip
Onions	Rutabaga	

## LIST 3. FRUIT EXCHANGES (carbohydrate, 10 gm.; calories, 40)

	Measure	Gm.
Apple	1 sm. (2" diam.)	80
Applesauce	½ cup	100
Apricots, fresh	2 medium	100
Apricots, dried	4 halves	20
Banana	½ small	50
Berries: straw., rasp., black	1 cup	150
Blueberries	¾ cup	100
Cantaloupe	¼ (6" diam.)	200
Cherries	10 large	75
Dates	2	15
Figs, fresh	2 large	50
Figs, dried	1 small	15
Grapefruit	½ small	125
Grapefruit juice	½ cup	100
Grapes	12	75
Grape juice	¼ cup	60
Honeydew melon	⅓ (7" diam.)	150
Mango	½ small	70
Orange	1 small	100
Orange juice	½ cup	100
Papaya	½ medium	100
Peach	1 medium	100
Pear	1 small	100
Pineapple	½ cup	80
Pineapple juice	⅓ cup	80
Plums	2 medium	100
Prunes, dried	2 medium	25
Raisins	2 tbsp.	15
Tangerine	1 large	100
Watermelon	1 cup	175

## LIST 4. BREAD EXCHANGES (carbohydrate, 15 gm.; protein, 2 gm.; calories, 68)

	Measure	Gm.
Bread	1 slice	25
Biscuit, roll	1 (2" diam.)	35
Muffin	1 (2" diam.)	35
Cornbread	1 (1½" cube)	35
Flour	2½ tbsp.	20
Cereal, cooked	½ cup	100
Cereal, dry (flake and puffed)	¾ cup	20
Rice, grits, cooked	½ cup	100
Spaghetti, noodles, etc., cooked	½ cup	100
Crackers, graham (2½" sq.)	2	20
Oyster	20 (½ cup)	20
Saltines (2" sq.)	5	20
Soda (2½" sq.)	3	20
Round, thin (1½" diam.)	6-8	20
Vegetables		
Beans and peas, dried, cooked (lima, navy, split pea, cow-peas, etc.)	½ cup	90
Baked beans, no pork	¼ cup	50
Corn	⅓ cup	80
Parsnips	⅔ cup	125
Potatoes, white, baked, boiled	1 (2" diam.)	100
Potatoes, white, mashed	½ cup	106
Potatoes, sweet, or yams	¼ cup	50
Sponge cake, plain	1 (1½" cube)	25
Ice cream (omit 2 fat exchanges)	½ cup	70

## LIST 5. MEAT EXCHANGES (protein, 7 gm.; fat, 5 gm.; calories, 73)

	Measure	Gm.
Meat and poultry (med. fat)	1 oz.	30
(beef, lamb, pork, liver, chicken, etc.)		
Cold cuts (4½" sq., ⅛" thick)	1 slice	45
Frankfurter	1 (8-9/lb.)	50
Fish: cod, mackerel, etc.	1 oz.	30
Salmon, tuna, crab	¼ cup	30
Oysters, shrimp, clams	5 small	45
Sardines	3 medium	30
Cheese, cheddar, American	1 oz.	30
Cottage	¼ cup	45
Egg	1	50
Peanut butter*	2 tbsp.	30

\* Limit use or adjust carbohydrate.

## LIST 6. FAT EXCHANGES (fat, 5 gm.; calories, 45)

	Measure	Gm.
Butter or margarine	1 tsp.	5
Bacon, crisp	1 slice	10
Cream, light, 20%	2 tbsp.	30
Cream, heavy, 40%	1 tbsp.	15
Cream cheese	1 tbsp.	15
French dressing	1 tbsp.	15
Mayonnaise	1 tsp.	5
Oil or cooking fat	1 tsp.	5
Nuts	6 small	10
Olives	5 small	50
Avocado	1 (4" diam.)	25



Table 124. Composition of Food Exchanges

<i>List</i>	<i>Food</i>	<i>Measures</i>	<i>Gm.</i>	<i>C</i>	<i>P</i>	<i>F</i>	<i>Cal.</i>
1	Milk exchanges	½ pint	240	12	8	10	170
2A	Vegetable exchanges	As desired	—	—	—	—	—
2B	Vegetable exchanges	½ cup	100	7	2	—	36
3	Fruit exchanges	Varies	—	10	—	—	40
4	Bread exchanges	Varies	—	15	2	—	68
5	Meat exchanges	1 oz.	30	—	7	5	73
6	Fat exchanges	1 tsp.	5	—	—	5	45

WALDO E. NELSON

# ELIMINATION DIETS (ROWE) FOR THE STUDY AND CONTROL OF FOOD ALLERGY

These diets may be modified by eliminating foods which elicit large dermal reactions or are disliked by the patient or disagree with him. They may be used before or after the failure of "test-negative diets."

The cereal-free diets exclude all cereals as well as milk, egg and other allergenic foods. Fruit-free elimination diets also exclude tomato and uncooked vegetables and fruits. The preliminary use of diet 4 is rarely satisfactory.

toms have been manifest. Thus relief for one week from symptoms occurring daily, for two weeks from symptoms recurring every two to three days, for three weeks from weekly recurring symptoms, and for three months from symptoms recurring every three to six weeks indicates that causative allergenic foods have been eliminated.

After relief has been assured, individual foods can be added, excluding any which reproduce symptoms. Each food should be taken daily for three to

Table 125. Elimination Diets

Diet 1	Diet 2	Diet 3	Diet 4
Rice	Corn, rye	Tapioca	Milk
Rice biscuit	Corn pone	White potato	Tapioca
Rice bread	Corn, rye muffin	Breads made of any combination of soy, lima, potato starch, and tapioco flours	Cane sugar
Tapioca	Rye bread, Ry-Krisp	Tomato	
Lettuce, chard	Beets, squash	Carrot	
Spinach, carrot	Asparagus, artichoke	Lima beans	
Sweet potato or yam	Chicken (no hens)	String beans	
Lamb	Bacon	Peas	
Lemon, grapefruit	Pineapple	Beef	
Pears	Peach, apricot	Bacon	
Cane sugar	Prune	Lemon	
Sesame oil, olive oil*	Cane or beet sugar	Grapefruit	
Salt	Mazola oil	Peach	
Gelatin, plain or flavored with lime or lemon	Sesame oil	Apricot	
Maple syrup or syrup made with cane sugar flavored with maple	Salt	Cane sugar	
Royal baking powder	Gelatin, plain or flavored with pineapple	Soy bean oil	
Baking soda	Karo corn syrup	Gelatin, plain	
Cream of tartar	White vinegar	Salt	
Vanilla extract	Royal baking powder	Syrup made with cane sugar	
Lemon extract	Baking soda	Cream of tartar	
	Cream of tartar	Corn starch-free baking powder	
	Vanilla extract		

Straight lines enclose foods in the cereal-free elimination diets.

\* Allergy to olive oil may occur with or without allergy to olive pollen. Mazola oil may be used if corn allergy is not present.

A minimal diet of lamb, white potato, tapioca cooked with pear and sugar, carrots, peas, pears, salt and sugar is a practical and simple one.

The patient should be given a list of allowed foods with menus and recipes and never a list of foods to avoid. Strict adherence to the diet is imperative. Allergens of foods remain in the body for more than a few days, so that dietary change must not be made until there has been an opportunity to evaluate the preceding one. The handling and odors of eliminated foods must also be avoided. Synthetic vitamins should be given as supplements to the diet.

The time necessary to maintain the elimination diets depends on the frequency with which symp-

five days before trying another. Symptoms may recur in a few minutes, hours or days according to the degree of allergy that exists.

ALBERT H. ROWE

## REFERENCES

- Rowe, A. H.: The Elimination Diets (Rowe). 5th Revision. Berkeley, California, Sather Gate Book Shop, 1958.
- : Elimination Diets (Rowe) for the Study and Control of Food Allergy. Quart. Rev. Allergy, 4:227, 1950.
- : Elimination Diets and the Patients' Allergies. Philadelphia, Lea & Febiger, 1944.



CONVERSION TABLES OF APOTHECARY'S  
MEASURES TO METRIC EQUIVALENTS

Weights

Apothecary	Metric		
	Approximate	More Nearly Accurate	
1 grain.....	60 mg.	0.06 gm.	0.06479 gm.
2 grains.....	120 mg.	0.12 gm.	
3 grains.....	180 mg.	0.2 gm.	
5 grains.....	300 mg.	0.3 gm.	
15 grains.....	1000 mg.	1.0 gm.	
60 grains or 1 dram.....		4.0 gm.	3.888 gm.
240 grains or 4 drams, ½ oz.....		15.0 gm.	
480 grains or 8 drams, 1 oz.....		30.0 gm.	31.103 gm.
			31.103 gm. (Troy)
			28.350 gm. (Avoir.)
12 oz. or 1 pound.....	360.0 gm.	373.24177 gm.	
12 oz. or 1 pound.....	360.0 gm.	373.24177 gm.	(Troy)
16 oz. or 1 pound.....	480.0 gm.	453.592 gm.	(Avoir.)
¾ grain.....	45 mg.		
½ grain.....	30 mg.		
⅜ grain.....	23 mg.		
¼ grain.....	15 mg.		
⅙ grain.....	10 mg.		
⅓ grain.....	8 mg.		
⅒ grain.....	6 mg.		
⅛ grain.....	4 mg.		
1/32 grain.....	2 mg.		
1/64 grain.....	1 mg.		
1/100 grain.....	0.6 mg.		
1/250 grain.....	0.25 mg.		
1/300 grain.....	0.2 mg.		
1/1000 grain.....	0.06 mg.		

Liquid Measures

1 minim.....	0.06 ml.....	0.06161 ml.
3 minims.....	0.2 ml.	
15 minims.....	1.0 ml.....	0.92415 ml.*
60 minims, 1 fl. dram.....	4.0 ml.....	3.6967 ml.
480 minims	1 fl. oz.....	30.0 ml.....
	16 fl. oz. or 1 pt.....	500.0 ml.....
	32 fl. oz. or 1 qt.....	1000.0 ml.....
		946.358 ml.

\* 1 ml. is equal to 16.23 minims.  
Quantity of drug prescribed in grams per 2 ounces (60 ml.) gives dose in grains per dram.

EQUIVALENT CENTIGRADE AND FAHRENHEIT  
TEMPERATURE READINGS

Centigrade Degrees	Fahrenheit Degrees	Centigrade Degrees	Fahrenheit Degrees
0.....	32.0	40.....	104.0
21.....	69.8	41.....	105.8
27.....	80.6	42.....	107.6
30.....	86.0	43.....	109.4
35.....	95.0	100.....	212.0
36.....	96.8		
37.....	98.6		
38.....	100.4		
39.....	102.2		

To convert Centigrade readings to Fahrenheit, multiply by 1.8 and add 32. To convert Fahrenheit readings to Centigrade, subtract 32 and divide by 1.8





# Index

NOTE: In this index the expression "re" has been used to mean "in relation to." Thus "Anomalies re unexpected death" is the equivalent of "Anomalies in relation to unexpected death."

The expression "vs." denotes "differential diagnosis." Thus "Abdomen, pain, vs. pleurisy" is the equivalent of "Abdomen, pain, differential diagnosis from pleurisy."

**Bold-face folios** in the index indicate main discussions in the text.

- ABDERHALDEN-Kauffmann-Lignac disease, 263-4
- Abdomen. See also *Ascites*; *Pelvis*; *Peritoneum*.  
 actinomycosis, 562  
 circumference, birth to 5 years, 56-7  
   measuring technique, 49  
 distention of, in pneumonia, 791, 792  
 muscles, hematoma in influenza, 511  
 newborn, 29  
 pain in, in appendicitis, 677  
   in brucellosis, 445  
   in dysentery, 436  
   in hyperlipemia, 278  
   in infectious lymphocytosis, 521  
   in poliomyelitis, 535  
   in porphyria, 281  
   in rheumatic fever, 908  
   in salmonellosis, 443  
   vs. pleurisy, 813  
 reflexes, in newborn, 300  
 tuberculosis, 467, 468
- Abdominal. See *Abdomen*.
- Abnormalities, congenital, **243-7**  
 death rates, 3, 9  
 etiology, 244-7  
 mortality, 243  
   re unexpected death, 350  
 environmental factors, 242  
 hereditary factors, **234-42**  
 in newborn, 314  
   re unexpected death, 350
- ABO incompatibility, 961
- Abrin, poisoning, 1383
- Abscess. See also *Ulcers*.  
 anorectal, 683  
 appendiceal, 688-9  
 brain, 1090  
 breast, in newborn, 340  
 due to *Salmonella*, 444  
 intraspinal, 1106  
 kidney, 1052  
 liver, 707-708  
 peritoneal, 688-9  
 psoas, 1262  
 pulmonary, 810-12  
 retroesophageal, 645  
 retropharyngeal, 753
- Accidents. See also *Trauma*.  
 causes, 143, 144
- Accidents, death rates, 3, 9, 36  
 incidence, 144  
 mortality rates, 143  
 prevention, 143-4
- Acetaldehyde, poisoning, 1387
- Acetaminophen, dose, 210
- Acetanilid, hemolytic anemia with, 264-5  
 poisoning, 1383  
 skin rash, 1282
- Acetazolamide, dose, 214
- Acetonuria, **1020**
- Acetophenetidin, 206  
 poisoning, 1383
- Acetylamino-phenol, 206
- Acetylsalicylic acid, 206  
 dose, 210  
   for common cold, 750  
   in acute bronchitis, 786  
   in nasopharyngitis, 750  
   in pharyngitis, 753  
   in pneumococcal pneumonia, 792  
   in rheumatic fever, 912  
   in rheumatoid arthritis, 920  
   poisoning, 1392
- Achalasia, 644  
 vs. pyloric stenosis, 660
- Achondroplasia, 1234-6
- Acid. See also specific acids.  
 corrosive, poisoning, 1383  
 fatty, essential, 102  
 in milks, 123
- Acid-base balance of newborn, 290
- Acid-base composition, plasma, 174
- Acid-base regulation, renal, 1008
- Acid-base relationships, 173
- Acidosis, **175-80**. See also *Ketosis*.  
 diabetic, 1207, 1209  
   treatment, 186, 189  
 general considerations, 175  
 hyperchloremic, 264  
   in cardiac surgery, 881  
   in glycogen disease, 270  
   in renal failure, 1050, 1051  
   metabolic, 177, 179  
   renal hyperchloremic, 1223  
   respiratory, 177-9  
   treatment, 191
- Acne in Cushing's syndrome, 1190
- Acne vulgaris, **1280**
- Acrocephalosyndactyly, 1227
- Acrocephalus, 1227
- Acrocephaly, in Laurence-Moon-Biedl syndrome, 1232
- Acrodynia, **1398-1401**
- Acromegaly, **1154-5**
- ACTH, 1150, 1151. See also *Corticotropin*; *Corticosteroids*.  
 dose, 210  
 in myoclonic seizure, 1120
- ACTH gel in infantile myoclonic seizures, 1120
- Actinomycosis, **562**  
 peritonitis in, 689  
 vs. nocardiosis, 566
- Activity, influence on growth and development, 41-2
- Adamantinoma, 1369
- Addis count, 1012  
   in acute glomerulonephritis, 1037  
   in pyelonephritis, 1032
- Addison's disease, **1182-5**  
 treatment, 1185  
 vs. Simmonds' disease, 1154
- Adenoidectomy in palatopharyngeal incompetence, 630-31
- Adenoiditis, suppurative, 761
- Adenoids, hypertrophy, **760-61**  
 in scarlet fever, 408  
 in school period, 36
- Adenoma, basophilic, 1151  
 chromophobe, 1151  
 eosinophilic pituitary, 1151, 1155
- Adenoma sebaceum, **1280**
- Adenovirus, 746  
 test(s), 387, 394
- Adie syndrome, 1333
- Adiponecrosis subcutanea neonatorum, 1278
- Adiposis dolorosa, 1279
- Adiposogenital dystrophy, **1162**
- Adolescence, **147-60**. See also *Puberty*.  
 anemia in, 154  
 calcium retention, 151, 153  
 characteristics, 26, 37-9  
 chronologic vs. physiologic age, 148-50  
 diabetes in, 152  
 diet in, 151  
 general considerations, 8  
 growth, 37-8  
 menarche re height, 149, 150  
 menstruation, 155

- Adolescence, metabolism in, 151, 153  
 nitrogen retention in, 151, 153  
 obesity, 154, 355  
 differential diagnosis, 1162  
 osseous development, 153  
 physical aspects, **147-56**  
 psychologic aspects, 156-60  
 psychologic problems, treatment, 159-60  
 school problems, 159  
 sex characteristics, secondary, 154  
 sex education, 158  
 sex hormones in, 154-5  
 sexual development, 38, 39  
 sexual problems, 158  
 thyroid disturbances, 154  
 tuberculosis, 152, 153
- Adrenal crisis, 1183
- Adrenalectomy. See *Adrenals, excision*.
- Adrenalin. See *Epinephrine*.
- Adrenals, cortex, deficiency, hypoglycemia in, 1217  
 tumor, re aldosteronism, 1191  
 re Cushing's syndrome, 1190  
 virilizing, 1189  
 vs. hyperplasia, 1188
- disorders, **1180-93**  
 in newborn, 343  
 ectopic, in liver, 1353  
 excision, bilateral, 1182-5  
 function, 1180-2  
 in infection, 382  
 general considerations, 1180-82  
 hemorrhage, 1182-5  
 in newborn, 320  
 hyperplasia, congenital, 1186-9  
 in female, 1187  
 in male, 1186  
 re electrolyte disturbance, 1188  
 treatment, 1189  
 virilizing, 1186-9  
 vs. tumor, 1188
- hypoplasia, congenital, 1182-5
- insufficiency, 1182-5. See also *Adison's disease*.  
 acute, 1183-5  
 clinical manifestations, 1183  
 electroencephalogram, 1121  
 treatment, 1185  
 vs. pyloric stenosis, 660
- of newborn, 292
- tumors, 1355-6  
 feminizing, 1191  
 re obesity, 355  
 weight at birth, 1180
- Adrenocorticotropin, 1150, 1151. See also *ACTH; Corticotropin*.
- Aerobacter infections, tests, 388
- Afibrinogenemia, 254  
 congenital, 982
- Agammaglobulinemia, **255-6**  
 re lymphocyte function, 964  
 re periodic neutropenia, 965
- Age, chronologic vs. physiologic, in adolescence, 148-50  
 re respiratory disorders, **743-4**
- Age factors, adolescence, 8, 26  
 embryonic, 26  
 infancy, 5, 26, **30-33**  
 neonatal, 4, 26  
 parturient period, 26  
 prenatal, 4, 26, 27  
 preschool (2-6 years), 7, 26  
 school (6-12 years), 7, 26
- Age periods, 1, 26, **27-39**  
 characteristics, 26, **27-39**  
 problems, 4-9
- Agensis, renal, bilateral, of newborn, 337
- Agglutination tests for rickettsiae, 554
- Aggression, 84-7
- Agranulocytic angina, 752, 965
- Agranulocytosis, **964-5**  
 vs. diphtheria, 416
- AHG. See *Antihemophilic globulin*.
- Akureyri disease, 550
- Alacta, 124
- Alastrim, 500
- Albamycin. See *Novobiocin*.
- Albers-Schönberg's disease, 1239
- Albinism, 260, 261, **1277**  
 partial, in Chediak-Higashi syndrome, 965
- Albright's syndrome. See *Polyostotic fibrous dysplasia*.
- Albumin, in urine. See *Albuminuria*.  
 plasma, 1403  
 serum, 1403  
 genetic defect of, 257  
 re jaundice, 702
- Albumin-globulin ratio, in nephrosis, 1047  
 plasma, 101
- Albuminuria, 1012, **1018**  
 adventitious, 1019  
 causes, 1039  
 febrile, 1019  
 in diphtheria, 417  
 in nephrosis, 1046  
 in scarlet fever, 409  
 lordotic, 1018  
 orthostatic, 1018
- Alcaptonuria, 259
- Alcohols, poisoning, 1383
- Aldehydes, poisoning, 1387
- Aldosterone, 1181
- Aldosteronism, primary, 1190  
 secondary, 1190
- Alkali mixture for "base-losing nephritis," 1224
- Alkali therapy in renal failure, 1051
- Alkalis, corrosive, 1389
- Alkalosis, **175-80**  
 congenital, 189  
 general considerations, 175  
 hypochloremic, therapy, 191  
 metabolic, 177-9  
 respiratory, 177, 179  
 tetany in, 1110-13
- Allergic diseases, **1304-28**. See also *Allergy*.
- Allergic eruptions of lips, 635
- Allergic reaction, anaphylactic, 382  
 bacterial, 382
- Allergic response, mechanism, 1311
- Allergic rhinitis, **1319-21**  
 vs. common cold, 749
- Allergy, **1304-28**. See also *Asthma; Dermatitis; Eczema; Hay fever; Urticaria*.  
 allergens, removal, 1309  
 desensitization, 1309  
 diets, elimination, 1306, 1412  
 elimination procedures, 1306  
 gastrointestinal, **1326-8**  
 diagnosis, 1327  
 general considerations, 381-4, 1304-12
- Allergy, goiter in, 1170, 1171  
 hyposensitization, 1309  
 nonspecific, 1311  
 in chronic rhinitis, 756  
 intestinal, re celiac disease, 726  
 pathogenesis, 1305  
 re bronchiectasis, 809  
 re diarrhea, 656  
 re pruritus ani, 683  
 tests, 1306-1309  
 passive transfer, 1308  
 skin, 1307-1309  
 to insulin, 1208  
 treatment, general, 1309-12
- Alopecia, **1281**  
 due to vitamin A, 363  
 in myotonic dystrophy, 1268
- Alopecia areata, 1281
- Alopecia totalis, 1281
- Alphaprodine, preanesthetic use, 229
- Aluminum in nutrition, 107
- Aluminum acetate, in dermatitis venenata, 1283  
 in ringworm of foot, 1292
- Aluminum salt, poisoning, 1383
- Alymphocytosis, 964
- Amanita phalloides*, poisoning, 1390
- Amaurosis. See also *Blindness*.  
 hysterical, 1068
- Amaurotic idiocy, 1094
- Ambenonium chloride in myasthenia gravis, 1272
- Amblyopia. See also *Blindness*.  
 hysterical, 1068  
 in strabismus, 1336
- Amblyopia ex anopsia, 1335
- Amebiasis, **610-13**  
 laboratory tests, 388  
 vs. actinomycosis, 562  
 vs. bacillary dysentery, 436
- Amebic abscess (liver) vs. kala-azar, 609
- Amelia, 1230
- Ameloblastoma, 620, 1369
- Amelogenesis imperfecta, 620
- Amenorrhea, in diabetes mellitus, 1207  
 with hirsutism, male type, 1201
- Amelia, primary undifferentiated, 1135
- Amethopterin, dose, 210
- Amidopyrine. See *Aminopyrine*.
- Amigen solution, 197
- Amino acid nitrogen, blood, 1404
- Amino acids. See also specific acids.  
 absorption, test for, 720  
 branched chain, defective metabolism, 267-8  
 defective metabolism, **258-68**  
 classification, 252  
 in malnutrition in infants, 353  
 in nutritional edema, 357  
 renal reabsorption, 1007  
 requirements, 101  
 tolerance curves, 698
- Amino-aciduria, and glycosuria, 262, 264  
 and phosphaturia, 262  
 in galactosemia, 275, 276  
 in nephrosis, 1047  
 in progeria, 1154  
 with rickets, 1222
- Aminophylline, 206  
 dose, 210  
 in asthma, 1323



- Aminopterin in leukemia, 969  
 Aminopyrine, re agranulocytosis, 965  
 skin rash, 1282  
 Aminosalicyclic acid, 470  
 in tuberculosis, 464  
 Ammonia, blood, 1404  
 deficient formation, 1223  
 in urine, 1013, 1021  
 renal excretion, 1009, 1010  
 Ammonia water in formaldehyde poisoning, 1388  
 Ammoniacal diaper rash, 1298  
 Ammoniated mercury, ophthalmic, 1331  
 Ammonium chlorate solution, 197  
 Ammonium chloride, as additive in fluid therapy, 197  
 dose, 210  
 in bromide poisoning, 1385  
 in hypochloremic alkalosis, 191  
 Ammonium mandelate, dose, 210  
 Amobarbital sodium, dose, 211  
 Amodiaquine in malaria, 608  
 Amphetamine, 206  
 for obesity, 356  
 in behavior problems, 1144  
 in narcolepsy, 1127  
 poisoning, 1383  
 Amphetamine sulfate, dose, 211  
 Amphotericin B, 564, 565, 571  
 dose, 211  
 Amylase, 718, 719  
 blood, 1405  
 Amyloidosis, **1345**  
 primary, 1345  
 re nephrosis, 1044  
 secondary, 1345  
 Amylorrhea, 724  
 Amyoplasia congenita, 1247  
 Amyotonia in Werdnig-Hoffmann disease, 1099  
 Amyotonia congenita syndrome, 1099-1100, **1267**  
 Amytal. See *Amobarbital sodium*.  
 Anal. See *Anus*.  
 Analbuminemia, 257  
 Analgesic drugs, 206  
 Anaphylactic reaction, 382  
 Anaphylactoid purpura, 920-22  
*Ancylostoma braziliense*, 583  
*Ancylostoma duodenale*, 583  
 Androgens, 1182  
 Andromedotoxin, poisoning, 1390  
 Anemia, **933-62**  
 aplastic, 934  
 classification, 935  
 congenital, 935  
 differential diagnosis, 937  
 due to chemicals, 936  
 due to infections, 936  
 due to radiation, 936  
 Fanconi, 935  
 idiopathic, 936  
 myelophthitic, 936  
 classification, 933  
 Cooley's, 946-9  
 erythroblastic, 946-9  
 ferrous sulfate for, 217  
 hemolytic, **944-62**  
 acquired, 953  
 congenital, 944-6  
 due to deficient glucose-6-phosphate dehydrogenase, 265  
 due to genetic defect, 953  
 hereditary, erythrocytes in, 955  
 Anemia, hemolytic, nonspherocytic, congenital, 946  
 of newborn, vs. cytomegalic inclusion disease, 525  
 re auto-agglutinins, 954  
 re inspissated bile syndrome, 334  
 re vitamin K, 379  
 with abnormal hemoglobins, 952  
 hypochromic, **941-3**  
 in malnutrition, 353  
 hypoplastic, congenital, **934**  
 tryptophane metabolism in, 265  
 in adolescence, 154  
 in cytomegalic inclusion disease, 524  
 in hookworm infection, 584  
 in hypothyroidism, 1166  
 in kala-azar, 609  
 in kwashiorkor, 359  
 in lead poisoning, 1376  
 in lupus erythematosus, 926  
 in nephrosis, 1047  
 in newborn, **335-6**  
 in osteopetrosis, 1240  
 in rickets, 377  
 in syphilis, 474  
 Lederer's, 954  
 Mediterranean, 946-9  
 megaloblastic, **938-41**  
 classification, 939  
 of infancy, 939-40  
 of intestinal origin, 940  
 myelophthitic, in osteopetrosis, 1240  
 myocardial insufficiency in, 894  
 of acute hemorrhage, **943-4**  
 of azotemia, **938**  
 of chronic hemorrhage, **944**  
 of chronic infection, **937-8**  
 of iron deficiency, **941-3**  
 pernicious, juvenile, 939  
 physiologic, of newborn, 932  
 porphyria in, 279  
 with renal failure, 1050  
 Anencephaly, 1075  
 Anesthesia, **227-31**  
 circulatory data, 230  
 examination for, 227, 228  
 induction, 230  
 medical aspects, general, 228-9  
 physiologic considerations, 230-31  
 postoperative care, 231  
 preanesthetic medication, 229  
 preoperative evaluation, 227-8  
 preparation for, 227-30  
 preoperative, 228-30  
 psychologic aspects, 228  
 respiratory data, 230  
 Aneurysm, **902**  
 cerebral, 1080  
 cirroid, of skin, 1359  
 Aneurysmal bone cyst, 1367  
 Anger, in emotional development, 68  
 Angiocardiology. See under *Cardiovascular system*.  
 Angio-edema, 1318  
 in serum sickness, 1326  
 Angiography, 1072  
 Angioma, cerebral, 1081  
 Angioma cavernosum, 1274  
 Angiomatosis, encephalo-trigeminal, 1080  
 Angioneurotic edema, 1318  
 in serum sickness, 1326  
 of lips, 635  
 Anhidrotic ectodermal dysplasia, 1276  
 Anhydrohydroxyprogesterone in gonadal dysgenesis, 1200  
 Aniline poisoning, 1383  
 Anion-cation balance, 174  
 Anions, mg. and mEq./L. in various salts, 1407  
 Annular pancreas, 718  
 Anodontia, 620  
 Anomalies. See *Abnormalities*.  
 Anorchia, **1059**, 1196  
 Anorectal. See *Anorectum*.  
 Anorectum. See also *Anus*; *Rectum*.  
 abscess, **683**  
 fistula, 684  
 plugs, in newborn, 331  
 stenosis, 680, 681  
 re megacolon, 674  
 Anorexia. See under *Appetite, disorders*.  
 Anoxia. See *Oxygen, deficiency*.  
 Ansolysen. See *Pentolinium tartrate*.  
 Ant bite, 599  
 Antepar. See *Piperazine citrate*.  
 Anthocyaninuria, 1021  
 Anthralin ointment in alopecia areata, 1281  
 Antibiotics, 207-208. See also specific antibiotics, as *Penicillin*; etc.  
 by inhalation, 742  
 general considerations, 207  
 ophthalmic, 1331  
 susceptibility tests, 396  
 Antibodies. See also *Antigens*.  
 anti-Duffy, 201  
 anti-Kell, 201  
 in blood matching, 201  
 Anticholinesterase compounds in myasthenia gravis, 1272  
 Anticoagulants, abnormal, 971  
 Anticonvulsants, 205-206  
 Antidote, in poisoning, 1380  
 universal, 1381  
 Antifungal agents, 207  
 Antigens. See also *Antibodies*.  
 in blood matching, 201  
 Antiglobulin technique, 958, 961  
 Antihemophilic globulin, 252-5 *passim*; 971, 972, 977-80 *passim*  
 deficiency, 977-80  
 Antihistamines, 207. See also under specific names.  
 in allergic rhinitis, 1320  
 in asthma, 1324  
 in serum sickness, 1326  
 in urticaria, 1318  
 Anti-lewisite, British. See *Dimer-caprol*.  
 Antimicrobial agents, 207-208. See also *Antibiotics*.  
 general considerations, 207  
 selection, **395-7**  
 Antimony poisoning, 1383  
 Antimony salts in schistosomiasis, 595  
 Antipyretic drugs, 206  
 Antithromboplastic substances, 971  
 Antitoxin, desensitization to, 419  
 tetanus, 433, 434  
 ANTU poisoning, 1383

- Antuitrin S for cryptorchism, 1059  
 Anuria. See *Urine, suppression*.  
 Anus. See also *Anorectum; Hemorrhoids; Rectum*.  
 absence, 680  
 anterior location, 681  
 disorders, **680-81**  
 fissure, **682**  
 fistula, 681, 684  
 imperforate, 680, 681  
 malformations, **680**  
 stenosis, 680, 681  
 stricture, re megacolon, 674  
 Anxiety, **81**  
 in emotional development, 67  
 Aorta, coarctation, **870-74**  
 associated anomalies, 871  
 in gonadal dysgenesis, 1199  
 in infancy, 873  
 with patent ductus arteriosus, 873  
 with ventricular septal defect, 859  
 dextroposition, in tetralogy of Fallot, 842-8  
 ruptured sinus of Valsalva, 866  
 Aortic arch, anomalies, **877-9**  
 right, 877  
 Aortic atresia, 854  
 Aortic insufficiency, 891  
 with ventricular septal defect, 858  
 Aortic stenosis, 892  
 congenital, **875-6**  
 Aorticopulmonary septal defect, **866**  
 Aphasia re speech development, 92  
 Aphonia, hysterical, 1068  
 Aphthae, allergic, 633  
 Bednar's, 301  
 Aphthous stomatitis, 491-2, 633  
 Apnea in newborn, 322-3  
 Apothecary measures, conversion tables, **1413**  
 Appendicitis, **676-8**  
 complications, 677  
 death rates, 3  
 differential diagnosis, 677  
 re abscess, 688-9  
 re peritonitis, 687-8  
 vs. bacillary dysentery, 436  
 vs. mesenteric lymphadenitis, 678  
 vs. pneumonia, 677, 789  
 vs. teniasis, 590  
 Appendix, carcinoid, 1351  
 Appetite, disorders, anorexia, **647**  
 anorexia nervosa, 89  
 Apresoline. See *Hydralazine*.  
 Apt's test, 337  
 Aqueduct of Sylvius, atresia of, 1076  
 Arachidonic acid, 102  
 Arachnidism, necrotic, 599  
 Arachnodactyly, **1243**  
 vs. Werdnig-Hoffmann disease, 1100  
 Arakawa test, 365  
 Aralen. See *Chloroquine*.  
 ARBOR viruses, laboratory tests for, 390  
 Ariboflavinosis, 365  
 Aristocort. See *Trimethaphan camphorsulfonate*.  
 Arnold-Chiari deformity, 1076, 1079  
 Arrhinencephaly, 1075  
 Arsenic, in acrodynia, 1398  
 in nutrition, 107  
 Arsenic, poisoning, 1383  
 BAL for, 211  
 skin rash, 1282  
 Arterenol, 1182  
 dose, 219  
 in adrenal insufficiency, 1185  
 Arterial oxygen saturation in cardiac disease, 833-5  
 Arterial pulse, 821-2  
 Arterial venous fistula, 902  
 Arteriogram, 837  
 Arteriography, 837  
 Arteriolar nephrosclerosis, 1049  
 Arteriosclerosis, 1049  
 in diabetes mellitus, 1208  
 in progeria, 1154  
 Arteriovenous fistula, cerebral, 1081  
 pulmonary, 855  
 Arthritis. See also *Gout*.  
 due to Salmonella, 444  
 in bacillary dysentery, 436  
 in brucellosis, 445, 446  
 in diphtheria, 417  
 in German measles, 488  
 in lupus erythematosus, 926  
 in meningitis, 428  
 in progeria, 1154  
 in scarlet fever, 409  
 in typhoid fever, 440  
 infections, acute, 1259  
 rheumatic, 906  
 rheumatoid, **915-20**. See also *Rheumatoid arthritis*.  
 syphilitic, 477  
 vs. scurvy, 371  
 Arthrogryposis, **1247**  
 Arthrogryposis multiplex congenita, 1099, 1247  
 Arthropod-borne virus encephalitis, 548, 549  
 pathology, 548  
 Arthropods, as agents in disease, **598**  
 tissue-invading, **599**  
 vectors of disease, 600  
 venenating, 598  
 Arthrosis, in anaphylactoid purpura, 921  
 in serum sickness, 1326  
 Artificial feeding, infant, **119-28**. See also under *Infant feeding*.  
 Artificial kidney, 1051  
 Artificial respiration, 740-42  
 nomogram for regulation, 738  
 Ascariasis, **575-8**  
 epidemiology, 574, 575  
 Hetrazan for, 218  
 pulmonary, vs. tropical eosinophilia, 602  
 treatment, 578  
 Aschoff body, 905  
 Ascites, **686**  
 chylous, 686  
 in galactosemia, 275  
 Ascorbic acid, 368, 371  
 and tyrosyluria in premature infant, 260  
 deficiency, 368-71  
 effects of, 109  
 excess, effects, 109  
 function, 109, 110  
 in celiac disease, 725  
 in congenital methemoglobinemia, 282  
 in infant feeding, 128  
 in malnutrition in infants, 353  
 in methemoglobinemia, 282  
 Ascorbic acid, in milk, 121  
 in premature, 310, 311  
 in scurvy, 371  
 in tuberculosis, 466  
 metabolism, 110  
 plasma level, 110  
 re teeth, 623  
 renal reabsorption, 1007  
 requirements, 107, 109, 111  
 serum, 1405  
 sources, 109  
 Aseptic meningitis due to Coxsackie virus, 529  
 due to ECHO virus, 531  
 Aseptic meningitis syndrome, 545-6  
 Asphyxia, death rates, 7  
 re unexpected death, 351  
 Aspidium poisoning, 1384  
 Aspiration pneumonia, **799-801**  
 in newborn, 327  
 Aspirin. See *Acetylsalicylic acid*.  
 Assassin bugs, vectors of disease, 600  
 Asterol poisoning, 1384  
 Asthma, 1321-5  
 atelectasis in, 803  
 clinical manifestations, 1322  
 diagnosis, 1321  
 epinephrine for, 216  
 hyposensitization, 1310  
 in tropical eosinophilia, 602  
 pathology, 1321  
 prognosis, 1322  
 pulmonary function in, 736  
 treatment, 1323  
 Astigmatism, 1332  
 Astrocytoma, 1085  
 A.T.-10. See *Dihydrotachysterol*.  
 Atabrine. See *Quinacrine*.  
 Ataractics, 206  
 Ataxia, 1074  
 cerebellar, acute, **1103**  
 Friedreich's, 1097  
 hereditary, 1097  
 hysterical, 1068  
 in cerebral palsy, 1138  
 Atelectasis. See *Lungs, collapse*.  
 Athetosis, 1065  
 in cerebral palsy, 1138  
 Athlete's foot, 1291  
 Athrepsia, 352  
 Atonia in cerebral palsy, 1138  
 Atonic diplegia, vs. Werdnig-Hoffmann disease, 1100  
 Atopic dermatitis, **1312-17**. See also *Eczema, infantile*.  
 Atopic erythroderma, 1317  
 Atopic reagin, 1304  
 Atresia, aortic, 854  
 of bile ducts, **714-16**  
 pulmonary, **848**  
 tricuspid, **848**  
 Atrial fibrillation, **885**  
 Atrial flutter, **885**  
 Atrial septal defect, 833-5, **859-62**  
 with pulmonary stenosis, 869, 870  
 with ventricular septal defect, 859  
 Atrioventricular block, 886  
 Atrioventricular canal, common, 861  
 Atropine, as preanesthetic, 229  
 in asthma, 1324  
 in pyloric stenosis, 661  
 ophthalmic, 1331  
 poisoning, 1384  
 skin rash, 1282



- Atropine sulfate, dose, 211  
 Audiogram, 764  
   interpretation, 768  
 Audiometer, 768  
 Auditory. *See* *Hearing*.  
 Aureomycin. *See* *Chlortetracycline*.  
 Auricle, abscess, 762  
   trauma, 762  
 Autism, and tryptophane metabolism, 265-6  
   infantile, 1149  
 Auto-agglutinins re hemolytic anemia, 954  
 Autonomic nervous system. *See* under *Nervous system*.  
 Avertin. *See* *Tribromoethanol solution*.  
 Azotemia, anemia of, 938  
 Azygos lobe, 781
- BABINSKI's sign, 299  
 Bacillary dysentery, 434-7  
 Bacitracin, 211  
   antimicrobial properties, 397  
   dose, 211  
 Bacteria, allergic reaction to, 382  
   cultures of, nasopharyngeal, 204  
   in milk, 121, 122  
   infections by, etiologic diagnosis, 384-97  
 Bacterial pneumonia, 787-92  
 Bacterial test, 384-97  
 Bacteriophage of typhoid bacilli, 441  
 Baker's modified milk, 124  
 BAL. *See* *Dimercaprol*.  
 Balanitis, 1057  
 Balanoposthitis, 1057  
 Balantidiasis, 614  
*Balantidium coli*, 614  
 Ballistocardiography. *See* under *Heart*.  
 Bang's disease. *See* *Brucellosis*.  
 Banthine. *See* *Methantheline*.  
 Banti's syndrome, 986-8  
   vs. kala-azar, 609  
 Barbiturates, 205, 206  
   as preanesthetics, 229  
   dose, 211  
   poisoning, 1384  
   picrotoxin for, 223  
   re agranulocytosis, 964  
   skin rash, 1282  
 Barium salts, poisoning, 1385  
 Basal cell carcinoma, 1362  
 Basal metabolism, 98  
 Basedow's disease. *See* *Goiter, exophthalmic*.  
 Basilar impression, 1228  
 Basophilic adenoma, 1151  
 Basophils, 963  
 BCG vaccine, 463  
 Bednar's aphthae, 301, 633  
 Bee sting, 599  
   re nephrosis, 1044  
 Beetle bite, 599  
 Behavior, disorders, 84-7  
   in celiac disease, 723  
   in pertussis, 422  
   re brain damage, 1143-4  
   re obesity, 354-5  
   evaluation, 67  
   growing pains, 67-72  
   infant, 34  
   preschool period (2-6 years), 36
- Behavior, problems, and prematurity, 312  
   re mental and emotional development, 64  
 Belladonna, alkaloids, as preanesthetics, 229  
   dose, 211  
   in enuresis, 1016, 1018  
   skin rash, 1282  
 Bell's palsy. *See* *Paralysis, facial*.  
 Benadryl. *See* *Diphenhydramine*.  
 Bence-Jones protein, 1019  
 Benodaine. *See* *Piperoxan*.  
 Benzalkonium chloride, in rabies, 515  
   in thrush, 634  
 Benzathine penicillin G, dose, 222  
 Benzedrine. *See* *Amphetamine*.  
 Benzene derivatives, poisoning by, 1385  
 Benzyl benzoate in scabies, 1295  
 Beriberi, 363-5  
 Beta-aminoisobutyric aciduria, 262  
 Beta-2-globulin deficiency, 256  
 Bethanechol chloride for bladder paralysis, 542  
 Bezoar, 664  
 Bial's reagent, 278  
 Bicarbonate, nomogram, 176  
   renal reabsorption, 1008, 1010  
   defective, 1223  
   solution, composition, 197  
   tetany, 1112  
 Bicarbonate-bound base, serum, 1402  
 Bicillin. *See* *Benzathine penicillin G*.  
 Bile, in urine, 1022  
   loss, 195  
   pigments, metabolism, 694, 695, 699  
   salts, re hepatic function, 700  
 Bile ducts, 714-16. *See* also *Gallbladder; Liver*.  
   congenital atresia, 714-16  
   cystic dilatation, 714  
 Bilirubin, clearance, rate, 699  
   test, 699  
   glucuronide, 932  
   hereditary defects, 281  
   in serum, 702  
   in urine, 702  
   increased, in newborn, 334  
   metabolism, 694, 695  
   serum level, 698, 1403  
 Bilirubinemia, increased levels, 933  
 Biopsy, brain, 1073  
   muscle, in neurologic disease, 1073  
 Biotin, 110  
 Birth, injury, 27, 28, 315-23  
   death rates, 7  
   re mental deficiency, 1135  
   weights, 19, 28  
 Bismuth, poisoning, 1385  
   skin rash, 1282  
 Bismuth glycolyarsanilate. *See* *Glycolyarsanilate*.  
 Bite, insect, 598-9  
 Bitot's spots, 362  
 Black water fever, 606  
 Black widow spider, 598  
 Blackheads, 1280  
 Bladder. *See* also *Urinary tract*.  
   "aparasymphathetic," 1026, 1028  
   calculus, 1055  
   in poliomyelitis, 541  
   control, 136  
   cord. *See* *Bladder, paralysis*.  
   diverticula, 1027
- Bladder, dysfunction, primary, 1028  
   exstrophy, 1024  
   foreign body, 1055  
   infant, 32  
   inflammation, 1055  
   neck of, obstruction, 1026, 1028  
   neuromuscular dysfunction, 1026, 1028  
   paralysis, 1026, 1028  
   in poliomyelitis, 541, 542  
   spasm, 1056  
   tumor, 1357  
 Blastomycin skin test, 563  
 Blastomycosis, 562-4  
   disseminate, 563  
   tests, 393  
 Bleeding. *See* also *Hemorrhage*.  
   disorders, 970-82  
   tests, 972  
   time, 1405  
   re cyanosis, 831  
 Bleorrhoea, inclusion, 1338  
 Blepharitis, 1337  
 Blepharospasm, hysterical, 1068  
 Blindness. *See* also *Vision, defects*.  
   in filariasis, 588  
   in osteopetrosis, 1240  
   in porphyria, 280  
   schools for, 1343  
   with myoclonic convulsions, 1102  
 Blood, amino acid nitrogen, 1404  
   ammonia, 1404  
   amylase, 1405  
   carbon dioxide, content, 1403  
   tension, 1403  
   cells. *See* also *Erythrocytes; Leukocytes; Lymphocytes*.  
   formation, 930  
   in newborn, 289  
   in urine, 1012  
   changes, in cardiac disease, 830  
   chemical constituents, 1402-1405  
   circulation, fetal, 839-40  
   in anesthesia, 230  
   in newborn, 30, 288, 289, 840  
   in shock, 181  
   circulation time, in tetralogy of Fallot, 845  
   clotting. *See* *Blood, coagulation*.  
   coagulation, 253, 970-72  
   disturbances, 977-82  
   schema, 254  
   coagulation time, 1405  
   re cyanosis, 831  
   collection, 203-204  
   composition, 197  
   concentration in shock, 182  
   creatinine, 1404  
   disturbances, in newborn, 335-7  
   dyscrasias. *See* also specific dyscrasias, as *Anemia*, etc.  
   vs. cytomegalic inclusion disease, 524  
   vs. diphtheria, 416  
   vs. scurvy, 371  
   electrolytes, levels, 1402-1405  
   formation, in liver, 696  
   iron, 1405  
   labile factor, deficiency, 981  
   lactic acid, 1402  
   lead in, 1376  
   nonprotein nitrogen, 1404  
   oxygen capacity, 1403  
   pancreatic enzymes, 720  
   phosphatase, 1404

- Blood, physical properties, **1402-1405**  
 plasma. See also *Plasma*.  
 acid-base composition, 174  
 electrolyte patterns in disease, 179  
 electrolytes, 174  
 platelets, 971  
 antiplatelet factors in newborn, 976  
 average values, 932  
 in thrombocytopenic purpura, 975  
 re cyanosis, 831  
 pressure, 146  
 arterial, abnormal, 822  
   by age, 822  
   technique, 822  
 high, 894-5  
   in acrodynia, 1399  
   in acute glomerulonephritis, 1037, 1038, 1040, 1042  
   in adrenal hyperplasia, 1186  
   in aldosteronism, 1191  
   in anaphylactoid purpura, 921  
   in Cushing's syndrome, 1190  
   in diabetes mellitus, 1208  
   in hypercalcemia, 1224  
   in hyperthyroidism, 1172  
   in nephrosis, 1046, 1049  
   in pheochromocytoma, 1191  
   in poliomyelitis, 541  
   in pyelonephritis, 1032  
   in renal hypoplasia, 1023  
   in vascular nephritis, 1049  
   reserpine for, 225  
   in anesthesia, 230  
   in newborn, 288, 298  
   low, in poliomyelitis, 541  
   in typhoid fever, 439  
 prothrombin, 253, 254, 971  
 consumption test, 972  
 deficiency, 255, 980-81  
   in galactosemia, 275  
 formation, 696  
 genetic defect in synthesis, 981  
 in vitamin K deficiency, 379  
 level, 698  
 time, plasma, 1405  
   re jaundice, 702  
 serum, albumin in, 1403  
   ascorbic acid, 1405  
   calcium, in tetany, 378  
   chemical constituents, 1402-1405  
   copper, 1405  
   electrolytes, levels of, 1402-1405  
   freezing point, 1405  
   globulin, 1404  
   iron, 1405  
   lead, 1405  
   physical properties, 1402-1405  
   protein, 1403  
     in nephrosis, 1047  
     in nutritional edema, 357  
   transaminases in, 697  
 specific gravity, 1405  
 stable factor, deficiency, 981  
 sulfates, 1402  
 sulfur, 1402  
 thromboplastin, 253, 254, 255, 971, 972  
   antecedent, plasma, 253, 254, 255  
   generation test, 972  
 transfused, composition, 197
- Blood, transfusion, **200-202**  
 cross-matching, 201, 954  
 exchange, 960, 962  
 in intracranial hemorrhage, 318  
 re hemolytic anemia, 954  
 reaction, 202  
   re renal failure, 1050-51  
 typing, 201, 202  
   factors interfering with, 954  
   in lupus erythematosus, 926  
 urea nitrogen, 1404  
 uric acid, 1404  
 venous, collection of, 203-204  
 oxygen saturation, 1403  
 viscosity, 1405  
 volume, in anesthesia, 230  
   in newborn, 288  
   in shock, 181  
 water content, 1403
- Blood vessels, diseases, **902-903**  
 hemostasis, 970-72
- Blount's disease, 1254
- Blue scleras in osteogenesis imperfecta, 1241
- Bockhart's impetigo, 1287
- Body, growth, general pattern, **13-16**  
 measurements, **47-61**  
 proportions, changes, **16-18**  
 types, 43, 44
- Body-rocking, 78
- Bones. See also specific bones, as *Ribs; Spine; etc.*  
 avascular necrosis, 1258  
 changes, in hyperparathyroidism, 1178  
 cyst, unicameral, 1367  
 defects, **1226-49**  
   in anemia, 935  
 development, **20-27**  
   in adolescence, 38, 153-4  
   normal, 372  
 epiphyses. See *Epiphyses*.  
 fibrous dysplasia, 1246  
 hydatid disease, 593  
 in hypercalcemia, 1224  
 in renal hyperparathyroidism, 1179  
 in rickets, **372-7**  
 in scurvy, **368-71**  
 in thalassemia, 947  
 lesions, in Gaucher's disease, 1000  
   in Hand-Schüller-Christian syndrome, 1002  
   in Letterer-Siwe disease, 1003  
   in leukemia, 967, 968  
   in metabolic disorders, **1221-5**  
   in sarcoidosis, 1346  
 marrow, in leukemia, 968  
 ossification centers, time of appearance, 23, 24  
 pain, in leukemia, 966  
 response to stress, 1250  
 tuberculosis, **1261-3**  
 tuberosus sclerosis, 1079  
 tumor, **1365-9**  
   giant cell, 1367  
   malignant, 1368
- Bonnevie-Ullrich syndrome, **1198-1200**
- Booster immunizations, 140, 141, 142
- Borate salts, poisoning, 1385
- Boric acid poisoning, 1385
- Bornholm disease. See *Pleurodynia, epidemic*.
- Boron in nutrition, 107
- Bosses in rickets, 374
- Boston exanthem, 531
- Botulism, **1374**  
 vs. poliomyelitis, 539
- Bowel movements, pattern, 136
- Bowleg, 1254  
 in rickets, 375
- Brachial palsy. See *Paralysis, brachial*.
- Brachydactyly, 1232
- Brachyphalangia, inheritance of, 242
- Bradycardia, 822, **886**  
 in hemorrhage, 943  
 re jaundice, 701, 705
- Brain. See also *Nervous system*.  
 abscess, **1090**  
   in cryptococcosis, 564  
   in typhoid fever, 441  
 angioma, 1080  
 biopsy, 1073  
 calcification, 469  
   in hypoparathyroidism, 1176  
   in pseudohypoparathyroidism, 1177  
 damage, with behavior problems, **1143-4**  
 degenerative disease, **1094-1102**  
 disease, hypertensive, in glomerulonephritis, 1035, 1038, 1040, 1042  
   in anaphylactoid purpura, 921  
 electroencephalogram, 1072, 1120  
 in adrenal insufficiency, 1184  
 in hypoglycemia, 1220  
 in post-traumatic syndromes, 1105  
 glycogen disease, 272  
 lesions, space-taking, **1082-93**  
   vascular, congenital, 1080  
   with precocious puberty, 1159-61  
 stem, glioma, 1085  
   symptoms of disease, 1074  
 telangiectasis, 1081  
 tuberosus sclerosis, 1079  
 tumor, **1084-7**  
   treatment, 1086  
   vs. hypoparathyroidism, 1176  
   vs. tuberculoma, 468
- Brain-injured child, **1143-4**
- Branchial cleft cyst, 639
- Breads in diet, 134
- Breast, abscess, in newborn, 340  
 development, 38, 39  
 engorged, in newborn, 340  
 hypertrophy, 1161, **1198**  
   re adrenal tumor, 1191  
 pigeon, deformity, 1233  
 secretion, in newborn, 30
- Breast feeding. See under *Feeding, infant*.
- Breast milk. See under *Milk*.
- Breath-holding, **78**  
 re convulsions, 1127
- Breathing. See *Respiration*.
- Bremil, 124
- Brill's disease, 553, **557**
- British anti-lewisite. See *Dimercaprol*.
- Bromate poisoning, 1385
- Bromides, dose, 212  
 poisoning, 1385  
 skin rash, 1282
- Bromine in nutrition, 107
- Bromsulphalein test, 700  
 in hepatitis, 705
- Bronchi. See *Bronchus*.



- Bronchiectasis, 808-10  
in influenza, 511  
in pertussis, 422
- Bronchiolitis, acute, 794-6  
capillary, 794-6
- Bronchitis, acute, 785-6  
arachidic, 774  
asthmatic, 1321  
chronic, 786  
death rates, 3  
dust, 799  
in pertussis, 422  
in typhoid fever, 440  
vegetal, 774
- Bronchodilators, 742
- Bronchopneumonia, pneumococcal, 790
- Bronchus. See also *Bronchiectasis*; *Bronchitis*; etc.  
adenoma, 1351  
cyst, 781  
foreign bodies in, 773, 774-7  
lesions, in tuberculosis, 456-7  
malformation, 781  
nomenclature, segmental, 782  
tumors, 1351
- Brucellin, 446
- Brucellin test, 446
- Brucellosis, 445-7  
age factor in, 445  
tests, 391  
treatment, 447
- Bruton's disease, 255-6
- Bruxism, 621, 625
- Buffer systems, 173  
carbonic acid-bicarbonate, 173
- Bullous emphysema, 807
- Bundle branch block, electrocardiogram, 829
- Buphthalmos, 1334
- Burns, 1302-1303  
composition of fluid loss, 195  
eye, 1341  
fluid therapy, 195  
mortality rates, 144  
re hemolytic anemia, 954  
shock in, 181
- Burov's solution. See *Aluminum acetate*.
- Butanol-extractable iodine, 1167, 1168
- Butler's solutions, composition, 197
- Butocaine poisoning, 1386
- CADMIUM poisoning, 1385
- Caffeine with sodium benzoate, dose, 212  
in narcosis, 323
- Caffey's disease, 1260
- Calamine lotion (Schamberg), 1301  
in varicella, 497
- Calciferol, 372
- Calcification, cerebral, 469  
in cryptococcosis, 564  
in toxoplasmosis, 616
- Calcium, deficiency, effects of, 103  
electrocardiogram in, 830  
excess, effects of, 103  
for tetany of newborn, 343  
function, 103  
in adolescence, 154  
in coagulation of blood, 253, 254  
in diet in epilepsy, 1125  
in milk, 121
- Calcium, in oral and parenteral solutions, 197  
in tetany, 378  
ionized, nomogram for, 1407  
metabolism, 105  
plasma level, 105  
re parathyroid, 1175  
requirements, 103, 105, 107, 111  
retention in adolescence, 151, 153  
serum, in nephrosis, 1047  
sources, 103  
storage, in adolescence, 151
- Calcium chloride, dose, 212  
in acute glomerulonephritis, 1040  
in lead colic, 1378  
in tetany in newborn, 343  
in tetany of vitamin D deficiency, 378
- Calcium disodium versenate, dose, 212
- Calcium gluconate, dose, 212  
in acute glomerulonephritis, 1040  
in hypoparathyroidism, 1176  
in lead colic, 1378  
in tetany in newborn, 343  
in tetany of vitamin D deficiency, 378
- Calcium lactate, dose, 212  
in tetany in newborn, 343
- Calculus, in urethra, 1058  
renal, 1054, 1223  
vesical, 1055
- Calf, circumference, annual increments, 14  
roentgenographic measurements, 16
- Caloric value of foods, 1408-1409
- Calories, basal, standard, 193  
for diabetic adolescent, 152  
in milk, 120, 121  
in nutrition, 99  
in oral and parenteral solutions, 197  
intake, reduced, in second year feeding, 132  
requirement, 98-100  
in milk formulas, 125  
of newborn, 290  
second year, 132  
sources, 99
- Camoquin. See *Amodiaquine*.
- Cancer. See also *Neoplasms*; *Tumors*; and specific organ or region.  
death rates, 3, 9
- Cancrum oris, 634
- Candida albicans*, 633  
tests, 387, 388, 393
- Candidiasis, 1293. See also *Moniliasis*.
- Canicola fever. See *Leptospirosis*.
- Cannulation, venous, 199-200
- Capillaries, fragility, in premature, 337  
resistance, in newborn, 288
- Capillary blood, collection, 203
- Captodiamine in behavior problems, 1144
- Caput medusae in cirrhosis, 709
- Caput succedaneum, 315
- Carbarsone, 613, 614
- Carbohydrates. See also *Glucose*.  
function, 99, 101  
in milk, 120, 121, 124, 125, 126, 127
- Carbohydrates, in proprietary milks, 124-5  
malabsorption, in celiac syndrome, 723  
metabolism, errors in, 252, 268-78  
requirements, 99, 101, 111  
source, 99  
tolerance tests, 697-8
- Carbolic acid poisoning, 1391
- Carbon dioxide, content, blood, 1403  
tension, 176  
blood, 1403  
nomogram, 176
- Carbon disulfide poisoning, 1385
- Carbon hydroxide in oral and parenteral solutions, 197
- Carbon monoxide poisoning, 1385  
electrocardiogram in, 830
- Carbon tetrachloride poisoning, 1388
- Carbonic acid, 173
- Carbonic acid-bicarbonate buffer system, 173
- Carbuncle, renal. See *Kidneys, abscess*.
- Carcholin as miotic, 1331
- Carcinoid of intestine, 1351  
endocardial disease in, 894
- Carcinoma, basal cell, 1362  
of ovary, 1358  
of testis, 1357  
of thyroid, 1173  
squamous cell, 1362
- Cardiac. See also *Heart*.  
cycle, schema of, 823  
glycosides, 208
- Cardio-esophageal relaxation, 642
- Cardiospasm, 644  
in newborn, 330
- Cardiovascular system, angiocardioraphy, 836  
in tetralogy of Fallot, 845
- Carditis, in lupus erythematosus, 926  
in periarteritis nodosa, 927  
rheumatic, 907
- Carelessness as factor in emotional development, 70-71
- Caries. See under *Teeth*.
- Carotene, 360
- Carotenemia, in diabetes mellitus, 1208  
in hypothyroidism, 1166
- Carotid sinus reflex, hyperactive, 1128
- Carpopedal spasm, 1113
- Carrier, typhoid fever, 439, 441
- Casal's necklace, 366
- Cascara, dose, 213
- Casac, 125
- Casein, in milk, 120, 121  
re hypoglycemia, 1220
- Castor oil, dose, 213
- Castration, female, preadolescent, 1198
- Cataract, 1333-4  
in arachnodactyly, 1243  
in diabetes mellitus, 1208  
in galactosemia, 275, 276  
in hypoparathyroidism, 1175, 1176  
in myotonic dystrophy, 1268  
in osteopetrosis, 1240  
re German measles, 1333  
re irradiation, 1372  
traumatic, 1334  
zonular, 1334
- Catarrhal stomatitis, 491-2
- Catatonia, hysterical, 1069

- Catatonic dementia praecox, 1149  
 Cat-bite fever. See *Cat-scratch fever*.  
 Cathartics, 208  
   dose, 219  
 Cathomycin. See *Novobiocin*.  
 Cation-anion balance, 174  
 Cation exchange resins, 1042  
   in nephrosis, 1048  
 Cations, mg. and mEq./L., in various salts, 1407  
 Cat-scratch fever, 522-4  
   re thyroiditis, 1171  
   skin test, 523  
 Cavernous sinus thrombosis, 1091  
   in erysipelas, 411  
   in mucormycosis, 565  
 CCA virus, tests, 387  
 Cedilanid. See *Lanatoside C*.  
 Ceepryn solution in herpetic infections, 494  
 Celiac crisis, 723  
 Celiac disease, **721-6**  
   carbohydrate absorption, impaired, 723  
   clinical manifestations, 722-4  
   etiology, 721  
   fat absorption, impaired, 723  
   prognosis, 724  
   starch intolerance, 724  
   tetany, 1111  
   treatment, 724-6  
   vs. allergy, gastrointestinal, 1327  
 Celiac syndrome, **721-30**  
   due to partial intestinal obstruction, 726  
   in giardiasis, 614, 726  
   in intestinal allergy, 726  
   re intestinal lymphatic obstruction, 726  
   re rickets, 1224  
   re vitamin A deficiency, 361  
   vs. megacolon, 676  
 Cellulitis, orbital, 1337  
   vs. erysipelas, 411  
 Centigrade to Fahrenheit temperature, **1413**  
 Centipede bites, 598  
 Cephalhematoma, 316  
 Cephalic zoster, 498  
 Cephalin flocculation, in hepatitis, 705  
   test, 697, 702  
 Cercarial dermatitis, 595  
 Cereal, in diet, 134  
   in infant feeding, 128  
 Cerebellar astrocytoma, 1085  
 Cerebellar ataxia, acute, 1103  
   in varicella, 497  
 Cerebellar symptoms, 1074  
 Cerebellar tumor, 1085  
 Cerebral. See also *Brain*.  
   abscess, 1090  
   angioma, 1080  
   angiomatosis, mental deficiency in, 1131  
   calcification, 469  
   in cryptococcosis, 564  
   in cytomegalic inclusion disease, 524  
   in hypoparathyroidism, 1176  
   in pseudohypoparathyroidism, 1177  
   in toxoplasmosis, 616  
   degeneration, with epilepsy, 1101  
   degenerative disease, **1094-1102**  
   edema, in newborn, 318  
   Cerebral hemispheres, tumors, 1086  
   hemorrhage, in nephritis, 1049  
   lesions, esophagitis with, 643  
   in hypothyroidism, 1167  
   in sickle cell disease, 951  
   vascular, congenital, 1080  
   with coarctation of aorta, 871  
   lipidoses, vs. Werdnig-Hoffmann disease, 1100  
   manifestations, in acute glomerulonephritis, 1036, 1038, 1040, 1042  
   mucormycosis, 565  
   palsy. See *Paralysis, cerebral*.  
   symptoms, 1074  
   telangiectasis, 1081  
   von Gierke's disease, 1095  
 Cerebromacular degeneration, 1094  
 Cerebrospinal fluid, 1082  
   cell count, 1405  
   chemistry, **1405-1406**  
   colloidal gold curve, 1406  
   examination, 1069-71  
   in lead poisoning, 1376  
   physical properties, **1405-1406**  
   pressure, 1070  
   protein, 1070  
   xanthochromic, 1071  
 Ceruloplasmin, deficiency, hereditary, 257  
   in Wilson's disease, 1098  
 Cervical caries re retropharyngeal abscess, 753  
 Cervical cyst, 639  
 Cesarean section, effect on newborn, 294  
 Chalasias, 643  
   in newborn, 330  
   vs. pyloric stenosis, 660  
 Chalazion, 1337  
 Chancre, in sporotrichosis, 567  
   syphilitic, 479  
   tuberculous, 1289  
 Charcot-Marie-Tooth's disease, 1100  
 Chediak-Higashi syndrome, **965**  
 Cheilitis, 634  
 Cheilosis, 365, 634  
 Chelates, in lead poisoning, 1377  
   in poisoning, 1381  
 Chemical poisoning, general considerations, **1378-83**  
 Chemical poisons, **1394-8**. See also specific chemicals.  
   principal poisonous agents, with symptoms and treatment, **1383-94**  
 Chemodectoma, 1348  
 Chemosis, 1332  
 Chenopodium poisoning, 1386  
 Chest. See *Thorax*.  
 Chickenpox, **495-7**  
   and herpes zoster, 494  
   esophagitis in, 643  
   quarantine for, 398  
   résumé, 400  
   tests, 391, 392, 394  
   Chickenpox encephalitis, 550  
 Chigoe infestation, 599  
 Child, as a patient, 10  
   care of, cleanliness, 137-8  
   clothing, 137  
   sleep, 136  
   clinical appraisal, **161-72**  
   eating habits, 133  
   exercise, 137  
   Child, feeding, 132-5. See also *Feeding of children*.  
   habit, development, 135  
   handicapped, 9-10  
   health, conferences, 145  
   hygiene, **135-8**  
   individuality, 10  
   interview with, 166  
   observation of, 166-7  
 Childhood, characteristics, 33-7  
   mortality rates, 6, 9  
   respiratory disorders in, 744  
 Child-parent relationship, 166  
 Chloral, skin rash, 1282  
 Chloral hydrate, 206  
   dose, 213  
 Chloramphenicol, antimicrobial properties, 397  
   dose, 213  
   in influenzal meningitis, 430, 431  
   in pertussis, 423  
   in pneumococcal meningitis, 430  
   in pneumonia in newborn, 328  
   in rickettsial diseases, 555  
   in typhoid fever, 441  
 Chlorguanide in malaria, 608  
 Chloride, acidosis due to, 179, 180  
   deficit, in dehydration, 185, 187  
   in oral and parenteral solutions, 197  
   in sweat, in fibrosis of pancreas, 729  
   test, 729  
   loss, from body fluids, 195  
 Chlorinated insecticides, poisoning, 1386  
 Chlorine, deficiency, effects of, 104  
   excess, effects of, 104  
   function, 104  
   in milk, 121  
   metabolism, 106  
   requirements, 104, 106  
   serum level, 106  
   sources, 104  
 Chlorisondamine chloride, dose, 216  
 Chlorobenzene poisoning, 1386  
 Chloromycetin. See *Chloramphenicol*.  
 Chloroquine, 608, 613  
   in lupus erythematosus, 1290  
   in malaria, 608  
 Chloroquine dihydrochloride in malaria, 607  
 Chloroquine phosphate in amebiasis, 613  
 Chlorothiazide, 897  
   dose, 216  
   for cirrhosis, 710  
 Chlorpromazine, dose, 226  
   in behavior problems, 1144  
   in infantile myoclonic seizures, 1120  
 Chlorprophenpyridamine maleate, dose, 213  
 Chlortetracycline, in herpetic infections, 494  
   ophthalmic, 1331  
 Chlor-Trimeton. See *Chlorprophenpyridamine maleate*.  
 Choanal atresia, 745  
 Cholecystitis. See *Gallbladder, inflammation*.  
 Choledochus cyst, 714  
 Cholelithiasis, 714  
   in sickle cell disease, 951  
 Cholera, immunization, 142



- Cholesterol, formation, 696  
 in hepatitis, 705  
 in hypothyroidism, 1166  
 re jaundice, 702  
 serum, in nephrosis, 1047  
 level, 1403
- Choline, in nutrition, 110  
 re fatty infiltration of liver, 696, 713
- Chondroblastoma, benign, 1365
- Chondrodysplasia, 1245
- Chondrodystrophia calcificans congenita, 1237
- Chondrodystrophy, **1234-9**  
 atypical, 1237-9  
 hyperplastic, 1234  
 prognosis, 1235  
 typical, vs. Morquio's disease, 1238  
 vs. gargoylism, 1239  
 vs. hypothyroidism, 1167  
 vs. osteogenesis imperfecta, 1243  
 vs. rickets, 376, 377
- Chondro-ectodermal dysplasia, 1237
- Chondromyxoid fibroma, 1366
- Chondrosarcoma, 1369
- Chordee, congenital, 1057
- Chordoblastoma, sacrococcygeal, 685
- Chordoma, 1369  
 of nasopharynx, 1348  
 sacrococcygeal, 685
- Chorea, 1065  
 differential diagnosis, 909  
 Huntington's, 1098  
 in typhoid fever, 441  
 Sydenham's, 906  
 treatment, 913
- Chorioepithelioma re gynecomastia, 1198
- Chorion, diseased, and congenital anomalies, 244
- Chorioretinitis, 1342  
 in cryptococcosis, 564  
 in toxoplasmosis, 616
- Choroiditis, syphilitic, 477  
 vs. retinoblastoma, 1342
- Christmas disease, 254
- Christmas factor deficiency, 980
- Chromates, poisoning, 1386
- Chromophobe adenoma, 1151
- Chromosomal sex. See under *Sex*.
- Chromosomes in fertilized ovum, 234
- Chrysarobin in psoriasis, 1286
- Chvostek's sign, 299, 1111
- Chylothorax, **818**  
 in tetralogy of Fallot, 847
- Chylous ascites, 686
- Chyluria, 1020
- Cicatrix, **1277**
- Ciliary body, tumor, 1341
- Circle of Willis, aneurysm, 1080
- Circulation. See under *Blood*.
- Cirrhosis. See under *Liver*.
- Cisternal puncture, 1071
- Citrate mixture, for "base-losing nephritis," 1224
- Citric acid in rachitic bone, 373
- Citrin in nutrition, 111
- Clark's rule, 208
- Clavicle, absence, 1232  
 fracture, in newborn, 321
- Cleaning solutions, poisoning, 1386
- Cleanliness, 137-8
- Cleft lip. See *Harelip*.
- Cleft palate, **628-30**. See also under *Palate*.
- Cleidal dysostosis, 1232
- Cleidocranial dysostosis, 1232
- Climate, effect on growth and development, 41
- Clinical appraisal, **10-11, 161-72**
- Clinical examination, implementation of results, 171-2
- Clinodactyly, 1232
- Clitoris, adherent, 1060  
 malformation, **1060**
- Cloaca, persistent, 1057
- Clostridium tetani*, 432
- Clot; Clotting. See under *Blood*.
- Clothing for infants and children, 137
- Clubbing of fingers, 1248
- Clubfoot, 1253
- Clutton's joints, 437
- Coagulation. See under *Blood*.
- Coal tar for eczema, 1316
- Coal tar paste, 1301
- Coats' disease, 1343
- Cobalt in nutrition, 107
- Cocaine poisoning, 1386
- Coccidioides immitis*, 571, 572
- Coccidioidin test, 572
- Coccidioidomycosis, **571-3**  
 erythema nodosum in, 1300  
 meningitis in, 572  
 serologic test, 572  
 vs. histoplasmosis, 567
- Codeine, dose, 213
- Colace. See *Diocetyl sodium sulfosuccinate*.
- Colchicum autumnale, poisoning, 1389
- "Cold viruses," tests, 387
- Colds, chronic, problem, 756  
 common, 292, 748-50
- Colic, in infant, 131  
 vs. appendicitis, 677
- Coliform bacilli re diarrhea, 655  
 tests, 387, 388, 389, 392, 393, 394
- Coliform infections. See *Escherichia coli infections*.
- Colitis, chronic, **679**  
 ulcerative, 679  
 vs. intussusception, 668
- Collagen diseases, **915-29**. See also *Mesenchymal diseases*.
- Colloidal gold reaction of blood serum test, 697
- Coloboma in arachnodactyly, 1243
- Colon, megacolon, **673-6**  
 aganglionic, 674-6  
 vs. psychogenic, 654  
 classification, 674  
 diagnosis, 675  
 due to anal stenosis, 681  
 psychogenic, 654  
 treatment, 676  
 with megaloureters, 1027
- Color blindness, test, 1330
- Colorado tick fever, tests, 391  
 transmission, 600
- Colostrum, 113
- Comedones, 1280
- Common cold, 292, 748-50
- Community responsibility for health, 10
- Compazine. See *Perchlorperazine*.
- Compulsions, **80**
- Conduct disorders, **84-7**  
 clinical manifestations, 85-6  
 etiology, 84-5  
 prognosis, 86
- Condyloma, syphilitic, 473, 479
- Conferences, health, 145
- Congenital defects, noncardiac, with cardiac lesions, 841  
 re growth and development, 40
- Congenital heart disease, **839-83**. See also *Heart disease, congenital*.
- Congenital hypoplastic anemia, tryptophane metabolism in, 265
- Congenital malformations, **243-7**. See also *Abnormalities*.
- Congo red test, 1345
- Coniine poisoning, 1386
- Conjunctiva, 1332  
 diphtheria, 415  
 examination, 1329  
 hemorrhage, 316, 1332  
 hyperemia, 1332  
 infectious, 1338  
 tumor, 1341  
 vernal catarrh, 1338
- Conjunctivitis, acute, catarrhal, 1338  
 allergic, 1338  
 due to drugs, 1338  
 gonorrheal, 1338  
 herpetic, 493  
 in lymphogranuloma inguinale, 518  
 phlyctenular, 1339  
 re vitamin A, 361
- Constipation, **652-4**. See also *Cathartics*.  
 causes, 653  
 in appendicitis, 677  
 in hypothyroidism, 1165, 1169  
 in infant, 131  
 in newborn, **330**  
 spastic, 654  
 treatment, 653-4
- Contact dermatitis, 1283, 1305
- Convalescent care, **231-3**  
 graded activity, 232
- Convulsions, **1114-28**. See also *Epilepsy*.  
 acute, 1116-17  
 prognosis, 1117  
 treatment, 1116  
 age incidence, 1114  
 causes, 1114-15  
 chronic, 1117-28  
 treatment, 1122-7  
 classification, 1115  
 electroencephalography in, 1120  
 febrile, 1116-17  
 prognosis, 1117  
 hypoglycemic, in newborn, 343  
 hysterical, 1069, 1127  
 in acute glomerulonephritis, 1038, 1041  
 in anaphylactoid purpura, 921  
 in anesthesia, 230  
 in craniosynostosis, 1227  
 in dehydration, 187  
 in exanthema subitum, 489  
 in hypoparathyroidism, 1176  
 in hypothyroidism, 1167  
 in infectious mononucleosis, 519  
 in lead poisoning, 1376, 1378  
 in leontiasis ossea, 1247  
 in malaria, 606

- Convulsions, in meningitis, 428  
   in newborn, 314  
   in pertussis, 422  
   in pleurodynia, 528  
   in pneumonia, 789  
   in poliomyelitis, 541  
   in tetanus, 433  
   in tetany, 378, 1113  
   in toxoplasmosis, 616  
   in tuberculous meningitis, 469  
   myoclonic, 1101, 1119-20  
     infantile, 1119  
   re mental deficiency, 1135  
   roentgenography in, 1121  
   treatment, drug, 1123-5  
     of attack, 1122  
   with hyponatremia, 192  
   with renal failure, 1050  
 Cooley's anemia, 946 9  
 Coombs' test, 201, 202  
   direct, 958  
   indirect, 958  
 Coordination, examination, 1066  
 Copper, deficiency, effects of, 105  
   excess, effects of, 105  
   function, 105, 106  
   in ceruloplasmin deficiency, 257  
   in milk, 121  
   metabolism, 107  
   plasma, in Wilson's disease, 1098  
   plasma level, 107  
   requirement, 105, 107  
   serum, 1405  
   sources, 105  
 Copper sulfate in phosphorus poisoning, 1392  
 Coproporphyrin, in lead poisoning, 1376  
   in urine, 697  
 Cor pulmonale in cystic fibrosis of pancreas, 127  
 Cor triloculare biatriatum, 854  
 Coramine. See *Nikethamide*.  
 Cornea, 1333  
   examination, 1329  
   in herpes zoster, 498  
   infection, 1339  
   opacities, 1333  
   in gargoylism, 1238  
   tumor, 1341  
   ulcer, 1339  
   ultraviolet burns, 1339  
 Coronary arteries, anomalous origin, 877-9  
   calcinosis, 897  
   fistula, 866  
   occlusion, in progeria, 1154  
 Corpus callosum, agenesis, 1075  
 Corrigan pulse, 822  
 Corrosive gastritis, 662  
 Cortef. See *Hydrocortisone*.  
 Cortical hyperostosis, infantile, 1260  
 Corticosteroids, 1181  
   cause of Cushing's syndrome, 1190  
   effect of cessation of, 1182  
   in acute hemolytic anemias, 954  
   in acute viral pericarditis, 901  
   in adrenal hyperplasia, 1189  
   in adrenal insufficiency, 1185  
   in allergy, 1311  
   in anaphylactoid purpura, 922  
   in aplastic anemia, 937  
   in celiac syndrome, 725  
   in cirrhosis, 710  
   Corticosteroids, in craniopharyngioma, 1086  
   in dermatitis venenata, 1283  
   in dermatomyositis, 925  
   in eczema, 1316  
   in encephalitis, 551  
   in erythema multiforme, 1299  
   in esophageal stricture, 644  
   in hemolytic disease of newborn, 960  
   in herpes simplex, 494  
   in hypercalcemia, 1225  
   in hypoglycemia, 1220  
   in hypophosphatasia, 1224  
   in infectious neuritis, 525  
   in Letterer-Siwe disease, 1004  
   in leukemia, 969  
   in lupus erythematosus, 927  
   in lymphosarcoma, 994  
   in nephrosis, 1047, 1048  
   in pancreatitis, 731  
   in psoriasis, 1286  
   in purpura, thrombocytopenic, 976, 977  
   in regional enteritis, 672  
   in rheumatic fever, 912-13  
   in rheumatoid arthritis, 919  
   in sclerema, 1278  
   in scleroderma, 928  
   in serum sickness, 1326  
   in Simmonds' disease, 1154  
   in transverse myelopathy, 1106  
   in tuberculosis, 464, 465, 470  
   in urticaria, 1318  
   in varicella, 497  
   re leukocytosis, 963  
 Corticotropin, 1150, 1151. See also *Adrenocorticotropin*; *ACTH*; *Corticosteroids*.  
   dose, 210  
   effect of cessation of, 1182  
   in hemophilia, 979  
   in myoclonic seizure, 1120  
 Cortisone, dose, 214  
   in adrenal hyperplasia, 1189  
   in dermatomyositis, 925  
   in diphtheria, 419  
   in idiopathic hypercalcemia with growth retardation, 1225  
   in infection, 382  
   in interstitial keratitis, 479  
   in leukemia, 969  
   in meningococcal meningitis, 428  
   in neonatal hepatitis, 335  
   in nephrotic syndrome, 1048  
   in rheumatoid arthritis, 919  
   in virilizing adrenocortical tumor, 1189  
   in Waterhouse-Friderichsen syndrome, 428  
 Cosmetics, poisoning, 1386  
 Cough medicines, poisoning, 1386  
 Cowpox virus, 501  
 Cow's milk. See under *Milk*.  
 Coxa vara in rickets, 375  
 Coxsackie infections, 526-9  
   general considerations, 526-7  
   in newborn, 348  
 Coxsackie virus, diseases due to, 526, 528-9  
   in encephalitis, 549  
   in meningitis, 529  
   in myocarditis, 529  
   in respiratory disease, 746, 747  
   tests, 388, 390, 391, 393  
 "Cradle cap," 1283  
 Cranial nerves, examination, 1064  
 Craniofacial dysostosis, 1228  
 Craniopharyngioma, 1086  
   re dwarfism, 1151  
   re Simmonds' disease, 1154  
 Craniosynostosis, 1226-8  
   in vitamin D-refractory rickets, 1227  
 Craniotabes, in newborn, 296, 338  
   in rickets, 374, 377  
 Cranium. See also *Brain*; *Head*.  
   asymmetry, in rickets, 374  
   fontanels, 31  
   fracture, 1104  
   in newborn, 316  
   re diabetes insipidus, 1155  
   lacunar, 1230  
   molding, in newborn, 296, 316  
   newborn, 29  
   premature synostoses, 1226-8  
   radiologic study, 1071  
   space-taking lesions, 1082-93  
   transillumination, 1067  
   trauma, 1104  
   re diabetes insipidus, 1155  
 Creatine, blood, 1404  
 Creatinine, blood, 1404  
   in urine, 1011, 1014  
   renal clearance, 1008  
 Creeping eruption, 584, 585  
 Creoline poisoning, 1391  
 Creosote poisoning, 1391  
 Cresol poisoning, 1391  
 Cretinism, defective metabolism in, 258  
   familial, 1165  
   goitrous, 1167  
   sporadic, 1165-8  
   vs. chondrodystrophy, 1235  
   vs. gargoylism, 1239  
   vs. mongolism, 1134  
 Crigler-Najjar disease, 703  
 Cross-eye, 1334-7. See also *Strabismus*.  
 Cross-matching. See under *Blood*, *transfusion*.  
 Crotonitron, 1295, 1296  
 Croup, spasmodic, 777  
   viruses in, 747  
   vs. diphtheria, 416  
 Crouzon's disease, 1228  
 Cruelty in mental and emotional development, 70  
 Crush syndrome, 1050-51  
 Cruveilhier-Baumgarten cirrhosis, 709  
 Cryptococcosis, 564  
   tests, 389  
   vs. cytomegalic inclusion disease, 564  
   vs. toxoplasmosis, 564  
 Cryptorchism. See *Testes*, *undescended*.  
 Crystoids Anthelmintic in ascariasis, 578  
 Cubebs, poisoning, 1392  
 Cubitus valgus in gonadal dysgenesis, 1199  
 Curare in tetanus, 434  
 Curd, in milk formulas, 125  
   milk, 121, 122  
 Curling's ulcer, 671  
 Cushing's syndrome, 1189-90  
   re pituitary tumor, 1151  
 Cutaneous blastomycosis, 563  
 Cutaneous diphtheria, 415



- Cutaneous larva migrans, 584, 585  
     in myiasis, 600  
     in strongyloidiasis, 586
- Cutaneous leiomyoma, 1362
- Cutaneous nocardiosis, 566
- Cutis hyperelastica, 974, **1277**
- Cutis laxa, 1277
- Cyanide poisoning, 1386
- Cyanocobalamin, in megaloblastic anemia, 939  
     in nutrition, 111
- Cyanosis, in methemoglobinemia, 282  
     in newborn, 314  
     re bleeding and clotting times, 831
- Cyclogyl. See *Cyclopentolate hydrochloride*.
- Cyclohexane, 1295, 1296
- Cyclopentolate hydrochloride, 1330
- Cycloplegics, 1330, 1331
- Cylindroma, 1362
- Cyst, aneurysmal, of bone, 1367
- choledochus, 714
- dermoid, 1361  
     mediastinal, 1350  
     ovary, 1358  
     sacrococcygeal, 685
- epidermoid, 1361
- in cytomegalic inclusion disease, 784
- liver, 712
- lung, in newborn, 329
- pancreas, **731**
- retention, on gums of newborn, 296
- urachal, 340
- Cystic fibrosis. See *Pancreas, fibrosis, cystic*.
- Cystic hygroma, 1360
- Cystine, metabolic genetic defects, 262-4
- Cystinosis, 263-4  
     re refractory rickets syndrome, 1223
- Cystinuria, 262-3
- Cystitis. See also *Bladder, inflammation*.  
     emphysematosa, 1055
- Cytomegalic inclusion disease, **524**  
     cysts in, 784  
     pathology, 548  
     tests, 390, 391, 392  
     vs. cryptococcosis, 564
- Cytopenia, splenic, 988
- DACRYOADENITIS**, 1337
- Dacryocystitis, acute, 1337  
     congenital, 1337
- Dactylitis, syphilitic, 475  
     tuberculous, 1261
- Dalactum, 124
- Dandy-Walker deformity, 1076
- Daphne poisoning, 1387
- Daraprim. See *Pyrimethamine*.
- Darier's disease, 1277
- Dark adaptation, subnormal, 1330  
     test, 362
- Darnel poisoning, 1387
- Darrow's solution, composition, 197
- Darvon. See *Dextro propoxyphene hydrochloride*.
- Dawdling in emotional development, 70
- Day terrors, 91
- Deaf-mutism, inheritance, 240
- Deafness, **766-70**  
     congenital, 766-7  
     detection, 767-9  
     due to meningitis, 428  
     in Laurence-Moon-Biedl syndrome, 1232  
     in mumps, 507  
     in nephritis, 1042  
     in neurologic disease, 1073  
     in osteogenesis imperfecta, 1241  
     in osteopetrosis, 1240  
     in palatopharyngeal incompetence, 630-31  
     re adenoiditis, 760  
     re cleft palate, 630  
     re German measles, 488  
     re speech development, 92  
     syphilitic, 477  
     with myoclonic convulsions, 1102
- Death, causes of, leading, 3  
     rates, in American countries, 2  
     sudden, re thymus, 998  
     unexpected, **350**
- Debré-de Toni-Fanconi syndrome, 262, 263-4, 1222
- Defects, congenital, effect on growth and development, 40-41
- Deficit therapy with parenteral fluids, **183-92**
- Dehydration, 175  
     deficit therapy, 186, 187  
     electrolyte deficits in, 185  
     hypertonic, treatment, parenteral fluid, 187-8  
     hypotonic, treatment, parenteral fluid, 188  
     in shock, 182  
     isotonic, treatment, parenteral fluid, 187  
     physical signs, 184  
     re allergy, 1305  
     re sclerema, 1278  
     treatment, deficit, 186  
     vs. acute glomerulonephritis, 1039  
     water deficits in, 185  
     with renal failure, 1050
- 7-Dehydrocholesterol, 371, 372
- De Lange's sign, 1067
- Delinquency, **84-7**
- Delirium, acute, 1148
- Deltra. See *Prednisone*.
- Deltrasone. See *Prednisone*.
- Dementia, progressive, 1101, 1102
- Dementia praecox, 1148
- Demerol. See *Meperidine*.
- Demyelinating encephalitides, 550  
     pathology, 548
- Dengue, tests, 391  
     vs. exanthema subitum, 490
- Dental. See *Teeth*.
- Dentin, hereditary opalescent, 620  
     interglobular, 621, 622
- Dentinogenesis imperfecta, 620
- Dentition. See *Teeth*.
- Depressants, central nervous system, 205
- Dercum's disease, 1279
- Dermal sinus, congenital, 1076, 1079
- Dermatitis. See also *Eczema; Urticaria*.  
     atopic, **1312-17**. See also *Eczema, infantile*.  
     cercarial, 595  
     contact. See *Dermatitis venenata*.  
     diaper, **1298**
- Dermatitis, eczematoid, infectious, **1284**  
     seborrheic, **1283**. See also *Seborrhea*.
- Dermatitis exfoliativa neonatorum, 1285
- Dermatitis medicamentosa, **1282**  
     vs. erysipelas, 411
- Dermatitis venenata, 1283
- Dermatofibroma, 1363
- Dermatofibrosarcoma protuberans, 1361
- Dermatomyositis, **922-5**  
     vs. myositis fibrosa, 1266
- Dermatopolyneuritis, **1398-1401**
- Dermorrhesis, 1277
- Dermoid cyst. See under *Cyst*.
- Derris root, poisoning, 1392
- Deslanoside, dose, 214
- Desmoid, 1363
- Desoxycorticosterone, 1181
- Desoxycorticosterone acetate, 1185, 1189  
     dose, 214  
     in Addison's disease, 1185  
     in adrenal hyperplasia, 1189
- D'Espine's sign, 456
- Desserts, 135  
     in infant feeding, 129
- Detergents, poisoning, 1387
- De Toni-Debré-Fanconi syndrome, 262, 263-4, 1222
- Deuterohemophilia, 255
- Development. See also *Growth and development*.  
     dental, 21-7  
     mental and emotional, **62-72**  
     motor, progression of, 64  
     osseous, 20-21  
     physical, **12-56**  
     sensory, 64-5  
     skeletal. See *Development, osseous*.  
     speech, 65
- Devil's gripe. See *Pleurodynia, epidemic*.
- Dexedrine. See *Dextro-amphetamine*.
- Dextran, in nephrosis, 1048  
     solutions, composition, 197
- Dextrinosis, limit, 271
- Dextro-amphetamine sulfate, 206  
     dose, 214  
     in behavior problems, 1144
- Dextrocardia, isolated, **855**  
     with situs inversus, **855**
- Dextro propoxyphene hydrochloride, dose, 214
- Diabetes insipidus, **1155-7**  
     clinical manifestations, 1156  
     differential diagnosis, 1156  
     etiology, 1155  
     in Hand-Schüller-Christian syndrome, 1002  
     nephrogenic, 261, 1156  
     Pitressin-resistant, 1156  
     posterior pituitary for, 223
- Diabetes mellitus, **1205-13**  
     acidosis, 179, 180, 1207, 1209  
     deficit therapy, 186, 189  
     treatment, parenteral fluid, 189-90  
     water and electrolyte deficits, 185  
     cataracts, 1333  
     chemical changes, 1207  
     clinical manifestations, 1206

- Diabetes mellitus, complications, 1207  
 diagnosis, 1207  
 diet, 1209-10  
   calculation, **1409-11**  
 etiology, 1205  
 in adolescence, 152  
 in fibrosis of pancreas, 728  
 incidence, 1205  
 insulin, **1210-13**  
 mucormycosis in, 565  
 pathologic physiology, 1205  
 pathology, 1206  
 prognosis, 1208  
 re pancreatitis, 731  
 transient, in newborn, 343  
 treatment, 1208-13  
   general considerations, 1213  
   vitamin A deficiency in, 360  
   vs. lead poisoning, 1376
- Diabetes mellitus syndrome in newborn, **1213**
- Diabetic acidosis. See *Diabetes mellitus, acidosis*.
- Diabetic women, infants of, 1214
- Diagnostic studies, laboratory, 170-71
- Diamox. See *Acetazolamide*.
- Diaper rash, **1298**
- Diaphragm, eventration, 693  
 hernia, 692
- Diaphysal aclasis, 1244
- Diarrhea, acidosis, 179, 180  
 acute, treatment, parenteral fluid, 187  
 amebic, 611  
 antibiotic-induced, 656  
 bacillary dysentery, 434-7  
 chronic, treatment, parenteral fluid, 189  
 composition of fluid loss, 195  
 death rates, 3  
 deficit therapy, 186, 187-9  
 due to ECHO viruses, 531  
 due to irradiation, 1372  
 etiology, 655  
 in acrodynia, 1399  
 in adrenal hyperplasia, 1188  
 in allergy, gastrointestinal, 1327  
 in celiac syndrome, 723, 724, 725  
 in children, 656  
 in histoplasmosis, 568  
 in hyperthyroidism, 1172  
 in infants, 656  
 in megacolon, 674, 675  
 in newborn, 315, **346**, 347, 655  
 in peritonitis, 687  
 in pertussis, 422  
 in regional enteritis, 672  
 in strongyloidiasis, 586  
 in ulcerative colitis, 679  
 mild, 657  
   treatment, parenteral fluid, 189  
   prevention, 658  
   re infant feeding, 130  
   re parenteral infections, 656  
   re sclerema, 1278  
 Salmonella, 443  
 severe, 657  
 treatment, general considerations, 188-9  
 water and electrolyte deficits, 185, 187
- Diarrheal disorder, **655-8**  
 diagnosis, 657
- Diastematomyelia, 1076
- Dibucaine poisoning, 1386
- Dick test, 405
- Dicoumarin poisoning, 1394
- Dicumarol, 973  
 re hypoprothrombinemia, 379
- Diet. See also *Food; Nutrition*.  
 basic, 133  
 calculation, method, **1409-11**  
 daily, 111  
 elimination, **1412**  
 for obesity, 356  
 history, 134  
 in diabetes mellitus, 1209-10  
 in establishment and maintenance of milk supply, 116  
 proper, 143  
 re dental caries, 625  
 re liver function, 696  
 requirements in adolescence, 151-2  
 self-selection in second year, 132  
 socio-economic factors, 111
- Diethylcarbamazine, 589  
 dose, 218
- Diethylene glycol poisoning, 1383
- Dietl's crisis, 1028, 1030
- Digestibility, in nutrition, 111  
 of milk, 122
- Digestion, in newborn, 289, 290  
 of milk, 121, 122
- Digestive disturbances, **647-58**  
 of newborn, 330-35
- Digitalis, in cardiac failure, 897  
 in glomerulonephritis, 1041  
 leaf, dose, 215  
 poisoning, 1387  
 skin rash, 1282  
 toxicity, 898
- Digitoxin, dose, 215  
 in cardiac failure, 897, 898  
 in glomerulonephritis, 1041
- Digoxin, dose, 215  
 in cardiac failure, 897, 898
- Dihydrotychsterol, in hypoparathyroidism, 1176
- Diiodohydroxyquinoline, 613
- Diiodotyrosine in thyroxine, 1163
- Dilantin. See *Diphenylhydantoin sodium*.
- Dimenhydrinate, dose, 216
- Dimercaprol, 1381  
 dose, 211  
 for chemical poisoning, 1381  
 in acrodynia, 1400  
 in arsenic poisoning, 1384  
 in lead poisoning, 1377  
 in mercury poisoning, 1390
- Dimethylaniline poisoning, 1383
- Dimethylsulfate poisoning, 1387
- Dinitro-ortho-cresol poisoning, 1387
- Dinitrophenol re cataracts, 1333
- Diocetyl sodium sulfosuccinate, dose, 216
- Diodoquin. See *Diiodohydroxyquinoline*.
- Diodrast. See *Iodopyracet*.
- Diphenhydramine hydrochloride, dose, 212
- Diphenyl, chlorinated, poisoning, 1389
- Diphenylhydantoin sodium, dose, 215  
 in epilepsy, 1123, 1124  
 re megaloblastic anemia, 940
- Diphtheria, **411-20**  
 antitoxin, 418  
   desensitization to, 419  
 carrier, management, 418  
 complications, 416
- Diphtheria, cutaneous, 415  
 death rates, 3  
   by age, 412  
 diagnosis, 415  
 differential diagnosis, 415  
 epidemiology, 412  
 esophagitis, 643  
 etiology, 411  
 faucial, 413  
 floccules, 418  
 immunity, 412  
   in newborn, 292  
 immunization, 139-40, 141  
   active, 418  
 laryngotracheal, 415, 419  
 myocarditis, 893  
 nasal, 415  
 paralysis in, 413, 417  
 prevention, 417  
 prognosis, 417  
 quarantine, 398  
 re chronic rhinitis, 756  
 résumé, 400  
 Schick test, 412, 414  
 tests, 387  
 toxin, 412  
 toxin-antitoxin, 418  
 toxoid, 418  
 treatment, 418  
 vaccine, 139-40, 141  
 vs. scarlet fever, 408
- Diphtheritic laryngitis, differential diagnosis, 778, 779
- Diphyllobothriasis, **591-2**  
 anemia, 592  
 eosinophilia, 592  
 epidemiology, 591
- Diplomyelia, 1076
- Disabilities, chronic, control of progression, 144-5
- Disaccharide metabolism, defective, **273**
- Discipline in mental and emotional development, 70
- Disease, detection, 145-7  
 mortality rate from, 143  
 prevention, 138-47  
   primary, 138-44  
   secondary, 144-5
- Disseminated sclerosis, 1096
- Distillates, solvent, poisoning, 1388
- Distribution curve, normal, 18
- Dithiazanine, in strongyloidiasis, 587  
 in trichocephaliasis, 582
- Diuretics, mercurial, in cardiac failure, 897
- Diuril. See *Chlorothiazide*.
- Diverticulitis, Meckel's, 669-71  
 of intestine, 669
- Diverticulosis, of intestine, 669
- Diverticulum, Meckel's, 669-71
- DOCA. See *Desoxycorticosterone acetate*.
- Dolichostenomelia, 1243
- Dominant traits, 235-8
- Donath-Landsteiner test, 1022
- Donnan effect, 1005
- Dorothy Reed cell, 994
- Doses, calculation, 208  
 drugs, table, **210-26**
- Douche, lactic acid, in nongonorrheal vulvovaginitis, 1060
- Downey cells, 519, 520
- Doxinate. See *Diocetyl sodium sulfosuccinate*.
- Dracontiasis, 589



- Dracunculosis, 589  
 Dramamine. See *Dimenhydrinate*.  
 Dreams, 90  
   terrifying, 90  
 Drepanocytosis, 949-52  
 Drugs. See also specific drugs.  
   administration, routes of, 209, 227  
   analgesics, 206  
   antifungal agents, 207  
   antihistaminics, 207  
   antimicrobial agents, proper use, 207  
   antipyretic, 206  
   cardiac glycosides, 208  
   cathartics, 208  
   central nervous system depressants, 205  
   central nervous system stimulants, 206  
   choice of, 205  
   classes, general, 205-208  
   dosage, based on surface area, 208  
     Clark's rule, 208  
     Fried's rule, 208  
     table of, **210-26**  
     Young's rule, 208  
   emetics, 208  
   eruptions, 1282  
   in premature infant, 311  
   poisoning, general considerations, **1378-83**  
   poisons, alphabetical list, **1394-8**  
     principal poisonous agents, with symptoms and treatment, 1383-94  
   preanesthetic, 229  
   prescription, 209  
   rashes, 1282  
     vs. exanthema subitum, 490  
     vs. German measles, 488  
     vs. measles, 486  
     vs. scarlet fever, 408  
   re agranulocytosis, 964  
   re nonthrombocytopenic purpura, 974  
   reactions, of gingivae, 632  
   therapeutic use, **205-27**  
     general considerations, 205  
     specific considerations, 205-27  
 Dryco, 124  
 Dubin-Johnson syndrome, 703  
 Duchenne-Erb's paralysis, 318-20  
 Ductus arteriosus, patent, 833-5, **863-6**  
   complications, 865  
   differential diagnosis, 865  
   in infancy, 864  
   with coarctation of aorta, 873  
   with ventricular septal defect, 858  
 Duodenum, intubation, 719  
   obstruction, 665  
     alkalosis, 179, 180  
     vs. pyloric stenosis, 660  
   ulcer. See *Peptic ulcer*.  
 Dural sinus thrombosis, 1091  
 Duroziez's sign, 891  
 Dust bronchitis, 799  
 Dusting powder, 1301  
 Dwarfism, in celiac syndrome, 723  
   in chondrodystrophy, 1234-6  
   in diabetes mellitus, 1208  
   in gargoylism, 1238  
   in Laurence-Moon-Biedl syndrome, 1232  
   Dwarfism, in osteopetrosis, 1240  
   in pseudohypoparathyroidism, 1177  
   Lévi-Lorain type, 1151  
   pituitary, 343, **1151-4**  
   primordial, 1152  
   rachitic, 375  
   renal, 1179-80  
   with gonadal dysgenesis, 1199  
 Dye dilution curves in cardiac catheterization, 833, 836  
 Dye test, for toxoplasmosis, 617  
   for ventricular-spinal obstruction, 1071  
 Dyschondroplasia, 1244, 1245  
 Dysentery. See also *Diarrhea*.  
   bacillary, **434-7**  
   epidemiology, 435  
   etiology, 435  
   treatment, 437  
   death rates, 3  
   vs. scurvy, 371  
 Dysgerminoma, 1358  
 Dysostosis, mandibulofacial, 1247  
 Dysostosis multiplex, 1238  
 Dysphagia, in Caffey's disease, 1260  
   re fetal postural deformity, 1250  
 Dysplasia of bone, 1246  
 Dysproteinemia, familial idiopathic, 253  
 Dysrhythmism, 1076  
 Dystonia, 1065  
 Dystonia musculorum deformans, 1098  
 EAR, **762-6**. See also *Deafness; Hearing*.  
   canal, foreign body, 762  
   drum, perforation, 763  
   lop, 762  
   malformations, 762  
   newborn, 29  
 Eating, 136. See also *Diet; Feeding; Food*.  
   disorders, **88**  
   habits, 133  
 Ebstein's disease, **852**  
 Echondrosis ossificans, 1244  
 Echinococcosis, 592  
 Echinococcus cyst of pancreas, 731  
 ECHO virus, diseases due to, 526, **529-31**  
   in encephalitis, 549  
   in respiratory disease, 746, 747  
   meningitis, 531  
   rashes due to, 526, 530, 531  
   test, 387, 388, 390  
 Ecolid. See *Chlorisondamine chloride*.  
 Ectasia, posterior, 1333  
 Ecthyma, **1288**  
 Ectodermal dysplasia, 1079-80  
   congenital, 1276  
 Ectodermoses, congenital, 1131  
 Ectomorph, 43, 44  
 Ectopia cordis, **856**  
 Ectromelia, 1230  
 Ectropion, 1332  
 Eczema, dehydration, 1311  
   in older child, 1313  
   infantile, **1312-17**  
     clinical manifestations, 1312  
     elimination diets, 1308, 1316, 1412  
     etiology, 1312  
 Eczema, infantile, hyposensitization in, 1309, 1316  
   treatment, local, 1315  
     nonspecific, 1311, 1317  
   nummular, 1313  
   re infant feeding, 114  
   re vitamin A deficiency, 361  
 Eczema herpeticum, 491  
 Eczema vaccinatum, 504  
 Eczematoid dermatitis, infectious, 1284  
 Edathamil, dose, 212  
   in lead poisoning, 1377  
   in poisoning, 1381  
 Edema. See also *Ascites*.  
   genital, in newborn, **1058**  
   in galactosemia, 275  
   in nephrosis, 1045  
   in newborn, **342**  
   in syphilis, 474  
   nutritional, 356  
   pulmonary, **807**  
 EDTA. See *Edathamil*.  
 Education, health, **145-7**  
   sex, 71-2, 158-9  
 Effusion, subdural, 1089  
 Eggs, in children's diet, 134  
   in infant feeding, 129  
 Ehlers-Danlos syndrome, 974, 1277  
 Eisenmenger syndrome, 833-5, **849-51**  
 Electrocardiogram. See under *Heart*.  
 Electroencephalogram. See under *Brain*.  
 Electrolytes, concentrations, disturbances in, treatment, parenteral fluid, 191-2  
   deficits, in dehydration, 185, 187  
   equilibrium, disturbances, **172-81**  
     Gamble chart, 174  
     in acidosis and alkalosis, 175-80  
     in dehydration, 175  
     physiologic considerations, 172  
   in sweat in fibrosis of pancreas, 727, 729  
   losses, abnormal, 195-6  
     urinary, 196  
     per calories metabolized, 193  
     mg. and mEq./L. per millimol of various salts, 1407  
   plasma, variations in disease, 179  
   requirements, 194  
     per 100 calories, 193  
 Elephantiasis, 588, 589, 990  
 Elimination, pattern, 136  
 Elimination diets, **1412**  
 Elliptocytosis, 952  
 Ellis-van Creveld syndrome, 1237  
 Ellsworth-Howard test, 1177  
 Embden-Meyerhof glycolytic pathway, 269, 277  
 Embolism, **902-903**. See also *Thrombosis*.  
   in diphtheria, 417  
   pulmonary, **808**, 903  
 Embryonic age factors, 26  
 Embryonic period, characteristics, 27  
 Emetics, 208  
 Emetine, for amebic abscess, 613  
   in liver fluke infections, 597  
 Emotional development, **62-72**  
   characteristics, **65**  
   environmental factors, 62  
   growing pains, 67-72  
   hereditary factors, 62  
   in adolescence, 156-60

- Emotional development, play in, 71  
 prophylaxis, 69  
 re learning, 64  
 role of pediatrician, 67-72  
 sex education, 71  
 training in, 70
- Emotional disturbance, re enuresis, 1017  
 re obesity, 355
- Emphysema, **805-807**  
 bullous, 781, 784, 807  
 in pneumonia, 791  
 compensatory, 805  
 eyelids, 1341  
 in influenza, 510  
 in pertussis, 422  
 in tuberculosis, 456  
 interstitial, 806  
 lobar, in newborn, **329**  
 obstructive, 805-807  
 acidosis in, 179, 180  
 generalized, 806  
 in bronchiolitis, 795  
 lobar, congenital, 805-806  
 localized, 805  
 pathogenesis, 775  
 pulmonary function, 736  
 subcutaneous, 807
- Empirin compound, 206
- Empyema, in diphtheria, 417  
 in influenza, 511  
 in pneumonia, 789  
 pleural, 815-16  
 putrid, 816
- Enamel, tooth. See under *Teeth*.
- Encephalitic viruses, test, 390
- Encephalitis, **547-52**. See also *Encephalomyelitis*; *Meningo-encephalitis*.  
 alkalosis in, 179, 180  
 arthropod-borne viruses, 548, 549  
 clinical manifestations, 547-8  
 demyelinating, 550  
 due to bacillary dysentery, 435, 436  
 epidemiology, 551  
 etiology, 549  
 herpetic, 493  
 in brucellosis, 446  
 in cat-scratch fever, 522  
 in German measles, 488  
 in infectious mononucleosis, 519  
 in measles, 486  
 in mumps, 507  
 in pertussis, 422  
 in pleurodynia, 528  
 in toxoplasmosis, 617  
 in typhoid fever, 441  
 in varicella, 497  
 influenzal, 511  
 myalgic, benign, 550  
 pathology, 547-8  
 postinfectious, 550  
 postvaccinal, 504, 551  
 re diabetes insipidus, 1155  
 re obesity, 355  
 subacute sclerosing, 552  
 treatment, 551  
 vs. lead poisoning, 1376  
 vs. poliomyelitis, 539
- Encephalitis periaxialis diffusa, 1096
- Encephalocele in nose, 745
- Encephalomyelitis, in Chediak-Higashi syndrome, 965  
 postvaccinal, 504  
 progressive, 1096
- Encephalopathy. See also *Brain, disease*.  
 lead, 1376-8
- Encephalo-trigeminal angiomas, 1080
- Enchondroma, 1365
- Encopresis, **654**
- Endarteritis with patent ductus arteriosus, 865
- Endocarditis, acute, **888**  
 bacterial, subacute, **888-9**  
 in brucellosis, 446  
 in lupus erythematosus, 926  
 in meningococcemia, 428  
 in scarlet fever, 409  
 rheumatic, **889-92**
- Endocardium, cushion defects, 861-2  
 diseases of, **888-92**  
 with carcinoid of intestine, 894  
 sclerosis, 895, 896  
 re unexpected death, 350  
 with ventricular septal defect, 859
- Endocrine disturbances re obesity, 354-5
- Endocrine factors re growth and development, 40
- Endocrine function of newborn, 291-2
- Endocrine system, disturbances of, in newborn, **343-4**
- Endomorph, 43, 44
- Endophthalmitis, 1339
- Enophthalmos, 1332
- Entamoeba histolytica, 610
- Enteric fever. See *Typhoid fever*.
- Enteritis. See also *Gastroenteritis*.  
 regional, **671-2**  
 tuberculous, 468
- Enterobiasis. See *Oxyuriasis*.
- Enterobius vermicularis, 579
- Enterococcus infections, tests, 392
- Enterokinase, 719
- Enteroviruses, in encephalitis, 549  
 infections by, **526-44**  
 tests, 388
- Entropion, 1332
- Enuresis. See *Urine, incontinence*.
- Environment, prenatal, 242  
 re congenital malformations, 244, 245  
 re growth and development, 40  
 re heredity, 236  
 re mental and emotional development, **62**
- Eosinophil, 963
- Eosinophilia, 963  
 in toxocariasis, 579  
 in trichinosis, 587  
 tropical, **602**
- Eosinophilic granuloma, **1004**
- Eosinophilic pituitary adenoma, 1151, 1155
- Eosinophilic pneumonia, 801
- Ependymoma, 1085
- Ephedrine, in asthma, 1323  
 poisoning, 1383  
 skin rash, 1282
- Ephedrine sulfate, dose, 216
- Epidemic influenza, **508-11**
- Epidemic myalgia, 528
- Epidemic parotitis. See *Mumps*.
- Epidemic typhus, 553, **555-6**
- Epidermoid cyst, 1361
- Epidermolysis bullosa, **1275**
- Epididymitis, **1059**
- Epididymo-orchitis in mumps, 506, 507
- Epidural hematoma, 1089
- Epidural (spinal cord) abscess, 1106
- Epigastric hernia, 692
- Epiglottitis, deformities with stridor, 771
- Epiglottitis, acute, 778-80
- Epilation due to irradiation, 1372
- Epilepsy, **1117-28**. See also *Convulsions*.  
 akinetic seizures, 1120  
 diet therapy, 1125  
 disorders simulating, 1127  
 electroencephalography, 1120  
 focal, 1118, 1119  
 grand mal, 1118  
 idiopathic, 1117  
 Jacksonian, 1118, 1119  
 ketogenic diet, 1125  
 myoclonic, infantile, 1119, 1120  
 organic, 1118, 1119  
 petit mal, 1119  
 prognosis, 1126  
 psychomotor seizure, 1119  
 re cranial injury, 1105  
 re migraine, 1128  
 re recurrent vomiting, 649  
 roentgenography, 1121  
 treatment, 1122-7  
 drug, 1123-5  
 general, 1122  
 of attack, 1122  
 with cerebral degeneration, 1101
- Epilepsy syndrome and cerebral degeneration, 1101
- Epinephrine, 1182. See also *Adrenol*.  
 dose, 216  
 in asthma, 1323  
 in conjunctivitis, 1338  
 in epistaxis, 746  
 in hypoglycemia, 1220  
 in reactions to hypersensitization, 1310  
 in vernal catarrh, 1338  
 tolerance test, 1219
- Epinephrine hydrochloride, dose, 216
- Epiphora, 1332
- Epiphyses, age of fusion, 24  
 age of ossification, 22-4  
 dislocation, in scurvy, 368-70  
 dysgenesis, in hypothyroidism, 1166  
 slipped, 153, 1257
- Epispadias, 1057
- Epistaxis. See *Nose, hemorrhage*.
- Epithelioma, calcifying, 1361
- Epithelioma adenoides cysticum, 1362
- Epsom salt. See *Magnesium sulfate*.
- Epstein's pearls, 296
- Eplis, 1349
- Equanil. See *Meprobamate*.
- Erb's muscular atrophy, 1270
- Erb's paralysis, 318-20
- Erb's sign, 1111
- Ergosterol, 372
- Ergot poisoning, 1387
- Ergothioneine in hypoglycemia, 267
- Erysipelas, **410**
- Erysipeloid lesions in nephrosis, 1046
- Erythemas, **1298-1301**
- Erythema annulare, 908
- Erythema arthriticum epidemicum, 481



- Erythema circinata, 1299  
 Erythema induratum vs. erythema nodosum, 1300  
 Erythema marginatum, 908  
 Erythema multiforme, 908, **1299**  
   in coccidioidomycosis, 571  
 Erythema nodosum, **1300**  
   in coccidioidomycosis, 571  
   in rheumatic fever, 908  
 Erythema toxicum, **338**  
 Erythredema, **1398-1401**  
 Erythremia, **962**  
 Erythroblastic anemia, 946-9  
 Erythroblastosis fetalis. See *Hemolytic disease of newborn*.  
 Erythrocine. See *Erythromycin*.  
 Erythrocytes, average values, **931-2**  
   life span, **932**  
   physiology, 930  
   sedimentation rate, 1405  
   in acute glomerulonephritis, 1037  
   test, 697  
 Erythrocytosis, **962**  
 Erythroderma, atopic, 1317  
 Erythroderma desquamativum, **1284**  
   vs. eczema, 1314  
 Erythrogenesis imperfecta. See *Anemia, aplastic*.  
 Erythromycin, antimicrobial properties, 397  
   dose, 217  
 Erythropoiesis, 931  
 Erythropoietic porphyria, 279-80  
 Erythropoietin, 931  
*Escherichia coli*, infections, in newborn, **344**, 346  
   re diarrhea, 655  
   re unexpected death, 350  
   test, 387, 388, 389, 392, 393, 394  
 Eserine salicylate as miotic, 1331  
 Esophagitis, 643  
 Esophagogastritis in thrush, 634  
 Esophagus, **639-47**  
   anomalies, 640-43  
   atresia, 640-42  
   in newborn, 330  
   vs. intestinal obstruction, 666  
   compression, external, 642  
   embryology, 640  
   examination, 639  
   foreign bodies, 645, 646  
   hemorrhage, treatment, 988  
   measurements, 639  
   neurogenic dysfunction, 642  
   perforation, 745  
   relaxation of cardia, 642  
   short, 642  
   spasm, 644  
   stenosis, 642  
   stricture, corrosive, 643  
   corticosteroids for, 644  
   Salzer technique, 644  
   varices, 645  
   control of bleeding, 710  
   in cirrhosis, 710  
 Espundia, 608  
 Essenamaine, 125  
 Esters, poisoning, 1387  
 Estrogens, 1182, 1193. See also specific preparations.  
   excretion, 1194  
   therapy, re gynecomastia, 1198  
 Ethers, poisoning, 1387  
 Ethyl alcohol poisoning, 1383  
 Ethylene chlorohydrin poisoning, 1389  
 Ethylene glycol poisoning, 1383  
 Ethylenediamine-tetra-acetic acid. See *Edathamil*.  
 Eucatropane as mydriatic, 1331  
 Eumydrin in congenital hypertrophic pyloric stenosis, 661  
 Eunuchoid syndromes, **1195-7**  
 Eunuchoidism, hypogonadotropic, 1196  
 Eurax. See *Crotamiton*.  
 Eustace Smith's sign, 456  
 Ewart's sign, 899  
 Ewing's tumor, 1368  
 Examination, physical, 167-70  
 Exanthem, Boston, 531  
 Exanthema subitum, **489-90**  
   vs. German measles, 488  
   vs. measles, 486  
   vs. scarlet fever, 408  
 Exchange transfusion, 960, 962  
 Exercise, 136  
   in menstrual irregularities, 155  
 Exercise test in cardiac disease, 838  
 Exophthalmic goiter, 1172  
 Exophthalmos, 1332  
   in Hand-Schüller-Christian syndrome, 1002  
   in leontiasis ossea, 1247  
 Exostosis, multiple, **1244**  
   inheritance, 235, 236  
   vs. Ollier's disease, 1244  
 Extrasystoles, **883**  
 Extremity, congenital absence of, 1230  
   fracture, in newborn, 321  
 Eyeball in filariasis, 588  
 Eyelids, 1332  
   edema, 1332  
   emphysema, 1341  
   examination, 1329  
   infection, 1337  
   lacerations, 1340  
   seborrhea, 1337  
   tumors, 1341  
 Eyes, **1329-44**. See also *Blindness; Conjunctiva; Retina; Vision*.  
   burns, 1341  
   care, in newborn, 303  
   cellulitis, 1337  
   in mucormycosis, 565  
   changes, in diabetes mellitus, 1208  
   defect, in craniosynostosis, 1227  
   in gonadal dysgenesis, 1199  
   examination, 146, **1329-31**  
   of newborn, 1329  
   foreign body, 1340  
   fundal examination, 1330  
   hygiene, 1343  
   in herpes simplex, 493  
   in riboflavin deficiency, 365  
   infections, **1337-40**  
   tests, 393  
   injury, **1340**  
   lesions, in brucellosis, 445  
   in Niemann-Pick disease, 1000  
   muscles, paralysis, in diphtheria, 417  
   newborn, 29, **1329**  
   disturbances, 340  
   strained, re television, 1343  
   therapeutic agents, 1331  
   tuberous sclerosis, 1079  
   tumor, **1341**  
 FACE. See also *Head; Jaws; Lips; Mouth; Nose*.  
   asymmetry, 628  
   bones, deformity, in leontiasis ossea, 1246  
   effects of mouth-breathing, 627  
   newborn, 29  
   paralysis, 1108  
   in leontiasis ossea, 1247  
   in newborn, 320  
   in otitis media, 765  
 Facial nerve paralysis, 632  
 Facies, in hypercalcemia, 1224  
   in renal agenesis, 337  
 Fahrenheit to Centigrade temperature, **1413**  
 Fainting. See *Syncope*.  
 Fallopian tubes, diseases, **1062**  
 Familial cirrhosis with glycogenosis, 270  
 Familial dysautonomia, 1107  
 Familial hyperlipemia, 278  
 Familial idiopathic dysproteinemia, 253  
 Familial periodic paralysis. See under *Paralysis*.  
 Family, interview, 165  
   re emotional development, 62  
 Fanconi-de Toni-Debré syndrome, 262, 263, 264, 1222  
 Farber test, 665  
 Farsightedness, 1331  
   test for, 146  
 Fasting, acidosis, in, 179, 180  
   deficit therapy in, 186  
 Fat. See also *Lipids; Obesity*.  
   absorption, Lipidol test, 720  
   digestion of, poor, 720-21  
   in diet, 134  
   in milk, 120, 121  
   in nutrition, 100, **102**  
   in proprietary milks, 124-5  
   in stool, test for, 720  
   malabsorption, 721  
   in celiac disease, 723  
   in fibrosis of pancreas, 729  
   metabolism, in liver, 696  
   necrosis, subcutaneous, of newborn, 1278  
   requirements, 102, 111  
   tolerance test, 720  
 Fatty acids, essential, 102  
 Fatty degeneration of liver, 713  
 Fatty infiltration of liver, 696, 713  
 Fava beans, poisoning, 1383  
   re glutathione defect, 264-5  
   re anemia, 953  
 Favism, 264-5, 953, 1383  
 Favus, **1293**  
 Fear, **81**  
   in emotional development, 67  
   prevention, 81-2  
   treatment, 81-2  
 Feces, bloody, 652  
   breast- vs. artificially fed infant, 114  
   carbohydrate, 652  
   curdy, 652  
   fat, 651  
   green, 652  
   infant, 130  
   mucous, 651  
   newborn, 30, 290  
   normal, **650**  
   of breast milk, 651  
   of cow's milk, 651  
   preservation, for amebic study, 612

- Feces, soap, 651  
 test, for fat, 720  
 for starch, 720  
 trypsin in, 719
- Feeble-mindedness re speech development, 92
- Feeding, infant, **112-35**. See also *Infant feeding*.  
 of children, 132-5  
 snacks, 133  
 of newborn, 304  
 of premature infant, 309-11  
 re emotional development, 65  
 thickened, in pyloric stenosis, 661
- Feer's disease, **1398-1401**
- Ferrous sulfate, 941-2  
 dose, 217  
 poisoning, 1389
- Fetal hemoglobin, 275, 286, 930
- Fetal period, characteristics, 4, 26, 27
- Fetus, abnormalities, 243  
 anoxia, 321  
 circulation, 839-40  
 deaths, 286  
 cause, 306  
 endocarditis, 895-6  
 infection, 243  
 injuries, 242  
 peritonitis, 689  
 posture, re deformities, 1250-52  
 respiration, 28
- Fever, in acrodynia, 1399  
 in diabetes insipidus, 1156  
 in ectodermal dysplasia, 1276  
 in newborn, 315  
 transitory, newborn, **342**
- Fever blister, 635
- Fibrin, disorders, 982
- Fibrinogen, 971  
 disorders, 982  
 formation, 696  
 hereditary absence, 254  
 plasma, 1403  
 level, 101
- Fibrinolysis in hemorrhagic disorder, 982
- Fibroelastosis, 895, 896
- Fibrolipoma of larynx, 773
- Fibroma, 1363  
 chondromyxoid, 1366  
 juvenile aponeurotic, 1363  
 nonosteogenic, 1366  
 osteogenic, 1366
- Fibromatosis, congenital, generalized, 1363  
 of plantar fascia, 1363
- Fibrosarcoma, of bone, 1369  
 of soft tissues, 1364
- Fibrous dysplasia, of bone, 1246  
 with precocious puberty, 1159
- Fièvre boutonneuse, **559**
- Filaria in tropical eosinophilia, 602
- Filariasis, **588**  
 epidemiology, 574, 588  
 Hetrazan for, 218
- Fingers, clubbing of, 1248  
 hereditary, 1248  
 hypertrophy of, 1232
- Fish poisoning, 1388
- Fissure in ano, **682**
- Fistula, anal, 681, **684**  
 arteriovenous, **902**  
 cerebral, 1081  
 between mouth and ear, 632  
 preauricular, 762  
 rectal, 681, **684**
- Flatfoot, 1252
- Flea, infestation, 599  
 vector of disease, 600
- Fluids. See also *Milk; Water*.  
 and electrolytes, disturbances, **172-81**  
 clinical, 175-80  
 body, composition of external losses, 195  
 equilibrium, physiologic considerations, 172  
 parenteral, administration, 198-202  
 requirements, in infant feeding, 125, 127  
 therapy, in poisoning, 1382  
 in renal failure, 1051  
 parenteral, **183-202**  
 deficit, **183-92**  
 for abnormal losses, **195**  
 maintenance, **192-5**  
 supplemental, 196, **198**
- Flukes. See also *Schistosomiasis*.  
 infection, **593-8**  
 epidemiology, 574, 596, 597  
 intestinal, 596  
 liver, 596  
 lung, 597
- Fluorescein in eye abrasions, 1341
- Fluorescein solution, ophthalmic, 1331
- Fluoride poisoning, 1388
- Fluorine, deficiency, effects of, 104  
 excess, effects of, 104  
 for dental caries, 626  
 function, 104, 106  
 requirements, 104  
 sources, 104, 106
- Fluoroacetate poisoning, 1388
- Fluoroscopy, roentgen doses in, 1371
- Fly as cause of disease, 600
- Fly amanita, poisoning, 1390
- Folic acid, in megaloblastic anemia, 940  
 in nutrition, 111
- Fölling's disease, 259-60
- Fontanels, skull, 31
- Food. See also *Diet; Feeding; Nutrition*.  
 availability, 111  
 caloric value, **1408-1409**  
 composition, **1408-1409**  
 goitrogenic, 1170  
 poisoning, **1374-5**  
 chemical, 1374  
 cyanide, in silver polish, 1374  
 insecticides, 1374  
 Salmonella, 442, 443, **1375**  
 staphylococcal, **1374**  
 streptococcal, **1375**  
 trichinosis, 587  
 solid, in infant feeding, 128
- Foot, normal, 1252  
 pronation, 1252  
 split, 1231
- Foramen ovale, patent, 859-62
- Foramina of Luschka and Magendie atresia of, 1076
- Foreign body, and bronchiectasis, 809  
 in bladder, 1055  
 in bronchus, 773, 774-7  
 in ear canal, 762  
 in esophagus, 645-6  
 in eye, 1340  
 in intestine, 663  
 in larynx, 773-4  
 in nose, 745, 756
- Foreign body, in stomach, 663  
 in trachea, 773, 774  
 in urethra, 1058  
 in vagina, 1060, 1062  
 vs. nasal diphtheria, 416
- Formaldehyde poisoning, 1388
- Formula, Holz's, in galactosemia, 276
- Formulary, ocular, 1331  
 skin diseases, 1301
- Fractured incisors, 628
- Fractures. See also under specific bones.  
 in newborn, 321  
 in osteogenesis imperfecta, 1241  
 in osteopetrosis, 1240  
 in rickets, 375
- Franceschetti-Klein syndrome, 632
- Freckles, **1277**
- Fredet-Ramstedt operation, 661
- Fredjka splint, 1255
- Frei test, 518
- Freiberg's disease, 1258
- Frenum of tongue, ulceration, 637
- Friedländer's bacillus, in pulmonary abscess, 810  
 pneumonia, 793
- Fried's rule, 208
- Friedreich's ataxia, 894, 1097
- Frölich's syndrome, 355, 1162
- Frostbite, **902**
- Fructose, intolerance, with hypoglycemia, 274  
 metabolism, 274  
 tests for, 273
- Fructosuria, acquired, 273  
 essential, 273
- Fruits, in diet, 134  
 in infant feeding, 128
- Fuadin. See *Stibophen*.
- Fungizone. See *Amphotericin B*.
- Fungus infections, **562-73**  
 etiologic diagnosis, **384-97**  
 myocarditis in, 893  
 of skin, **1291-4**  
 pulmonary, 798  
 tests, 384-97
- Funnel chest, 1234
- Furadantin. See *Nitrofurantoin*.
- Furunculosis, **1288**
- Fusospirochetal infections, tests, 393
- GALACTOSE, metabolism, 275  
 tolerance test, 698
- Galactosemia, **274-6**  
 cataracts in, 1334  
 hypoglycemia in, 1217
- Galactosuria, **1020**
- Gallbladder, **714**. See also *Bile ducts*.  
 anomalies, 714  
 inflammation, 714  
 in typhoid fever, 440
- Gametes in fertilized ovum, 234
- Gamma globulin, deficiency, 255-6  
 dose, 217  
 in agammaglobulinemia, 256  
 in complications of smallpox vaccination, 505  
 in German measles, 489  
 in hepatitis, 706, 707  
 in lupus erythematosus, 926  
 in measles, 486, 487  
 in mumps, 507  
 in nephrosis, 1047



- Gamma globulin, in newborn, 253-4  
 in pertussis, 423  
 in pneumonia in newborn, 328  
 in premature, 312  
 in scarlet fever, 410  
 in thyroiditis, 1171  
 levels, 383  
 serum, 1403  
 source, 381
- Ganglioneuroma, 1356
- Gangrene, gas, tests, 394  
 in acrodynia, 1399  
 in diabetes mellitus, 1207  
 pulmonary, 812
- Gangrenous pancreatitis, 730
- Gantrisin. See *Sulfisoxazole*.
- Gargoylism, 268, 1238  
 myocardial involvement, 896  
 vs. hypothyroidism, 1167  
 vs. Morquio's disease, 1238
- Gas gangrene, tests, 394
- Gases, partial pressures, **739**
- Gasoline poisoning, 1388
- Gastric. See also *Stomach*.  
 replacement solution, 197  
 ulcer. See *Peptic ulcer*.
- Gastritis, acute, 662  
 corrosive, 662  
 infectious, 662
- Gastroenteritis. See also *Food, poisoning*.  
 death rates, 3, 9  
 due to *Salmonella*, 442, 443  
 vs. appendicitis, 677
- Gastrointestinal allergy, **1326-8**
- Gastrointestinal infection, test, 388
- Gaucher's disease, **999-1000**  
 chronic, 1000  
 infantile form, 999
- Gavage, gastric, 204
- Gee-Herter disease, **721-6**
- General factors in care of sick children, **161-233**
- Genes, dominant, 235  
 expressivity, 236  
 in fertilized ovum, 234  
 lethal, 242  
 parental incompatibilities, 238  
 penetrance, 236  
 recessive, 235, 238  
 sex-linked, 240  
 symbols for, 235
- Genetic defect re hemolytic anemia, 953
- Genetic factors, in prenatal disturbances, **234-42**  
 in rickets, 372  
 multiple, 241
- Genetics re obesity, 355
- Genitals. See also *Genitourinary system*; *Gonads*; *Penis*; *Vulva*.  
 edema, in newborn, 1058  
 growth, 15  
 herpes simplex, 492  
 in newborn, 299
- Genitourinary system, **1005-62**  
 disturbances, in newborn **337-8**  
 infections, tests, 392
- Genotype, 235
- Gentian violet. See *Methylosaniline*.
- Genu recurvatum, congenital, 1254
- German measles. See *Rubella*.
- Giant cell pneumonia, 797
- Giardia lamblia*, 613
- Giardiasis, **613-14**  
 re celiac disease, 726
- Gigantism, pituitary, **1154-5**
- Gilbert's disease, 281, 702
- Gilles de la Tourette's disease, 83
- Gill's sign, 1257
- Gingiva, biopsy, in amyloidosis, 1345  
 diseases, **632**
- Gingivitis, 632
- Gingivostomatitis, herpetic, 491-2
- Glaucoma, **1334**  
 secondary, 1334  
 to staphyloma, 1333  
 with refractory rickets (Lowe), 1223
- Gliadin tolerance test, 722
- Glioma, of brain stem, 1085  
 of optic chiasm, 1080, 1086
- Globulin. See also *Gamma globulin*.  
 antihemophilic (AHG), 253, 254, 255  
 (beta-2), deficiency, 256  
 plasma, 1404  
 serum, 1404  
 re jaundice, 702
- Glomerular filtration, 1006, 1013
- Glomerulonephritis. See *Nephritis, glomerular*.
- Glomerulosclerosis in diabetes mellitus, 1208
- Glomus tumor, 1359
- Glossina flies, vectors of disease, 600
- Glossitis, 636  
 Hunter's, 637
- Glossoptosis in hypoplasia of mandible, 631
- Glucagon in hypoglycemia, 1216, 1218
- Glucocorticoids, 1181
- Glucocorticosteroids in hypoglycemia, 1220
- Glucose, in parenteral solutions, 197  
 metabolism, 268-9, 1216  
 reabsorption, renal, 1007  
 defective, 261  
 test, 1014  
 tolerance test, intravenous, 1219  
 oral, 698
- Glucose-6-phosphate, dehydrogenase, deficiency of, 265  
 re hemolytic anemia, 265
- Glucuronic acid, 698  
 re bilirubin, 332
- Glucuronide, 695, 698, 932  
 synthesis, 281
- Glutamine in celiac disease, 721, 722
- Glutathione, defective metabolism, **264-5**  
 in hypoglycemia, 267  
 in leukemia, 968  
 reduced, in hemolytic anemia, 953  
 stability test, 953
- Gluten in celiac disease, 721, 723, 725
- Glycerol monoacetate in fluoroacetate poisoning, 1388
- Glycine, genetic metabolic defect, 262  
 in cystinosis, 264
- Glycinuria, simple, 262
- Glycobiarsol in amebiasis, 613
- Glycocol in urine, 1012
- Glycogen, formation, 269  
 liver content, 102  
 muscle content, 102
- Glycogen disease, **268-73**  
 classification, 272  
 of heart, 271
- Glycogen disease, of liver and muscle, 271  
 of skeletal muscle, 272  
 myocardial involvement, 896  
 storage, cerebral, 1095  
 hepatic, hypoglycemia in, 1218
- Glycogenesis, 102
- Glycogenolysis, 102
- Glycogenosis with cirrhosis, 270
- Glycols, poisoning, 1383
- Glycolysis, 102
- Glycosides, cardiac, 208
- Glycosuria, **1019-20**. See also *Diabetes mellitus*.  
 alimentary, 1020  
 and amino-aciduria, 262, 264  
 and phosphaturia, 262, 264  
 differential diagnosis, 1207  
 in acromegaly, 1155  
 in cystinosis, 264  
 in lead poisoning, 1376  
 in nephrosis, 1047  
 renal, 261, 1020  
 with refractory rickets, 1222
- Gnats, vectors of disease, 600
- Goat's milk, 123, 125
- Goiter, **1169-71, 1172**  
 congenital, 1171  
 endemic, 1169  
 exophthalmic, 1172  
 iatrogenic, 1170  
 iodine-deficient, 1169  
 re cobalt, 1170  
 re iodide therapy, 1170, 1171  
 re para-aminosalicylic acid, 1170  
 re resorcinol, 1170  
 sporadic, 1170  
 toxic, 1172
- Goitrogenic foods, 1170
- Goitrous cretinism, 1167
- Gold poisoning, BAL for, 211
- Gonadotropic follicle-stimulating hormone, 1194
- Gonadotropic hormone, 1150
- Gonadotropin, for cryptorchism, 1059  
 urinary, 1150
- Gonads. See also *Ovary*; *Testes*.  
 disorders, **1193-1203**  
 dysgenesis, female, 1198-1200  
 in pituitary dwarfism, 1153
- Gonococcal infections, tests, 392, 393
- Gonorrheal conjunctivitis, 1338
- Gonorrheal vulvovaginitis, 1060
- Gout, 261
- Graefe's sign, 1172
- Graham-Steell murmur, 850, 891, 892
- Grand mal epilepsy, 1118
- Granulocytes, 963
- Granuloma of umbilicus, 341
- Granulosa cell tumor, 1201
- Graphs of growth, 45-7
- Grasp reflex, 299
- Graves' disease, 1172
- Greenfield's disease, 1095
- Grocco's triangle (sign), 814
- Growing pains, 908  
 in emotional development, 67-72
- Growth, adolescence, 37-8  
 adolescent patterns, 148-50  
 and development, activity factors, 41  
 characteristics during age periods, **27-39**

- Growth, and development, climatic factors, 41  
 endocrine factors, 40  
 environmental factors, 40  
 evaluation, 42-61  
 factors affecting, **39-42**  
 general considerations, 12  
 heredoconstitutional factors, 39  
 metabolic factors, 40  
 physical, **12-56**  
 racial factors, 40  
 re congenital defects, 40  
 re illness, 41  
 re malnutrition, 41  
 re prematurity, 40  
 sex factors, 40  
 traumatic factors, 42  
 variations, 18-20, 39-42  
 annual increments, 14  
 body as a whole, **13-16**  
 body proportions, changes in, **16-18**  
 failure, with hypercalcemia, 1224  
 general, 15  
 genital, 15  
 graphs, 45, 46  
 lymphatic system, 15  
 measurements, **47-61**, 146  
 muscular, 15, 16  
 nature of, 150-51  
 neural, 15  
 osseous, **20-27**  
 school period (6-12 years), 36  
 subcutaneous tissue, 15, 16
- Growth hormone. See *Somatotropin*.
- Guanatol. See *Chlorgananide*.
- Guanidine tetany, 1111
- Guarnieri bodies, 499
- Guillain-Barré syndrome, 525  
 vs. poliomyelitis, 539
- Gumma, 476, 477
- Gums, abscess, lateral, 632  
 boil, 632  
 diseases, **632**  
 epulis, 1349  
 myoblastoma, 1349  
 periapical infections, 626  
 retention cysts, 296
- Gynecomastia. See *Breast, hypertrophy*.
- HABIT spasms. See *Tics*.
- Habits, eating, 133  
 elimination, 136  
 formation, 135  
 picking, **78**  
 sleep, 136
- Hageman factor (HF), 253, 254, 255  
 deficiency, 255
- Hair, disturbances of, 1281  
 in kwashiorkor, 359  
 newborn, 29  
 sexual, premature, 1161
- Hairball in stomach, 664
- Hamartomas, 1347
- Hand, split, 1231
- Handicapped child, general considerations, 9, **1145-7**  
 treatment, **1145-7**
- Hand-Schüller-Christian syndrome, **1002**  
 re diabetes insipidus, 1155  
 re dwarfism, 1152
- Haptoglobin deficiency, 256
- Harelip, **628-9**
- Harlequin color change, 295
- Harrison spot test, 706
- Harrison's groove, 375
- Hartnup disease, 267  
 vs. pellagra, 267
- Hashimoto's struma, 1171
- Haverhill fever, 481
- Hay fever, **1319-21**  
 hyposensitization, 1310
- Head. See also *Brain; Cranium; Face; Neck*; etc.  
 asymmetry, in rickets, 374  
 circumference, annual increments, 14  
 birth to 5 years, percentiles, 56-7  
 infant, 31  
 graph, 45  
 measuring technique, 49  
 infant, 31
- Headache, **87**. See also *Migraine*.  
 in neurologic disease, 1073  
 psychosomatic illness, 87  
 re intracranial pressure, 1082
- Health, community responsibility, 10  
 physical, problems of, 157-8  
 school, 145
- Health conferences, 145
- Health education, 145-7
- Hearing. See also *Ear*.  
 conservation, 769  
 development, 65  
 disorders, 93  
 re language function, **93**  
 examination, 1064  
 impaired, 766-70  
 detection, 146, 767-9  
 in neurologic disease, 1073  
 re torticollis, 1265  
 in newborn, 65  
 loss, prevention, 769
- Heart, **819-914**  
 angiocardiology, 836  
 anomalies, re German measles, 488  
 area, determination of, 826  
 arrest, in poliomyelitis, 541  
 arrhythmias, **883-7**  
 in poliomyelitis, 541  
 auscultation, 820  
 ballistocardiography, 838  
 block, **886**  
 congenital, complete, 887  
 in cardiac surgery, 881  
 with ventricular septal defect, 859  
 catheterization, 831-6; 900  
 blood oxygen content, 834  
 dye dilution curves, 833, 836  
 formulas for hemodynamics, 833  
 in tetralogy of Fallot, 833-5, 844  
 normal values, 833  
 pressures obtained by, 835  
 disease, arterial oxygen saturation in, 833-5  
 congenital, **839-83**  
 anomalous pulmonary venous return, 874  
 aortic arch, anomalies, 877-9  
 aortic atresia, 854  
 aortic stenosis, 875  
 aorticopulmonary septal defect, 866  
 arteriography in, 837  
 atrial septal defect, 859-62  
 coarctation of aorta, 870-74  
 dextrocardia, 855
- Heart, disease, congenital, diagnosis, 841  
 diverticulum of left ventricle, 856  
 Ebstein's disease, 852  
 ectopia cordis, 856  
 etiology, 841  
 fistula of coronary artery, 866  
 in arachnodactyly, 1243  
 in mongolism, 1134  
 incidence, 840  
 levocardia with situs inversus, 855  
 Lutembacher syndrome, 860  
 mitral stenosis, 876  
 patent ductus arteriosus, 863-6  
 postoperative complications, 881  
 pulmonary arteriovenous fistula, 855  
 pulmonary atresia, 848  
 pulmonary stenosis, 866-70  
 re German measles, 488  
 ruptured sinus of Valsalva, 866  
 single ventricle, 854  
 tetralogy of Fallot, 842-8  
 transposition of great vessels, 833-5, 851-2  
 treatment, principles of, 880-81  
 surgical, 880  
 tricuspid atresia, 848  
 truncus arteriosus, 853  
 with craniosynostosis, 1227  
 with cyanosis, **842-56**  
 with little or no cyanosis, **856-83**  
 death rates, 3, 9  
 hematologic variants, 830  
 in fibrosis of pancreas, 727  
 in scarlet fever, 409
- electrocardiogram, 826-30  
 abnormal patterns, 827-30  
 duration of systole, 829  
 in acute glomerulonephritis, 1038  
 in bundle branch block, 829  
 in Friedreich's ataxia, 1097  
 in hyperkalemia, 827, 830  
 in hypocalcemia, 830  
 in hypokalemia, 830  
 in hypoparathyroidism, 1176  
 in left ventricular hypertrophy, 829  
 in pericarditis, 900  
 in rheumatic fever, 910  
 in right ventricular hypertrophy, 828  
 in Wolff-Parkinson-White syndrome, 885  
 normal, 827  
 P wave in abnormal conditions, 827  
 prolongation of P-R interval, 828  
 Q-T interval, 829  
 S-T segment and T wave abnormalities, 830  
 enlargement. See *Heart, hypertrophy*.  
 examination, 819-39  
 extrasystoles, 883  
 failure. See *Heart, insufficiency*.  
 fluoroscopy, 825



- Heart, glycogen disease, 271-2  
hypertrophy, idiopathic, 896  
in sickle cell disease, 951  
in acute glomerulonephritis, 1036, 1038, 1041  
in beriberi, 364, 365  
in diphtheria, 416  
in gargoylism, 1238  
in hyperthyroidism, 1172  
in lupus erythematosus, 926  
in mucormycosis, 565  
in muscular dystrophy, 1269, 1270  
in newborn, 297  
in periarteritis nodosa, 927  
in rheumatic fever, 890-92, 907  
inspection, 819  
insufficiency, congestive, 825  
in acute glomerulonephritis, 1041  
in cardiac surgery, 881  
in diphtheria, 416  
in hyperthyroidism, 1172  
in nephritis, chronic, 1049  
pulmonary, function in, 736  
re congestion of liver, 700  
treatment, 897  
vs. acute glomerulonephritis, 1039  
murmur, accidental, 821  
ejection systolic, 820  
functional, 821  
Graham Steell, 850, 891, 892  
innocent, 821  
regurgitant systolic, 820  
venous hum, 821  
neoplasms, **1350**  
orthodiagraphy, 826  
palpation, 819  
percussion, 819  
phonocardiography, 837  
premature contractions, 883  
rates by age, 821  
rhythm, 822  
roentgenographic examination, 824-6  
schema of, 824  
roentgenokymograms, 837  
sinus arrhythmia, 822  
size, measurements, 826  
sounds, 820  
tamponade, 899, 900  
telerentgenograms, 826  
thrill, 819  
topography, 824  
tuberous sclerosis in, 1079  
tumors, **1350**  
use of exercise test, 838  
Heat prostration in fibrosis of pancreas, 728  
Hecht's giant cell pneumonia, 797  
Height, adolescence, 37-8  
annual increments, 14  
birth to 6 years. See under *Length*.  
5-18 years, percentiles, **52-5**  
measuring technique, 48  
preschool period (2-6 years), 33  
re menarche, 149, 150  
school period (6-12 years), 36  
sitting, 16  
percentiles, **60-61**  
2-13 years, graph, 46  
Heller's disease, 1101  
Helminthic infections, epidemiology, 574  
Hemadsorption virus, 747  
Hemangioma, bone, 1367  
cavernous, of skin, 1359  
giant, with thrombocytopenia, 977  
newborn, 29  
skin, 1358  
Hemangiopericytoma, 1359  
Hemarthrosis in hemophilia, 978  
Hematologic variants in cardiac disease, 830  
Hematoma, epidural, 1089  
subdural, chronic, in infants, 1087-9  
Hematoma ex vacuo, 1088  
Hematopoiesis, 930  
Hematuria, and deafness, 1042  
causes, 1020, 1039  
in leptospirosis, 480  
in leukemia, 966  
in purpura, 974  
Hemianopsia, 1073  
Hemicrania, 1128  
Hemihypertrophy, **1248**  
Hemimelia, 1231  
Hemiplegia, hysterical, 1068  
in pertussis, 422  
in progeria, 1154  
in syphilis, 476  
infantile, acute, **1103**  
Hemivertebrae, 1233  
Hemoconcentration. See *Blood, concentration*.  
Hemoglobin, abnormal, 257  
with hemolytic anemias, 952  
buffer system, 173  
concentration, in anesthesia, 230  
defective synthesis of, **257**  
degradation, 932  
fetal, 257, 286, 930  
in methemoglobinemia, 282  
metabolism, 694, 695  
values, 19  
at various ages, 1403  
average, 931-2  
Hemoglobin M, 282  
in methemoglobinemia, 282  
Hemoglobinuria, causes, 1021  
cold, 1022  
march, 256-7  
paroxysmal, 1022  
cold, 954  
nocturnal, 1022  
Hemolytic anemia. See under *Anemia*.  
Hemolytic disease, due to A or B incompatibilities, 961  
due to Rh incompatibility, 956  
of newborn, **955-62**  
breast feeding in, 115  
diagnosis, 958, 959  
exchange transfusion, 960  
prevention, 139  
prognosis, 959  
re inspissated bile syndrome, 334  
treatment, 960-61  
vs. cytomegalic inclusion disease, 525  
Hemolytic jaundice. See under *Jaundice*.  
Hemolytic reaction due to blood transfusions, 954  
Hemophilia, 254-5, **977-80**  
antithromboplastin in, 971  
vascular, 254, 980  
Hemophilia A, 254-5, 977-80  
diagnosis, 978  
treatment, 978-80  
Hemophilia B, 254-5, 980  
Hemophilia C, 255, 980  
*Hemophilus influenzae*, in laryngeal infections, 778-80  
laboratory tests, 387, 389  
pneumonia, 793  
*Hemophilus pertussis*, 420  
Hemorrhage, adrenal, in newborn, 320  
anemia due to, 943-4  
cause of death, in premature, 308  
conjunctival, 1332  
due to irradiation, 1372  
gastric, 663  
genital, **1062**  
in leukemia, 966  
in newborn, **336**  
in peptic ulcer, 671  
in pertussis, 422  
in premature infant, 289  
in scurvy, 368-71  
intestinal, in allergy, gastrointestinal, 1327  
intracranial, in newborn, 316-18  
Meckel's diverticulum, 669  
pulmonary, in newborn, 959  
re cirrhosis, 709  
re hypochromic anemia, 941  
re neurologic disease, 1077  
re shock, 181  
re unexpected death, 351  
retrobulbar, 1332  
transplacental, 335  
from fetus, 943  
umbilical, 341  
Hemorrhagic cystitis, 1055  
Hemorrhagic diatheses, defects of synthesis of plasma proteins in, 253  
Hemorrhagic disease of newborn, 336  
Hemorrhagic disorder due to fibrinolysins, 982  
Hemorrhagic pancreatitis, 730  
Hemorrhagic phenomena in hepatitis, 705  
Hemorrhoids, **684-5**  
re cirrhosis, 709  
Hemosiderosis, pulmonary, 801-802  
Hemostasis, defects, in small vessels, **973-7**  
classification, 973  
vascular, **970-72**  
Hemothorax, **818**  
Henoch-Schönlein's purpura, vs. appendicitis, 677  
vs. intussusception, 668  
Heparin, 973  
dose, 217  
Hepatic. See also *Liver*.  
amebiasis, 611, 612, 613  
trematodiasis, 596  
Hepatitis, due to Coxsackie virus, 527  
from blood transfusion, 202  
gamma globulin for, 217, 706, 707  
in infectious mononucleosis, 519  
in typhoid fever, 440  
infectious, **704-707**  
treatment, 707  
vs. serum homologous, 706  
neonatal, 334, 706, 715-16  
plasma cell, 710  
serum, **704-707**  
syphilitic, 474

- Hepatocellular. See *Liver, cells*.  
 Hepatolenticular degeneration, 257, 1098  
 Hepatoma, 1352  
 Hepatomegaly. See *Liver, hypertrophy*.  
 Hepatosplenomegaly, due to vitamin A, 363  
   in gargoylism, 1238  
   in hyperlipemia, 278  
   in osteopetrosis, 1240  
 Hereditary hyperuricemia, 261  
 Hereditary spastic paraplegia, 1097  
 Heredity, chromosomes in, 234, 235  
   dominant traits in, 235-8  
   environment and, in mental and emotional development, 62-3  
   environmental effects, 236  
   genes in, 234-5  
   genetic factors in, 241  
   heterozygosity in, 235  
   homozygosity in, 235  
   in disease, **234-42**  
   in mental and emotional development, **62**  
   in metabolic diseases, 250-85  
   incompatibilities of parental genes, 238  
   lethal traits, 242  
   mendelian pattern, 235-41  
   modification, 236  
   pedigree chart, 237  
   re congenital anomalies, 244  
   re obesity, 355  
   recessive traits, 238-40  
     sex-linked, 240  
   "skipping" of generation, 236  
   teratogenic factors in, 245  
 Heredo-constitutional factors re growth and development, 39  
 Hermaphroditism, **1202**  
   true, 1203  
 Hernia, **690-93**  
   diaphragmatic, 692  
   epigastric, 692  
   incisional, 692  
   inguinal, 690-91  
     incarcerated, 691  
   intra-abdominal, 686  
   umbilical, 341  
     in chondrodystrophy, 1235  
     in gargoylism, 1239  
     in hypothyroidism, 1166  
 Hernia cerebri, 1083  
 Herpangina, 528  
   tests, 393  
 Herpes febrilis, 490  
 Herpes iris, 1299  
 Herpes labialis, 490, 635  
 Herpes simplex, **490-95**  
   encephalitis, pathology, 548  
   epidemiology, 493  
   general features, 493-4  
   in newborn, 493  
   lips, 635  
   meningoencephalitis, 493  
   mucous membranes, 491-2  
   ocular lesions, 493  
   pathology, 493  
   primary, 490  
   re eczema, 491  
   re encephalitis, 549  
   recurrent, 490  
   tests, 390-94 *passim*  
   traumatic, 491  
 Herpes simplex, vs. cytomegalic inclusion disease, 525  
   vs. diphtheria, 416  
 Herpes simplex progenitalis, 492  
 Herpes zoster, **497-8**  
   and varicella, 494  
   encephalitis, pathology, 548  
   re encephalitis, 549  
   tests, 390, 393, 394  
   vs. pleurisy, 813  
 Herpesvirus *hominis*, 490  
 Herpesvirus *simii*, in encephalitis, 548, 550  
 Herpesvirus *varicellae*, 495  
 Herpetic gingivostomatitis, 491-2  
 Herpetic stomatitis vs. herpangina, 528  
 Heterophile antibody test, 519  
 Heterophobia, 1334  
 Heterotropia, **1334-7**. See also *Strabismus*.  
 Hetrazan. See *Diethylcarbamazine*.  
 Heubner-Herter disease, 721-6  
 Hexose, metabolism, defective, **273**  
 Hexylresorcinol, dose, 218  
 Hexyresorcinol crystalloids, 578, 582  
 Hip, dislocation, congenital, 1255  
   in arachnodactyly, 1244  
   dysplasia, congenital, 1254  
   infection, 1256  
   subluxation, 1254  
   synovitis, 1256  
   trauma, 1256  
   tuberculosis, 1262  
 Hippuric acid test, 700  
 Hi-Pro, 124  
 Hirschsprung's disease, 674-6  
 Hirst and Hare test, 509  
 Hirsutism, male type, with amenorrhea, 1201  
 Histaminase in serum sickness, 1326  
 Histamine in pheochromocytoma, 1192  
 Histidine, requirements, 101  
*Histoplasma capsulatum*, 567, 569  
   culture, 570  
 Histoplasmin test, 570  
 Histoplasmosis, **567-71**  
   differential diagnosis, 570  
   tests, 391  
 History, 162-7  
   dietary, 134  
   in allergy, 1306  
   in neonatal pediatrics, **293-5**  
   in neurologic disease, 1063  
   in planning deficit parenteral fluid therapy, 183  
   in psychotherapy, 74  
   medical, 42, **162-7**  
   outline, **162-4**  
 Hives. See *Urticaria*.  
 Hodgkin's disease, **994-5**  
   cryptococcosis in, 564  
   vs. cat-scratch fever, 523  
   vs. histoplasmosis, 571  
   vs. regional enteritis, 672  
 Holz's formula in galactosemia, 276  
 Homatropine as mydriatic, 1331  
 Homogentisic acid, 258, 259  
 Homozygous, 235  
 Hookworm infection, 583-5  
   epidemiology, 574, 583  
   re hypochromic anemia, 941  
   treatment, 585  
 Hoover's test, 1068  
 Hordeolum, 1337  
 Hormones, adrenocorticotrophic,  
   dose, 210  
   antidiuretic, 1151, 1155-7  
   gonadotropic, 1194  
   oxytocic, 1151  
   pituitary, 1150-51  
   sex, 154  
 Horner's syndrome, 1333  
   in tetralogy of Fallot, 847  
 Horse serum, test for hypersensitivity, 1326  
 Hospitalization, general care, 171  
   preparation for, 170  
 Household measures of sugars in infant formulas, 127  
 Humidification therapy, 742  
 Hunter's glossitis, 637  
 Huntington's chorea, 1098  
 Hurler's syndrome, 268, 1238  
 Hutchinson-Gilford syndrome, 1153  
 Hutchinson's teeth, 475, 622  
 Hutchinson's triad, 477  
 Hyaline membrane disease, 308, 324-6  
   in infants of diabetic mothers, 1214  
   pulmonary function in, 736  
 Hydatid disease, **592**  
   epidemiology, 574, 592  
 Hydreltra. See *Prednisolone*.  
 Hydralazine, dose, 218  
   in acute glomerulonephritis, 1041  
   in hypertensive encephalopathy, 1041  
 Hydranencephaly, **1093**  
 Hydriodic acid, syrup of, in acute bronchitis, 785  
 Hydroa aestivale, 280, **1301**  
 Hydrocarbons, halogenated, poisoning, 1388  
   pneumonia, 799-800  
   poisoning, 1388  
 Hydrocele, **691-2**  
   communicating, 691  
   in newborn, 691  
   noncommunicating, 691  
   vs. hernia, 690  
   with undescended testis, 1059  
 Hydrocephalus, **1092**  
   dye test, 1071  
   chondrodystrophy, 1235  
   in cryptococcosis, 564  
   in cytomegalic inclusion disease, 525  
   in gargoylism, 1238  
   in meningitis, 428  
   in toxoplasmosis, 616  
   toxic, 1092  
 Hydrocortisone, dose, 218, 224. See also *Corticosteroids*.  
   in hypoadrenocorticism, 1185  
   in infantile eczema, 1316  
   in interstitial keratitis, 479  
 Hydrogen ions, renal excretion, 1009, 1010  
 Hydrogen peroxide in phosphorus poisoning, 1392  
 Hydronephrosis, 1027-30, 1031  
 Hydroperitoneum in newborn with urinary obstruction, 1027  
 Hydrophobia. See *Rabies*.  
 Hydrophthalmos, 1334  
   with refractory rickets, 1223  
 Hydropneumothorax, 816



- Hydrops fetalis, 957, 959. See also *Hemolytic disease of newborn*.
- Hydrothorax, **817**  
vs. pleural effusion, 814
- Hydroxystilbamidine in North American blastomycosis, 564
- Hygiene, cleanliness, 137  
clothing, 137  
exercise, 136  
habits, 135  
in infant care, **135-8**  
in mental development, 67  
sunlight and fresh air, 137
- Hygroma, subdural, 1089
- Hygroma colli, 1360
- Hykinone, 379
- Hymen, imperforate, 1060
- Hymenolepiasis, **591**  
epidemiology, 591
- Hyperadrenalism, **1185-92**
- Hyperadrenocorticism, **1185-91**
- Hyperbilirubinemia, congenital, 703  
constitutional, 702  
in newborn, 334  
re kernicterus, 1077  
re vitamin K, 380
- Hypercalcemia, idiopathic, **1224**  
vs. hyperparathyroidism, 1178
- Hypercapnia, in poliomyelitis, 539  
re respiratory center, 733
- Hyperchloremia in acidosis, 264
- Hyperchloremic acidosis, renal, 1223
- Hyperchloremic disorders in galactosemia, 276
- Hyperelectrolytemia, 179, 180  
in nephrogenic diabetes insipidus, 1156
- Hyperinsulinism re hypoglycemia, 1217
- Hyperkeratosis, 361
- Hyperlipemia, causes, 278  
idiopathic, 278
- Hypernephroma, 1354
- Hyperopia, 1331  
test, 146
- Hyperosmolarity, 179, 180
- Hyperostosis, cortical, infantile, 1260  
due to vitamin A, 363
- Hyperparathyroidism, **1177-80**  
primary, 1177-9  
re adenoma, 1177  
re hyperplasia, 1177  
secondary, 1179  
with renal disease, **1179-80**, 1223
- Hypersensitivity, general considerations, 381-4
- Hypersplenism. See *Splenomegaly*.
- Hypertelorism, 1229
- Hypertension. See *Blood, pressure, high*.
- Hyperthermia in diabetes insipidus, 1156
- Hyperthyroidism, 1172. See also *Goiter*.  
electroencephalogram in, 1120  
in adolescence, 154  
in newborn, 343
- Hypertonia in acrodynia, 1400
- Hyperuricemia, hereditary, 261
- Hyperventilation tetany, 1111
- Hypervitaminosis A, 108, 363  
vs. Caffey's disease, 1260
- Hypnotics, 205-6
- Hypoadrenocorticism, **1182-5**
- Hypoallergenic milk powder, 125
- Hypochloremia, alkalosis in, 178, 180
- Hypogammaglobulinemia, 217  
physiologic, 256
- Hypogenitalism in Laurence-Moon-Biedl syndrome, 1232
- Hypoglycemia, **1215-20**  
casein in, 267  
clinical manifestations, 1218  
diagnosis, 1218  
electroencephalogram in, 1121  
etiology, 1217-18  
in adrenal insufficiency, 1184  
in pituitary dwarf, 1152  
in Simmonds' disease, 1154  
in vomiting sickness of Jamaica, 711  
leucine in, 267, 1220  
partial pancreatectomy, 1220  
physiologic considerations, 1216  
protein in, 267  
treatment, 1220  
vomiting due to, 648, 650  
with craniopharyngioma, 1086  
with fructose intolerance, 274
- Hypoglycemia, idiopathic, and leucine, 267
- Hypogonadism, female, primary, **1198-1200**  
secondary, **1200**  
in acromegaly, 1155  
in anemia, 935  
in diabetes mellitus, 1207  
in gargoylism, 1239  
in hypothyroidism, 1166  
in myotonic dystrophy, 1268  
in pituitary dwarfism, 1153  
in sickle cell disease, 951  
in Simmonds' disease, 1154  
male, **1195-6**  
re obesity, 355
- Hypokalemia, deficit therapy in, 192  
in aldosteronism, 1191
- Hyponatremia, deficit therapy in, 191
- Hypoparathyroidism, **1175-7**  
cataracts in, 1333  
idiopathic, 1175-6  
in newborn, 342  
re Addison's disease, 1183  
re megaloblastic anemia, 941  
surgical, 1175  
tetany in, 1111
- Hypophosphatasia, **1224**  
vs. chondrodystrophy, 1235  
vs. hyperparathyroidism, 1178  
vs. osteogenesis imperfecta, 1243
- Hypopituitarism, hypogonadism in, 1200
- Hypoplasia of mandible, **631-2**
- Hypopotassemia, deficit therapy in, 192
- Hypoproteinemia, 356  
idiopathic, 253, 342
- Hypoprothrombinemia, 255, 379  
in newborn, 981
- Hypopyon, 1339
- Hypospadias, 1057
- Hypostatic pneumonia, **801**
- Hypotension. See *Blood, pressure, low*.
- Hypothalamus, lesion of, with precocious puberty, 1159-61  
re Cushing's syndrome, 1190  
re hypoglycemia, 1217  
re obesity, 1162
- Hypothermia in encephalitis, 551
- Hypothyroidism, acquired, **1168**  
congenital, **1165-8**  
electrocardiogram in, 830  
endemic cretinism, 1170  
hypogonadism in, 1200  
in adolescence, 154  
in Simmonds' disease, 1154  
prognosis, 1167  
re chronic rhinitis, 756  
re obesity, 355  
treatment, 1167  
vitamin A deficiency, 360  
vs. glycogen disease, 273  
vs. mongolism, 1134
- Hypotonia, benign, congenital, vs. Werdnig-Hoffmann disease, 1100  
in cerebral palsy, 1138  
in Werdnig-Hoffmann disease, 1099
- Hypoxia. See *Oxygen, deficiency*.
- Hypsarrhythmia, 1120
- Hysteria, **82**, 1068  
examination in, 1068  
re torticollis, 1265  
vs. poliomyelitis, 539
- Hysterical convulsion, 1127
- ICELAND disease. See *Encephalitis, myalgic, benign*.
- Ichthammol ointment in furunculosis, 1288
- Ichthyl in inflammation of rectal mucosa, 683
- Ichthyosis, **1275**  
inheritance, 242
- Icterus. See also *Jaundice*.  
index, 699, 1403  
test, 699  
neonatorum, 289, 333  
praecox, 961
- Idiocy, amaurotic, 1094  
hereditary, 1131
- Idiot, I.Q., 1129
- Ileostomy, composition of fluid loss, 195
- Ileus, meconium. See *Meconium ileus*.  
paralytic, 666
- Illness, psychosomatic, 87  
re growth and development, 41
- Ilotycin. See *Erythromycin*.
- Imbecile, I. Q., 1129
- Imferon, dose, 218
- Immunity, general considerations, **381-4**  
of newborn, 292  
passive, breast-fed vs. artificially fed infant, 114
- Immunization. See also *Vaccination*.  
booster injections, 140, 141, 142  
cholera, 142  
diphtheria, 139-40, 141  
epidemic typhus, 142  
foreign travel, 142  
infection, **139-42**  
paratyphoid, 142  
passive, 142  
pertussis, 139-40, 141  
plague, 142  
poliomyelitis, 140, 141  
procedures, recommended, 141  
routine, 139-41  
smallpox, 141  
tetanus, 139-40, 141

- Immunization, typhoid, 142
    - yellow fever, 142
  - Impetigo contagiosa, **1287-8**
  - Impetigo neonatorum, **339**
  - Inanition, 352
  - Inborn errors of metabolism. See under *Metabolism*.
  - Incisional hernia, 692
  - Inclusion blennorrhea, 1338
    - tests, 394
  - Incubator care of premature, 308
  - Indian childhood cirrhosis, **711-12**
  - Indican, 266
    - in urine, 1011, 1020
  - Indicanuria, 1011, **1020**
  - Individuality of child, 10
  - Indole, 266
  - Infancy, characteristics, 5, 26, **30-33**
    - general factors, 5
    - mortality rates, 5, 7, 8
  - Infant, behavior, 34
    - bladder, 32
    - chest circumference, 31
    - cleanliness, 137
    - clinical appraisal, **161-72**
    - clothing, 137
    - death, unexpected, 350
    - exercise, 136
    - feeding, 32, **112-35**
      - amounts per feeding, 126
      - artificial, **119-28**
        - formulas, water in, 126
        - milks, **120-28**
        - technique, 120
      - breast, **113-19**
        - adequacy, 118
        - advantages, 114
        - colostrum, 113
        - contraindications, 114
        - disadvantages, 114
        - from nonmother, 119
        - hygiene, 116
        - maternal diet, 116
        - menstruation during, 115
        - preparation of mother for, 115
        - psychologic factors, 115
        - stimulation, 116
        - supplements for, 115, 117, 119
        - technique, 117-19
        - weaning, 119
      - cereal, 128
      - colic in, 131
      - constipation, 131
      - desserts, 129
      - eggs, 129
      - first year, **129-32**
      - fruits, 128
      - growth factors in, 31-2
      - meats, 129
      - milk formulas, 122-8
      - newborn, 304
      - parental instruction for, 112
      - premature, 309-11
      - problems, 129-32
      - psychologic aspects, 112-13
      - regurgitation, 130
      - schedule, 113
      - second year, 132
      - self-feeding, 132
      - self-regulating, 113
      - self-selection of diet, 132
      - solid foods, 128
      - starchy foods, 129
      - stools, 130
  - Infant, feeding, times per day, 126
    - vegetables, 129
    - vitamins, 128
    - vomiting, 130
  - furunculosis in, 1288
  - growth, length, 31
  - habits, 135
  - head, 31
    - circumference, graph, 45
  - health conferences, 145
  - hygiene, **135-8**
  - larynx, 32
  - length, graph, 45
  - mineral requirements, 107
  - motor development, 32, 34
  - nasal passages, 32
  - nutritional requirements, 31
  - of diabetic mother, **1214**
  - overfeeding, 130
  - reflexes, 32
  - respiratory disorders in, 743, 744
  - skull, fontanel, 31
  - sleep, 136
  - speech, 34
  - subcutaneous tissue, 31
  - sunlight and fresh air, 137
  - sweat glands, 32
  - taste, 32
  - teeth, 32
  - underfeeding, 130
  - vision, 32
  - vitamin requirements, 107
  - weight, gain, 30
    - graph, 45
- Infantile atrophy, 352
- Infantile autism, 1149
- Infantile myoclonic seizures, 1119
- Infarction, pulmonary, **808**
  - renal, 1053
- Infection, age factors in, 382
  - eye, tests for, 393
  - gastrointestinal, tests for, 388
  - general considerations, **381-4**
  - genitourinary, tests for, 392
  - nervous system, tests for, 389
  - prevention, **139-42**
    - in premature, 311
  - re neurologic disease, 1078
  - re unexpected death, 350
  - respiratory, tests for, 387
  - shock due to, 182
  - skin, tests for, 393, 394
  - systemic, tests for, 389
- Infectious diseases. See also specific diseases.
  - etiologic diagnosis, **384-97**
  - isolation measures for, **397-9**
- Infectious hepatitis, **704-707**
- Infectious mononucleosis, **518-20**
  - vs. diphtheria, 416
  - vs. German measles, 488
  - vs. infectious hepatitis, 706
  - vs. infectious lymphocytosis, 521
  - vs. scarlet fever, 408
- Infectious neuronitis, **525**
- Influenza, death rates, 3, 9
  - epidemic, **508-11**
    - clinical manifestations, 510
    - complications, 511
    - epidemiology, 509
    - re encephalitis, 549
    - vaccination, encephalitis due to, 551
    - viral, 508-11
- Influenzal meningitis, 430
- Infratentorial tumor, 1085
- Infusion, intramedullary, 200
  - intravenous, 199, 200
  - subcutaneous, 200
- Inguinal hernia. See under *Hernia*.
- Inhalation therapy, **742**
- Injuries. See also *Accidents; Burns; Trauma; Wounds*.
  - actinic, prenatal, 243
  - birth, 27, 28
    - death rates, 7
  - chemical, in disease, 242
  - factors in disease, 234
  - from infection, 243
  - mechanical, in disease, 242
  - prenatal, 242
- Inositol in nutrition, 110
- Insanity, manic-depressive, 1148
- Insect bites, 599
- Insecticides, chlorinated, poisoning, 1386
- Insomnia, 89
- Inspissated bile syndrome, 334
- Insulin. See also *Diabetes mellitus; Pancreas*.
  - in diabetes mellitus, 1210-13
  - in diabetic acidosis, 190
  - in newborn, 292
  - local reaction to, 1208
  - shock, 1212
  - tolerance test, 1219-20
  - types, 1210-11
- Intellect, development, **62-72**
  - growth, tests, 66
- Intelligence quotients in mental deficiency, 1129
- Intelligence tests, 66
- Intersexuality, **1202**
- Interstitial keratitis, 476, 479
- Intertrigo, **1298**
- Interview, with child, 166
  - with parent, 165-6
- Intestinal amebiasis, 611, 612, 613
- Intestinal fluid, composition, 195
  - loss, replacement of, 197
- Intestinal keratitis, 1339
- Intestinal lipodystrophy, 726
- Intestinal trematodiasis, 596
- Intestines, disorders, **664-78**
  - diverticulitis, 669
  - foreign bodies in, 663
  - infections, fluke, 596
  - tests for, 388
  - malabsorption, re celiac disease, 726
    - re hypoglycemia, 1217
  - malformations, 664
  - malpositions, 664
  - obstruction, acquired, **666-9**
    - congenital, classification, **665**
    - clinical manifestations, 665, 666
    - differential diagnosis, 666
    - lymphatic, re celiac disease, 726
    - re Meckel's diverticulum, 670
    - vs. adrenal hyperplasia, 1188
  - perforation, with Meckel's diverticulitis, 669
  - pneumatosis, 672
  - polyposis, multiple, 1351
  - tumors, **1351**
- Intracranial hemorrhage, in newborn, 316-18
  - in purpura, 974
  - re unexpected death, 351



- Intracranial pressure, anatomic considerations, 1082  
increased, **1082-93**  
benign, 1092  
symptoms, 1082  
treatment, 1084  
without mass lesions, 1091-3  
physiology, 1082
- Intramedullary infusions, 200
- Intraspinal abscess, 1106
- Intrauterine position re orthopedic disturbance, **1250-52**
- Intravenous infusion; 199
- Intussusception, **667-9**  
chronic, 668  
differential diagnosis, 668  
predisposing factors, 667  
recurrent, 668  
treatment, 668  
vs. appendicitis, 677  
vs. bacillary dysentery, 436  
with Meckel's diverticulum, 669
- Inulin clearance test, 1006, 1013
- Inversine. See *Mecamylamine*.
- Iodides, skin rash, 1282
- Iodine, butanol-extractable, 1167, 1168  
deficiency, effects of, 104  
excess, effects of, 104  
function, 104  
geographic distribution, 1169  
in endemic goiter, 1170  
in moniliasis, 1294  
in thyroxine, 1163-4  
metabolism, 106  
poisoning, 1389  
protein-bound, 1164, 1167, 1405  
in hyperthyroidism, 1172  
serum, 1405  
radioactive, 1164, 1167  
in hyperthyroidism, 1172  
requirements, 104, 106, 107, 111  
serum (protein-bound), 1405  
sources, 104
- Iodopyracet, renal clearance, 1008, 1013
- Ions, concentration of, physical signs of variations in, 184
- Ipecac, in croup, 778  
syrup, 208  
dose, 219
- I.Q. determination, 66
- Iridocyclitis, 1339
- Iris, examination, 1330  
tumors, 1341
- Iron, blood, 1405  
deficiency, **941-3**  
effects of, 104  
in erythrocytosis, 962  
excess, effects of, 104  
for premature infant, 932  
function, 104  
in milk, 121  
metabolism, 106  
requirements, 104, 106, 107, 111  
salts, poisoning, 1389  
serum, 1405  
level, 106  
sources, 104
- Iron-dextran mixture, 942
- Irradiation, effects, early, 1372  
late, 1372  
injury, **1371-3**  
prevention, 1372  
nephritis, 1042
- Irradiation, re mental deficiency, 1132  
sickness, therapy for, 1372
- Iso-immunization re mental deficiency, 1132
- Isolation measures for infections, **397-9**
- Isoleucine, defective metabolism, **267-8**  
requirements, 101
- Isoniazid, dose, 219  
in tuberculosis, 464, 467, 470
- Isotopes in neurologic examination, 1072
- JAUNDICE, 700-703**  
catarrhal, 704-707  
chronic idiopathic, 703  
clinical manifestations, 701  
familial, nonhemolytic, 281  
with kernicterus, 703  
hemolytic, 701-702  
congenital, 944-6  
with oxycephaly, 1227  
in A and B incompatibilities, 961  
in cirrhosis, 708-12  
in Cocksackie myocarditis, 529  
in cryptococcosis, 564  
in cytomegalic inclusion disease, 524  
in galactosemia, 275  
in hemolytic disease of newborn, 957, 958  
in hypothyroidism, 1165  
in infectious mononucleosis, 519  
in leptospirosis, 480  
in leukemia, 966  
in newborn, 315, **332-5**, 715-16  
in syphilis, 474  
in toxoplasmosis, 616  
in yellow atrophy, 712  
laboratory data, 702  
nonhemolytic hereditary, 702  
obstructive, 701-702  
differential diagnosis, 715-16  
physiologic, in newborn, 333  
teeth, 620  
with oxycephaly, 1227
- Jaws, disturbances, **627-32**. See also *Teeth*.
- Jealousy in emotional development, 67
- Joints, Clutton's, 477  
in hemophilia, 978  
infections, **1259-60**  
pains, 908
- Juliusberg's pustulosis vacciniiformis acuta, 491
- Juvenile paresis, 476
- Juvenile tabes, 476
- KAHN test**, falsely positive, 520
- Kala-azar in children, **608-10**
- Kanamycin, in staphylococcal meningitis, 431  
in tuberculosis, 464
- Kanamycin sulfate, dose, 219
- Kantrex. See *Kanamycin*.
- Kaposi's varicelliform eruption, 491
- Kartagener's syndrome, 809, 855
- Kayser-Fleischer ring, 1099
- Keloid, **1277**
- Keratitis, 498  
interstitial, syphilitic, 476, 479  
intestinal, 1339
- Keratoconjunctivitis, epidemic, 1338  
tests, 394  
herpetic, 493
- Keratoconus, 1330
- Kerato-ectasia, 1333
- Keratomalacia, 361
- Keratosis follicularis, **1277**
- Keratosis palmaris et plantaris, **1275**
- Keratosis pilaris, **1287**
- Kernicterus, 308, 335, 957, 958, 959, 961, 962, 1077  
clinical manifestations, 1077  
in nonhemolytic jaundice, 281  
re bilirubin and bile salts, 701  
re hyperbilirubinemia, 334  
re mental deficiency, 1132  
re vitamin K, 303, 380  
vs. Werdnig-Hoffmann disease, 1100
- Kerosene, pneumonia, 799-800  
poisoning, 1388
- Ketogenic diet in epilepsy, 1125
- Ketones, formation, 696
- Ketonuria, 353, 1020  
in acidosis, 178  
in diabetes mellitus, 1207
- Ketosis. See also *Acidosis*.  
in acidosis, 179, 180  
in diabetes mellitus, 1207  
in glycogen disease, 270  
in recurrent vomiting, 649
- 17-Ketosteroids, 1182  
excretion, 1194-5
- Kidneys, abscess, 1052  
agenesis, 337, **1023**  
artificial, 1042  
calcinosis, 1223, 1225  
calculus, **1054**, 1223  
in poliomyelitis, 541  
cortical necrosis, 1050-51  
cyst, solitary, 1024  
defect, in reabsorption of phosphate, 261  
in reabsorption of purines, 261  
in reabsorption of water, 261  
disease, in galactosemia, 275, 276  
in lupus erythematosus, 926  
with hyperparathyroidism, 1179  
displacement, **1030**  
dysfunction, in galactosemia, 275, 276  
dystopia, 1030  
embryoma, 1353  
failure, 1050-51  
in acute glomerulonephritis, 1041  
in nephrosis, 1046, 1047  
in vascular nephritis, 1050  
treatment, in nephrosis, 1049  
function, **1005-10**  
in acute glomerulonephritis, 1038  
in infants, 1009  
in newborn, 290  
glomerular filtration, 1013  
hyperchloremic acidosis, 1223  
hypoplasia, 1023  
in anaphylactoid purpura, 921  
in leptospirosis, 480  
in lupus erythematosus, 926  
in newborn, 337  
infarction, 1050-51, 1053

- Kidneys, insufficiency, in anaphylactoid purpura, 922  
in scleroderma, 928  
with obstructive lesions, 1028  
malformations, **1022-30**  
movable, 1030  
multicystic, 1023  
necrosis, cortical, 1050-51  
physiology, 1005-10  
polycystic disease, 1024  
re acid-base regulation, 1013  
regulation of acid-base, 1008  
stones, 1054  
tests, diagnostic, **1012-14**  
tuberculosis, **1052**  
tuberosus sclerosis in, 1079  
tubular acidosis, 261, 1223  
tubular defects, hereditary, 261-2  
tubules, disorders, 1051  
excretion, 103, 1008  
function, hereditary defects of, 261-2  
reabsorption by, 1007  
tumors, **1353-5**  
uric acid infarcts, 1010  
vascular thrombosis, 1050-51, 1053  
weight, 1010  
Kimmelstiel-Wilson syndrome, 1208  
Klim, 124  
Klinefelter's syndrome, 1197  
re gynecomastia, 1198  
re obesity, 1162  
Klippel-Feil syndrome, 1233  
Klumpke's paralysis in newborn, 319  
Knee, hyperextension, 1254  
Knock knee, 1254  
in rickets, 375  
Koehler's disease, 1258  
Koplik's spots, 484  
Krabbe's disease, 1095  
Krameria solution in inflammation of rectal mucosa, 583  
Krebs cycle, 269  
Kunkel's syndrome, 710  
Kwashiorkor, **357-60**  
liver dysfunction, 711  
Kwell. See *Cyclohexane*.  
Kynex. See *Sulfamethoxypyridazine*.  
Kyphosis, in arachnodactyly, 1243  
in chondrodystrophy, 1235  
in rickets, 375  
Kyphosis dorsalis juvenilis, 1106
- LABILE factor, 253, 254, 255, 971, 973  
deficiency, 255, 981  
Laboratory data in planning deficit parenteral fluid therapy, 184  
Laboratory microbiology, clinical use, **384-97**  
Laboratory studies in clinical appraisal, **170**  
Labyrinthine examination, 769  
Labyrinthitis, 765  
Lacrimal apparatus, 1332  
infection, 1337  
Lacrimal glands, newborn, 20  
Lactalbumin in milk, 120, 121  
Lactic acid, blood, 1402  
douches, in nongonorrheal vulvovaginitis, 1060  
Lactose, in milk, 120, 121  
metabolism, 275  
Lactum, 124
- Lacunar skull, 1230  
Lanatoside C, 897, 898  
dose, 214  
Landau reflex, 1067  
Landouzy and Déjérine, muscular dystrophy, 1270  
Language, disorders, **91-7**  
function, re auditory disorders, 93  
re reading disorders, 95-7  
re speech disorders, 91-3  
stuttering, **93-5**  
Lanugo, 29  
Larkspur poisoning, 1390  
Laryngeal. See also *Larynx*.  
nerve, paralysis, 1250  
(recurrent) paralysis, 772  
stridor, 771  
re thymus, 998  
Laryngitis, acute, **778-80**  
spasmodic, 777  
differential diagnosis, 777, 778, 779  
diphtheritic, 415  
humidification for, 742  
in measles, 486  
in scarlet fever, 409  
viruses in, 747  
vs. diphtheria, 416  
Laryngospasm in tetany, 1113  
Laryngotracheobronchitis, acute, **778-80**  
Larynx, **770-80**  
birth trauma, 772  
fibrolipoma, 773  
foreign bodies in, 773-4  
infant, 32  
infections, acute, **777-80**  
general considerations, 777  
malformations, congenital, 770  
neoplasms, 773  
obstruction, symptoms, 770  
stenosis, acute, 772  
chronic, 772  
trauma, 772  
vocal nodules, 773  
web of, 772  
Lateral sinus thrombosis, 765, 1091  
*Latrodectus mactans*, 598  
Laurel, mountain, poisoning, 1390  
Laurence-Moon-Biedl syndrome, 1162, 1232  
Lavage, gastric, 204  
L.E. cell, phenomenon, 926  
in thrombotic purpura, 976  
Lead, colic, treatment, 1378  
encephalopathy, 1376-8  
treatment, 1378  
in blood, 1376  
poisoning, **1375-8**  
acute, 1376  
chronic, 1376-8  
prognosis, 1377  
treatment, 1377  
contaminated food in, 1374  
general considerations, 1375  
re hypoglycemia, 1217  
re treatment, 1378  
serum, 1405  
Learning, re mental and emotional development, **64**  
Leber's optic atrophy, 1101  
*Leche de higuérón* in trichocephal-  
iasis, 582  
Leiderer's anemia, 954  
Legg-Calvé-Perthes disease, 1257, 1258
- Legs, circumference, 5-18 years, 58-9  
measuring technique, 49  
deformities, **1254**  
newborn, 30  
pain, 908  
Leiner's disease. See *Erythroderma desquamativum*.  
Leiomyoma, cutaneous, 1362  
Leiomyosarcoma of soft tissue, 1365  
Leishmaniasis, **608-10**  
Length, and weight, table, 50-51  
annual increments, 14  
infant, 31  
graph, 45  
measuring, technique, 48  
stem. See *Height, sitting*.  
prenatal, 13  
0 to 5 years, 50-51  
2-6 years, graph, 46  
6 months to 18 years, 60-61  
Lens, dislocation, **1334**  
fibrovascular sheath of, vs. retinoblastoma, 1342  
luxation of, in Marfan's syndrome, 1243  
Lentigo, 1277  
Leontiasis ossea, **1246**  
*Leptospira canicola*, 480  
*Leptospira icterohaemorrhagiae*, 480  
Leptospirosis, **480**  
tests, 389  
vs. infectious hepatitis, 706  
Léri, 1246  
Lethal genes, 242  
Letterer-Siwe disease, **1003**  
Leucine, defective metabolism, 267-8  
re hypoglycemia, 1220  
requirements, 101  
Leucinuria, 697  
Leukemia, **966-70**  
chronic, 967  
clinical manifestation, 966  
cryptococcosis in, 564  
differential diagnosis, 968  
laboratory data, 967  
myelocytic, 967, 968  
re irradiation, 1372  
treatment, 969-70  
types, 966  
vs. cytomegalic inclusion disease, 525  
vs. histoplasmosis, 567  
vs. infectious lymphocytosis, 521  
vs. lymphosarcoma, 992, 993  
vs. rheumatic fever, 909  
Leukocytes, average values, 932  
disorders, 963-70  
normal, 963-4  
Leukocytosis due to corticosteroids, 963  
Leukodystrophy, cerebral, 1095-7  
Leukoencephalitis, subacute, sclerosing, **552**  
Leukoma of cornea, 1333  
Leukopenia, 964  
due to irradiation, 1372  
Levallorphone in opiate poisoning, 1391  
Levarterenol bitartrate, dose, 219  
Lévi-Lorain dwarfism, 1151  
Levocardia with situs inversus, **855**  
Levophed. See *Levarterenol*.  
Levulosuria, 273  
Leyden-Moebius, muscular dys-  
trophy, 1270



- Leydig cell tumor, 1197
- Libman-Sachs syndrome, 926
- Lice, vectors of disease, 600
- Lichen scrofulosorum, **1290**
- Lichen urticatus, 1300
- Lightwood syndrome, 1223
- Lignac disease, 263-4
- Limit dextrinosis, 271
- Lindau's disease, 1080, 1354, 1359
- Linoleic acid, 102
- Lipase, 718, 719
- Lipidoses, **999-1002**  
cerebral, 1094-5
- Lipids. See also *Fat*.  
blood levels, 1403  
in nutrition, 102  
in urine, in nephrosis, 1046  
metabolism, disturbances, **999-1002**  
inborn errors, **278**  
classification, 252
- Lipiodol test, fat absorption, 720
- Lipochoondrodystrophy, 1238
- Lipodystrophy, **1279**  
due to insulin, 1208
- Lipoid pneumonia, 800
- Lipomas, 1362
- Lipomatosis, diffuse, 1362  
due to insulin, 1208
- Lipophagia granulomatosis, 726
- Liposarcoma of soft tissue, 1364
- Lipotropic factors, deficiency of, 696
- Lips, allergic eruptions, 635  
angioneurotic edema, 635  
cleft. See *Harelip*.  
disturbances, **634-5**  
fissures, 634  
mucous retention cysts, 635
- Lipuria, **1020**
- Lisping, 93
- Listeria monocytogenes* in newborn, **347**
- Lithuria, **1020**
- Liver, **693-716**. See also *Bile ducts*.  
abscess, 707-708  
amebic, 612  
vs. actinomycosis, 562  
amino acid metabolism in, 698  
anatomy, 693  
anomalies, 694  
atrophy, yellow, 712  
biopsy, 700  
blood formation in, 696  
carcinoma, **1352**  
cells, dysfunction, 701  
circulatory disturbances, 700  
cirrhosis, **708-12**  
clinical management, 709  
Cruveilhier-Baumgarten, 709  
diagnosis, 709  
etiology, 708  
forms, 709  
in cystic fibrosis of pancreas, 727  
in galactosemia, 275  
in hemolytic disease of newborn, 957  
Indian childhood, **711-12**  
portal, in splenomegaly, 986  
re cardiac failure, 700  
re infectious hepatitis, 707  
siderotic, 711  
treatment, 710  
with arthritis and amenorrhea, 710  
with glycogenosis, 270
- Liver, congestion, chronic, 700  
Crigler-Najjar disease, 703  
cysts, **712**  
in hydatid disease, 593  
with polycystic kidneys, 1024  
detoxifying functions, 696  
disease, hypoprothrombinemia in, 981  
re gynecomastia, 1198  
disturbances, tests of, 297  
Dubin-Johnson syndrome, 703  
dysfunction, constitutional, 702  
extract, in megaloblastic anemia, 940  
failure, in galactosemia, 276  
in porphyria, 281  
fat metabolism in, 696, 698  
test, 698  
fatty degeneration, 713  
fatty infiltration, 696, **713**  
flake infections, 596  
function, in newborn, 289  
re bile salts, 700  
re diet, 696  
tests of, **697-700**, 702  
Gilbert's disease, 702  
glycogen disease of, 268-72  
hemangioendothelioma, 1352  
hypertrophy, in cardiac failure, 825  
in cryptococcosis, 564  
in cytomegalic inclusion disease, 524  
in diabetes mellitus, 1208  
in Löffler's syndrome, 801  
in lupus erythematosus, 926  
with polycystic kidneys, 1024  
in newborn, 28, 299  
in schistosomiasis, 594  
in syphilis, 474  
infections, **704-708**  
lesions, re hypoglycemia, 1218  
malpositions, 694  
metabolic functions, 695-7  
nutritional disturbances, 711  
physiology, 695-7  
poisoning, **712**  
protein metabolism in, 698  
test, 698  
rupture, in newborn, 320  
size, 693  
teratoma, **1353**  
tuberos sclerosus in, 1079  
tumors, 1352  
vitamin A deficiency in, 360  
vitamins stored in, 696  
weight, 693
- Lobar emphysema in newborn, 329
- Lobster claw, 1231
- Lockjaw. See *Tetanus*.
- Loeffler's syndrome, **801**  
in tropical eosinophilia, 602
- Lorfan. See *Levallorphone*.
- Lotio alba in acne vulgaris, 1280, 1281
- Lower nephron nephrosis, 1050-51
- Lowe's syndrome, 1223
- Loxosceles bites, 599
- Lückenschädel, 1230
- Lumbar puncture. See under *Spinal puncture*.
- Luminal. See *Phenobarbital*.
- Lungs, abscess, 810-12  
in influenza, 511  
vs. actinomycosis, 562  
absence of, 781
- Lungs, accessory, 781  
adenomatoid malformations, 781  
anomalous circulation, 781  
anomalous fissures, 781  
anomalous lobes, 781  
azygos lobe, 781  
blastomycosis, 536  
brown induration, 801-802  
collapse, **802-804**  
acquired, 802-804  
etiology, 802  
death rates, 7  
in diphtheria, 416  
in newborn, **324**  
in tuberculosis, 456, 457  
massive, 804  
obstructive, pathogenesis, 775  
compliance, 734  
values for, 734  
cryptococcosis, 564  
cysts, 781, 784  
in newborn, **329**  
edema, 807  
acidosis in, 179, 180  
in poliomyelitis, 541  
embolism, 808, 903  
in poliomyelitis, 541  
examination, in newborn, 297  
fibrosis, acidosis in, 179, 180  
flake infections, 597  
function, **733-43**  
gangrene, 812  
hemorrhage, in newborn, 959  
hemosiderosis, **801-802**  
hypoplasia, 781  
infarction, 808  
infection in fibrosis of pancreas, 728  
mycotic, 798  
malformation, 781, 784  
mucormycosis, 565  
nocardiosis, 566  
normal, roentgenogram, 783  
resistance, 736  
values for, 734  
subdivisions, 734, 782, 783  
suppuration, **808-12**  
thromboses, re unexpected death, 351  
trematodiasis, 597  
tuberos sclerosus in, 1079  
tumors, **1350**  
volume, values for, 734
- Lupus erythematosus, antithromboplastin in, 971  
discoid type, **1290**  
L.E. cell phenomenon in, 926  
re nephrosis, 1044  
systemic, **925-7**
- Lupus erythematosus disseminata, 925
- Lupus vulgaris, **1289**
- Lutembacher syndrome, 860
- L-Xyluluria, 277
- Lye poisoning, 643, 1389
- Lygranum, 518
- Lying in emotional development, 68
- Lymph nodes, diseases, **991-6**  
hilar, tuberculosis of, 454-7  
in cat-scratch fever, 522  
neoplasms, 992-6  
superficial, tuberculosis, 467  
tuberculosis, 466
- Lymph vessels, diseases, **990**
- Lymphadenitis, acute, **991-2**  
chronic, **992**  
mesenteric, **678**

- Lymphadenopathy, herpetic, 492  
 in infectious mononucleosis, 518  
 in lymphogranuloma venereum, 518
- Lymphangiectatic edema, 1233
- Lymphangioma, 1359-60  
 cystic, 1360
- Lymphangioma circumscriptum, 1359
- Lymphangitis, acute, 990  
 in filariasis, 588
- Lymphatic system, 990  
 growth, 15
- Lymphedema, 990  
 congenital, 991  
 in gonadal dysgenesis, 1199
- Lymphocytes, 964
- Lymphocytic choriomeningitis, 550  
 tests, 390
- Lymphocytosis, 964  
 acute, infectious, **520**
- Lymphogranuloma inguinale, 518
- Lymphogranuloma venereum, **518**  
 tests, 392
- Lymphoid tissues in immunity, 381
- Lymphoma, cryptococcosis in, 564  
 re celiac disease, 726
- Lymphopenia, 964  
 in agammaglobulinemia, 256
- Lymphosarcoma, **992-4**  
 vs. regional enteritis, 672
- Lysine, requirements, 101
- Lysol poisoning, 1391
- McCUNE-ALBRIGHT's syndrome, 1159
- Macewen's sign, 1066
- Macroductyly, 1232
- Macrogenitosomia praecox, 1186
- Macroglossia, **636**  
 stridor with, 771
- Macroteeth, 622
- Macula of cornea, 1333
- Maggots in wounds, 600
- Magnesium, deficiency, tetany in, 111  
 effects of, 103  
 excess, effects of, 103  
 function, 103  
 in milk, 121  
 metabolism, 105  
 plasma level, 105  
 requirements, 103, 105  
 sources, 103
- Magnesium hydroxide, dose, 219
- Magnesium sulfate, dose, 219  
 in biliary obstruction, 716  
 in constipation, 654  
 in digitalis poisoning, 1387  
 in hypertensive encephalopathy, 1040, 1042  
 in pertussis, 423
- Malaria, **604-608**  
 clinical manifestations, 606  
 diagnosis, 606  
 epidemiology, 605  
 etiology, 604  
 mixed infections, 605  
 pathology, 605  
 tests, 391  
 transmission, 600  
 treatment, 607
- Malformations. See *Abnormalities*
- Malnutrition, **352-80**  
 in children, 353-4  
 in infants, 352-3  
 re growth and development, 41  
 re hypochromic anemia, 941  
 re liver disease, 711  
 third-degree, 357-60  
 vs. Werdnig-Hoffmann disease, 1100
- Malta fever. See *Brucellosis*.
- Mandelamine. See *Methenamine mandelate*.
- Mandelic acid, 1034
- Mandible, hypoplasia, **631-2**  
 stridor with, 771  
 unilateral, 632
- Manganese, 107
- Manic-depressive insanity, 1148
- Mannitol clearance test, 1006, 1013
- Maple sugar urine disease, 267
- Marasmus, 352
- March hemoglobinuria, 256-7
- Marfan's syndrome, **1243**  
 cardiovascular lesions, **880**
- Marie-Strümpell disease, 1103
- Mastitis in breast feeding, 114, 122
- Mastitis neonatorum, **340**
- Mastoiditis, **765**  
 in influenza, 511
- Masturbation, **79**  
 treatment, 80
- Maturity, age periods before, 26, 27-39
- Mauriac syndrome, 1208
- Mead's lactic acid milk, 124
- Mead's powdered protein milk, 124
- Meals, lunches between, 133, 135
- Measles, **483-7**  
 clinical manifestations, 484  
 death rates, 3  
 differential diagnosis, 485-6  
 encephalitis, 486, 550  
 epidemiology, 483  
 etiology, 483  
 gamma globulin for, 217  
 German. See *Rubella*.  
 immunity, in newborn, 292  
 immunization, active, 486  
 passive, 486  
 of fetus, 243  
 pathology, 484  
 prevention, 486  
 prognosis, 486  
 quarantine for, 398  
 re nephrosis, 1049  
 resumé, 400  
 tests, 391  
 vs. exanthema subitum, 490  
 vs. scarlet fever, 408  
 vs. smallpox, 500
- Measurements, techniques, 42-3, 48-9
- Meat in infant feeding, 129
- Mebaral. See *Mephobarbital*.
- Mecamylamine hydrochloride, dose, 218
- Mechlorethamine, dose, 221
- Meckel's diverticulitis, 669  
 vs. bacillary dysentery, 436
- Meckel's diverticulum, 669-71  
 in intestinal obstruction, 670  
 vs. appendicitis, 677
- Meconium, 289
- Meconium bodies, 331
- Meconium ileus, 331-2  
 in fibrosis of pancreas, 728
- Meconium peritonitis, 332
- Meconium plugs, 331
- Meconium stools, 30
- Mediastinum, abscess, 645  
 lipoma, 1350  
 teratoma, 1350  
 tumor, **1349**
- Medication, preanesthetic, 229-30
- Medicational precocity, 1161
- Medicel, dose, 225
- Mediterranean anemia, 946-9
- Medulloblastoma, 1085
- Megacolon. See under *Colon*.
- Megalencephalon, 1076
- Megaloblastosis, 1026, 1027, 1028
- Megaloblastic anemia. See under *Anemia*.
- Megalocornea, 1330  
 in arachnodactyly, 1243
- Megaloureter, 1026, 1027, 1028  
 with megacolon, 676
- Mehlnährschaden, 358
- Melanoma, juvenile, 1361  
 malignant, 1361
- Melanuria, 1022
- Melena in allergy, gastrointestinal, 1327
- Melena neonatorum, 337
- Melorheostosis, **1246**
- Menadione, 379
- Menarche, 39, 1193  
 re height, 149, 150  
 re osseous development, 21
- Mendelian pattern of inheritance, 235-41
- Meningismus in pneumonia, 789
- Meningitis, aseptic, syndrome, **545-6**  
 coccidioidomycosis, 572  
 cryptococcosis, 564  
 death rates, 3, 9  
 due to *Aerobacter aerogenes*, 424  
 due to coliform bacilli, 424  
 due to Cocksackie virus, 529  
 due to ECHO virus, 531  
 due to Friedländer bacillus, 424  
 due to Gonococcus, 424  
 due to *Lactobacillus lactis*, 424  
 due to *Listerella monocytogenes*, 424  
 due to Pseudomonas, 424  
 due to Salmonella, 424, 444  
 due to Streptococcus, 429  
 herpetic, 493  
 in brucellosis, 446  
 in leptospirosis, 480  
 in pleurodynia, 528  
 in typhoid fever, 441  
 influenzal, **430**
- meningococcal, **425-9**  
 complications, 428  
 treatment, 428
- mucormycosis, 565
- pneumococcal, **429-30**
- purulent, **424-31**  
 treatment, 425  
 vs. aseptic meningitis, 545
- re subdural effusion, 1089
- serous, 1092
- staphylococcal, 431
- streptococcal, **429**
- syphilitic, 474, 476, 477, 479
- torulosis, 564
- tuberculous, **469-70**  
 and hyponatremia, 192  
 vs. bacillary dysentery, 436  
 vs. tetanus, 433



- Meningitis, with pneumococcal pneumonia, 791
- Meningocele, 1076, 1079
- in lacunar skull, 1230
- Meningococcal infections, death rates, 3, 9
- Meningococcal meningitis, **425-9**
- Meningococcemia, **425-9**
- Meningococcus, tests, 387, 389
- Meningoencephalitic viruses, tests, 390
- Meningoencephalitis, **546-52**
- herpetic, 493
- in infectious lymphocytosis, 521
- in mumps, 507
- Meningomyelocele, 1076, 1079
- Meniscocytosis, **949-52**
- Menstruation, 155
- disorders, re acne, 1280
- irregularities, 39, 155
- precocious, **1157**
- re breast feeding, 115
- Mental and emotional development, 62-72
- Mental deficiency, **1129-37**. See also *Phenylketonuria*.
- and tryptophane metabolism, 265-6
- classification, 1129-30
- custodial care, 1136
- familial, 1130
- in diabetes insipidus, 1155, 1157
- in galactosemia, 276
- in gargoylism, 1238
- phenylketonuria in, 259, 260
- psychologic considerations, 1129
- training programs, 1136
- treatment, 1135-7
- Mental development, emotional factors, 62
- hereditary factors, 62
- prophylaxis, 69
- re reflex actions, 63
- re sensory development, 64
- re speech, 65
- role of pediatrician, 62, 63, 67
- role of play, 71
- sex education, 71
- 2-9 years, 35
- Mental hygiene, **67**
- Mental retardation, in craniosynostosis, 1227
- in gonadal dysgenesis, 1199
- in hypoparathyroidism, 1176
- in hypothyroidism, 1166
- in Laurence-Moon-Biedl syndrome, 1232
- in pertussis, 422
- in pseudohypoparathyroidism, 1177
- in toxoplasmosis, 616
- progressive, 1101, 1102
- syphilitic, 474, 476, 477, 479
- with hypercalcemia, 1225
- Mepacrine. See *Quinacrine*.
- Meperidine, 206
- as preanesthetic, 229
- Meperidine hydrochloride, dose, 214
- Mephobarbital, dose, 219
- in epilepsy, 1123
- Meprobamate, 206
- dose, 219
- in leukemia, 969
- Meralluride, dose, 220
- Mercaptopurine, dose, 220
- in leukemia, 969
- Mercurhydrin. See *Meralluride*.
- Mercurial diuretics, 897
- Mercurophen, ophthalmic, 1331
- Mercury, in acrodynia, 1398, 1400
- poisoning, 1389
- BAL for, 211
- re nephrosis, 1044
- Merycismus, 649
- Mesantoin, dose, 220
- Mesenchymal diseases, **915-29**
- symptomatology, 916
- Mesenchymal dysplasia, inheritance, 237
- Mesenteric adenitis in scarlet fever, 409
- Mesenteric chyladenectasis, 726
- Mesenteric lymphadenitis, acute, 678
- chronic, 678
- Mesentery, cyst, 1360
- tumors, **689**
- Mesodermal tumor, 1364
- Mesomorph, 43, 44
- Metabolism, basal, 98
- disorders, with osseous lesions, **1221-5**
- disturbances, of newborn, 342
- errors of, inborn, **250-85**
- carbohydrate, **268-78**
- classification, 251-2
- effect on growth and development, 40
- general considerations, 250-52
- lipids, **278**
- classification, 252
- pigments, **279-83**
- protein, **253-68**
- in adolescence, 151, 153
- in newborn, 290
- Metaldehyde poisoning, 1387
- Metaphen, ophthalmic, 1331
- Methanethline bromide, dose, 211
- Methemoglobin, blood level, 1403
- metabolism, 694
- Methemoglobinemia, congenital, 281
- hemoglobin M in, 282
- hereditary, 281
- in poisoning, 1379
- methylene blue for, 220
- Methenamine mandelate, 1034
- dose, 219
- Methimazole, dose, 220
- in hyperthyroidism, 1173
- Methionine, re fatty infiltration of liver, 696, 713
- re urine acidification, 1034
- requirements, 101
- Methotrexate, dose, 210
- in leukemia, 969
- Methycaine poisoning, 1386
- Methyl alcohol poisoning, 1383
- Methyl bromate poisoning, 1389
- Methyl chloride poisoning, 1389
- Methyl salicylate, poisoning, 1392
- Methyl testosterone in hypogonadism, 1196
- Methylene blue, dose, 220
- in cyanide poisoning, 1387
- in methemoglobinemia, 282
- test, 706
- Methylrosaniline, dose, 217
- in moniliasis, 1294
- in nongonorrheal vulvovaginitis, 1060
- in oxyuriasis, 580
- Methylrosaniline, in strongyloidosis, 586
- in thrush, 330, 634
- Meticortelone. See *Prednisolone*.
- Meticorten. See *Prednisone*.
- Metoquine. See *Quinacrine*.
- Metrazol. See *Pentyleneetetrazole*.
- Metric measures, conversion tables, **1413**
- Microcephaly, 1076
- hereditary factors, 246
- in anemia, 935
- in cytomegalic inclusion disease, 525
- in German measles, 488
- in toxoplasmosis, 616
- Microcornea, 1330
- Microdrepanocytosis, 952
- Micromelia in chondrodystrophy, 1234-6
- Microphthalmia in toxoplasmosis, 616
- Microphthalmos, in Laurence-Moon-Biedl syndrome, 1232
- Microteeth, 622
- Micturition. See *Urination*.
- Migraine, 87, 1074
- re epilepsy, 1128
- Mikulicz's disease, 638
- Mikulicz's syndrome, 638
- Milia in newborn, **339**
- Miliaria rubra, **1298**
- Miliary tuberculosis, 457
- Milibis. See *Glycobiarsol*.
- Milium, **1280**
- Milk, acid, 123
- bacterial content, 122
- breast, **113-19**. See also *Infant feeding, breast*.
- comparison with cow's milk, 120-22
- constituents, 120-22
- calories in, 120
- carbohydrate in, 120
- cow's, 120-23
- acid, 123
- certified, 122
- comparison with breast milk, 120-22
- condensed, 123
- constituents, 120-22
- dried, 123
- evaporated, 122, 124
- fermented, 123
- homogenized, 122
- lactic acid, 123, 124
- pasteurized, 122
- raw, 122
- skimmed, 123, 124
- vitamin D, 123
- whole, 122, 123, 124, 128
- digestibility, 122
- fat in, 120-21
- formulas, 125-8
- amount per feeding, 126
- calculation, 127
- evaporated milk, 127
- feeding schedule, 126
- fluid requirements, 125-6
- preparation, 125-8
- sterilization, 127
- sugar in, 126, 127
- water in, 126, 127
- whole milk for, 126, 127
- goat's, 123, 125
- hypoallergenic, 123, 125
- minerals in, 121

- Milk, prepared, 123  
 proprietary, list, **124-5**  
 protein in, 120  
   in formula, 123  
 substitutes, 123, 125  
   in galactosemia, 276  
 vitamins in, 121-2  
 water in, 120  
 whole, in formulas, 128
- Milk of magnesia. See *Magnesium hydroxide*.
- Milk sickness, poisoning, 1390
- Milliequivalents to milligrams, conversion, **1406**
- Milligrams to milliequivalents, conversion, **1406**
- Milliosmolar solution, 1407
- Millon's test, 259
- Milroy's disease, 991
- Miltown. See *Meproamate*.
- Mineral, body content, 102  
 deficiency, effects of, 103-105  
 excess, effects of, **103-105**  
 function, 103-105  
 in milk, 121  
 in proprietary milks, 124-5  
 requirements, **102-107**, 111  
 sources, 103-105
- Mineralo-corticoids, 1181
- Miotics, 1331
- Mirror vision, 1330
- Mite, bites, 599  
 vector of disease, 600
- Mitral insufficiency, 890
- Mitral stenosis, 890  
 congenital, 876
- Moebius' sign, 1172
- Moebius' syndrome, 1065
- Molecular diseases, hereditary, **250-85**. See also *Metabolism, errors of, inborn*.
- Molluscum contagiosum, **1297**  
 tests, 393, 394
- Moloney test, 140
- Monge's disease, 962
- Mongolian spots, 296
- Mongolism, **1132-5**  
 vs. glycogen disease, 273
- Moniliasis, **633**  
 drugs for, 207, 217  
 esophagitis in, 643  
 in hypoparathyroidism, 1176  
 in newborn, **330**  
 of skin, 1293  
 oral, 633  
   in newborn, 330  
 pneumonia in, 798  
 re Addison's disease, 1183  
 re megaloblastic anemia, 941  
 tests, 387, 388, 393  
 vs. diphtheria, 416  
 vs. eczema, 1314
- Monk's hood root, poisoning, 1390
- Monocytes, 964
- Monocytosis, 964
- Moon teeth, 476
- Moro reflex, 299, 1067
- Moron, I.Q. of, 1129
- Morphea, **928**
- Morphine, 206  
 as preanesthetic, 229  
 in asthma, 1324  
 in rheumatic fever, 913
- Morphine sulfate, dose, 220
- Morquio's disease, 1237  
 vs. gargoylism, 1239
- Mortality, leading causes, 3  
 perinatal, **306**  
 rates, by age, 5-9  
   childhood, 6, 9  
   comparative, in American countries, 2  
   infancy, 5, 7, 8  
   neonatal, 5, 7, 8  
     due to obstetric factors, 293
- Mosquitoes, vectors of disease, 600
- Motor development, infant, 32, 34  
 re mental and emotional development, 64
- Motor system, examination, 1065-6
- Mountain laurel, poisoning, 1390
- Mountain sickness, 962
- Mouth, **619-38**  
 diseases, **633-4**  
 examination, 619  
 hygiene, 619
- Mouth-breathing, effects on face and teeth, 627  
 in gingivitis, 632
- Movements, involuntary, 1065  
 rhythmic, 78
- Mucopolysaccharide, defective metabolism, **268**
- Mucormycosis, **565**
- Mucoviscidosis, **726-30**
- Mulberry teeth, 476
- Mull-Soy, 125
- Multiple exostoses, inheritance, 235, 236
- Multiple pregnancies, **304-306**
- Mumps, 505-508  
 encephalitis, 507  
 immunity, in newborn, 292  
 pancreatitis, 730  
 prevention, 507  
 quarantine for, 398  
 re labyrinthitis, 765  
 skin test, 505  
 tests, 390, 391
- Murine typhus, **553**, 556
- Murmurs. See under *Heart*.
- Muscles, absence, 1264  
 in arthrogryposis, 1248  
 aplasia, 1065  
 biopsy, in neurologic disease, 1073  
 congenital defects, **1264**  
 development, in adolescence, 38  
 disturbances, **1264-73**  
 fasciculations, 1065  
 fibrillation, 1065  
 growth, 15, 16  
 hypertrophy, 1065  
 hypoplasia, 1065  
 involuntary movements, 1065  
 of respiration, 733  
 physical examination, 1065-6  
 rigidity, 1065  
 skeletal, glycogen disease, 272-3  
   in cardiac glycogen disease, 271  
 strength, test of, 1065  
 tone, disorders, 1065  
 tremors, 1065
- Muscular atrophy, inheritance, 239
- Muscular dystrophy, facioscapulo-humeral form, 1270  
 inheritance, 241  
 juvenile muscular atrophy, 1270  
 myocarditis in, 894  
 of Erb, 1270  
 of Landouzy-Déjérine, 1270  
 of Leyden-Moebius, 1270
- Muscular dystrophy, progressive, **1268-71**  
 pseudohypertrophic form, 1269
- Mushroom, *Amanita muscaria*, poisoning, 1390
- Mustargen. See *Mechlorethamine*.
- Mutations, cause of congenital anomalies, 244
- Myalgia, epidemic. See *Pleurodynia, epidemic*.
- Myalgic encephalitis, 550
- Myasthenia gravis, **1271-2**  
 in newborn, 1271  
 vs. Werdnig-Hoffmann disease, 1100  
 re thymus, 997  
 vs. poliomyelitis, 539
- Mycetismus nervosus, poisoning, 1390
- Mycetoma pedis, 566
- Mycobacterium tuberculosis*, 449
- Mycostatin. See *Nystatin*.
- Mycotic infections, **562-73**  
 etiologic diagnosis, 384-97  
 pulmonary, **798**  
 tests, 384-97
- Mydriatic solutions, 1330, 1331
- Myelitis, in cat-scratch fever, 522  
 in mumps, 507  
 in pertussis, 422  
 re rabies vaccination, 515
- Myelodysplasia, 1076, 1079
- Myelography, 1072
- Myelomas, multiple, 1369
- Myelopathy, transverse, 1106
- Myelophthisic aplastic anemia, 936
- Myiasis, 600
- Myocarditis, due to Coxsackie virus, 529  
 in diphtheria, 413, 416, 893  
 in fungal infections, 893  
 in glomerulonephritis, 893  
 in infant, 529  
 in influenza, 510  
 in mumps, 507  
 in muscular dystrophy, 894  
 in parasitic infections, 893  
 in poliomyelitis, 541  
 in scarlet fever, 409  
 in thyroid disturbances, 894  
 in toxoplasmosis, 617  
 in trichinosis, 587  
 in typhoid fever, 893  
 in viral infections, 893  
 re unexpected death, 350
- Myocardium, diseases, **893-8**  
 insufficiency, in blood diseases, 894  
 involvement, in gargoylism, 896
- Myoclonic convulsions, juvenile, 1102
- Myoclonic jerks, 1065
- Myoclonic seizure, 1119-20  
 infantile, 1101, 1119
- Myoclonus with epilepsy and degeneration, 1101
- Myopathy, congenital, vs. Werdnig-Hoffmann disease, 1100
- Myopia, 1332  
 test for, 146
- Myositis fibrosa, **1265**
- Myositis ossificans, progressive, 1266
- Myositis ossificans circumscripta, 1266
- Myotonia congenita, **1267**
- Myotonic dystrophy, **1268**
- Myotonus, 1065
- Myringitis, acute, 763



- Mysoline. See *Primidone*.  
 Myxedema in hypothyroidism, 1166, 1169  
 Myxoma, 1364  
   heart, 1350  
 Myxoviruses, 747  
   in encephalitis, 549  
   tests, 387
- N-ACETYL-p-aminophenol, dose, 210  
 Nail-biting, 77  
 Nalline. See *Nalorphine*.  
 N-allyl normorphine in newborn, 303, 323  
 Nalorphine, 206  
   in narcosis, 323  
   in opiate poisoning, 1391  
 Nalorphine hydrochloride, dose, 220  
   in newborn, 303  
 Naphthalene, chlorinated, poisoning, 1389  
   hemolytic anemia with, 264-5  
   poisoning, 1385  
   re cataracts, 1333  
   re hemolytic anemia, 953  
 Narcolepsy, 1127  
 Narcosis in newborn, 323  
 Narcotics, 205-206  
   as preanesthetics, 229  
 Nasal. See also *Nose*.  
   diphtheria, 415  
   instillations, in nasal pharyngitis, 750  
 Nasolacrimal duct, obstruction, 1337  
 Nasopharyngitis, acute, 748-50  
   chronic, 756  
   differential diagnosis, 749  
 Nasopharynx, angiofibroma, 1347  
   bacterial cultures, 204  
   carcinoma, 1348  
   chordoma, 1348  
 Natal factors, 4  
 Navel. See *Umbilicus*.  
 Nearsightedness, 1332  
 Nebula, 1333  
*Necator americanus*, 583  
 Neck, congenital, webbed, 1233  
   teratoma, 1349  
   tumors, 639, 1349  
   webbed, in gonadal dysgenesis, 1199  
 Necrobiosis lipoidica diabetorum, 1208  
 Necrosis of subcutaneous fat in newborn, 1278  
 Negativism, 70  
 Neighborhood, effects on development, 62  
*Neisseria intracellularis*, 425  
 Nematode, infections, 575-89  
 Nembutal. See *Pentobarbital sodium*.  
 Neomycin, antimicrobial properties, 397  
   in diarrhea in newborn, 347  
 Neomycin sulfate, dose, 221  
 Neonatal disturbances, perinatal factors in, 138-9  
 Neonatal factors, 4  
 Neonatal hepatitis, 334, 706, 715-16  
 Neonatal herpes simplex, 493  
 Neonatal jaundice, 315, 332-5, 715-16  
 Neonatal pediatrics, history in, 293-5
- Neonatal period, characteristics, 26, 28-30  
 Neoplasms, 1347-70. See also *Cancer*; *Tumors*; and organ affected.  
   brain, 1084-7  
   death rates, 3, 9  
   due to irradiation, 1372  
   eye, 1341  
   general considerations, 1347  
   larynx, 773  
   lymph nodes, 992-6  
   mesentery, 689  
   nose, 745  
   pancreas, 731  
   parathyroid, 1177  
   peritoneum, 689  
   pituitary, 1151  
   rectum, 684-5  
   sacroccygeal, 685  
   sigmoid, 684-5  
   stomach, 663  
   testis, 1197  
   tonsils, 757  
 Neostigmine, dose, 221  
   for abdominal distention in pneumonia, 792  
   in myasthenia gravis, 1272  
 Neo-Synephrine. See *Phenylephrine*.  
 Nephazoline poisoning, 1383  
 Nephritis, 1035-52  
   acidosis in, 178, 179, 180  
   and deafness, 1042  
   "base-losing," with rickets, 1223  
   chronic, and rickets, 1179-80, 1223  
   re hyperparathyroidism, 1179  
   due to spider bite, 598  
   glomerular, acute, 1035-42  
     cardiac symptoms, 1036, 1038, 1041  
     clinical manifestations, 1036-9  
     diagnosis, 1039  
     etiology, 1035  
     pathology, 1035  
     prognosis, 1039  
     renal failure in, 1038, 1039, 1041-2  
     treatment, 1040-42  
     urine in, 1037  
   chronic, 1043-4  
     re hyperparathyroidism, 1179  
     in scarlet fever, 409  
     myocarditis in, 893  
     re nephrosis, 1043, 1044, 1045  
     serologic tests for, 392  
   hemorrhagic, acute. See *Nephritis, glomerular*.  
   in diphtheria, 417  
   in influenza, 511  
   in leptospirosis, 480  
   in Schönlein-Henoch syndrome, 1042  
   irradiation, 1042  
   suppurative, 1052  
   vascular, 1049  
   vs. anaphylactoid purpura, 922  
   vs. orthostatic albuminuria, 1019  
   vs. scurvy, 371  
 Nephrocalcinosis, 1223, 1224  
   in poliomyelitis, 541  
 Nephrogenic diabetes insipidus, 261, 1156  
 Nephrosclerosis, 1049  
 Nephrosis, 1044-9  
   acidosis in, 179, 180  
   clinical manifestations, 1045-7  
   corticosteroids in, 1047, 1048
- Nephrosis, hypoglycemia in, 1217  
   in aldosteronism, 1191  
   lower nephron, 1050-51  
   prognosis, 1047  
   re renal vein thrombosis, 1053  
   treatment, 1048-9  
 Nephrotic crisis, 1046  
 Nephrotic syndrome, 1044  
 Nerves, cranial, examination, 1064  
   lesions, in beriberi, 364  
   in pellagra, 366-7  
   peripheral, newborn, 318-20  
   phrenic, paralysis, 320  
 Nervous system, anomalies, 1075-9  
   autonomic, diseases, 1107  
   examination, 1066  
   central, failure, in newborn, 323  
   depressants, 205  
   developmental lesions, 1075-9  
   growth, 15  
   infections, tests for, 389  
   re hyponatremia, 191  
   static lesions, 1075-9  
   stimulants, 206  
   tuberculosis, 468-70  
 Nervous vomiting, 648  
 Nervousness, 75-7  
   treatment, 76  
 Nesidioblastoma re hypoglycemia, 1217  
 Neurilemmoma, 1363  
 Neurinoma, 1363  
 Neuritis, 1107-1108  
   chronic, 1107  
   in German measles, 488  
   in influenza, 511  
   in mumps, 507  
   in typhoid fever, 441  
   peripheral, due to bacillary dysentery, 435, 436  
   vs. poliomyelitis, 539  
   vs. lead poisoning, 1376  
 Neuroblastoma, 1355  
 Neurofibroma, 1364  
 Neurofibromatosis, 1079, 1366  
   mental deficiency, 1131  
 Neurogenic swallowing dysfunction, 642  
 Neurohypophysis, 1151  
 Neurologic disease, examination, 1063-73  
   in newborn, 1067  
   history, 1063  
   symptoms, 1073-4  
 Neurologic infections re mental deficiency, 1135  
 Neurologic lesions re unexpected death, 351  
 Neuroma, 1363  
 Neuromotor development, 2-9 years, 35  
 Neuromuscular glycogen disease, 272  
 Neuromyelitis optica, 1096  
 Neuritis, infectious, 525  
   vs. poliomyelitis, 539  
 Neuropathy, 1107-1108  
 Neuroses re cranial injury, 1105  
 Neurosyphilis, 474, 476, 477, 479  
 Neurotic traits, 75-83  
 Neutropenia, cyclic, 965  
   in agammaglobinemia, 256  
   malignant, 964-5  
   periodic, 965  
   primary splenic, 988  
 Neutrophils, 963

- Nevus, **1274**  
 blue, 1361  
 pigmented, 1361  
 strawberry, 1274, 1358
- Nevus flammeus, 1274, 1359
- Nevus sebaceus, 1362
- Nevus vasculosus, 1274
- Nevus vinosus, 1358
- Newborn, **286-349**  
 abdomen, 29  
 acid-base balance, 290  
 adrenal glands, 292  
 adrenal hemorrhage, 320  
 afibrinogenemia, 982  
 allergy, gastrointestinal, 1327  
 anemia in, **335-6**  
   due to transplacental hemorrhage, 943  
   of hemorrhage, 943-4  
 anoxia, **321-3**  
 apnea, 322-3  
 aspiration of stomach, 301  
 atelectasis, **324**  
 birth injury, **315-23**  
 blood cells, 289, 931-2  
 blood disturbances, **335-7**  
 blood pressure, 288, 298  
 blood volume, 288  
 brachial palsy, 318-20  
 breast secretion, 30  
 breasts, engorged, 340  
 breathing, 297  
 caloric requirements, 290  
 capillary resistance, 288  
 carbohydrate metabolism, 287  
 carbonic anhydrase, 287  
 care of, **301-304**  
   eyes, 303  
   skin, 303  
 cerebral edema, 318  
 characteristics, 26, 27, **28-30**  
 characteristics of illness in, **314-15**  
 chest, 29  
 circulation, 30, 288, 289, 840  
 coliform infections, 344, 346  
 congenital anomalies, **314**  
 constipation, **330**  
 convulsions, 314  
 Coxsackie infections, **348**  
 craniotabes, 296  
 cryptococcosis, 564  
 cyanosis, 314  
 deaths by age, 286  
 diabetes mellitus syndrome, 1213  
 diarrhea, 315, **346-7**, 655  
 digestion, 289, 290  
 diseases, **314-48**  
 disturbances, of genitourinary system, **337-8**  
   of respiratory tract, **323-9**  
 Duchenne-Erb's paralysis, 318-20  
 ear, 29  
 edema, **342**  
 effects of cesarean section, 294  
 endocrine disturbances, **343-4**  
 endocrine function, 291-2  
 Erb's paralysis, 318-20  
 erysipelas, 410  
 esophageal atresia, 330  
 evaluation of respiratory status, 297-8  
 eyes, 29, 1329  
 face, 29  
   palsy, 320  
 feeding, 28, **112-28**, 304. See also *Infant feeding*.
- Newborn, fracture, of clavicle, 321  
   of extremities, 321  
   of nose, 321  
   of skull, 316  
 frenum of tongue, 29  
 gamma globulin, 253-4  
 gastric acidity, 289  
 gastric perforation, 663  
 general factors, 4  
 genetic factors, 293  
 genitals, 299  
   edema of, 1058  
 hair, 29  
 harlequin color change, 295  
 heart, 297  
   rate, 821  
 hemangiomas, 29  
 hemolytic disease, 955-62  
 hemorrhage, **336**  
 hepatic function, 289  
 hepatitis, 334, 706  
 herpes simplex, 493  
 history, **293-5**  
 hyaline membrane disease, **324-6**  
 hydrocele, 691  
 hyperbilirubinemia, 334  
 hyperthyroidism, 343  
 hypoprothrombinemia, 981  
 icterus, 289, 333  
 immunity, 292  
 infections, **344-8**  
 insulin in, 292  
 intracranial hemorrhage, 316-18  
 jaundice, 315, **332-5**, 715-16  
 kernicterus, 335  
 kidneys, 337  
   agenesis, 337  
   function, 290  
 Klumpke's paralysis, 319  
 lacrimal glands, 29  
 legs, 30  
*Listeria monocytogenes* in, **347**  
 liver, 28, 299  
   abscess, 708  
   rupture, 320  
 lobar emphysema, **329**  
 lung, cysts, **329**  
   volumes, 734  
 lymphosarcoma, 993  
 malaria, 605  
 maternal factors in, 293  
 meconium bodies, **331**  
 meconium ileus, **331-2**  
 meconium peritonitis, **332**  
 meconium plugs, **331**  
 megacolon, 674  
 metabolic disturbances, **342**  
 metabolism, 290  
 mongolian spots, 296  
 mortality, 306  
   rates, 5, 7, 8  
 myasthenia gravis, 1271  
 myoblastoma of gum, 1349  
 myocarditis, 529  
 narcosis, 323  
 nasal sinuses, 29  
 natal factors, 4  
 nervous system, examination, 1067  
 nursery care, **303-304**  
 obstetric factors in, 294  
 obstetric mortality rates of, 294  
 orthopedic disturbances, re intrauterine position, **1250-52**  
 oxygen saturation of arterial blood, 287, 288
- Newborn, pancreas, 292, 718  
 parathyroids, 292  
 parotitis, 637  
 peripheral nerve injuries, 318-20  
 peritonitis, 687  
 petechiae, 289, 337  
 phrenic nerve paralysis, 320  
 physical examination, **295-300**  
 physiologic anemia, 932  
 physiology of, **286-93**  
 pituitary, 292  
 plasma cell pneumonia, 798  
 pneumomediastinum, 328  
 pneumonia, 326-8  
 pneumothorax, **328**  
 prenatal factors, 4  
 prepuce, 30  
 pulmonary hemorrhage, 959  
 pulse rate, 288, 298  
 pupillary light reflex, 300  
 purpura, 337  
 reflexes, 299, 300, 1067  
   abdominal, 300  
   postural, 1067  
 respiration, 28, 286-8  
 respiratory disorders, 743  
 respiratory distress, **320-23**  
 respiratory quotient, 290  
 resuscitation, 301-303, 741  
 retrobulbar hemorrhage, 1332  
 Rh iso-immunization, 956-61  
 sclerema, 1278  
 seborrhea of scalp, 1283  
 skin, 295  
   lesions, **338-9**  
 skull, 29  
 spinal injuries, 318  
 staphylococcal infections, **344-6**  
 sternocleidomastoid, 320  
 stools, 30, 290  
 subconjunctival hemorrhages, 316  
 subcutaneous fat necrosis, 1278  
 tetany, **342**, 1111  
 thrombocytopenia, 976  
 thrush, **330**  
 thymus, 30  
 thyroid, 292  
 torticollis, 320  
 transitory fever, **342**  
 umbilical cord, 30  
   care of, 303  
 umbilicus, **340-42**  
 urinary tract infection, **338**  
 urination, 30, 1011  
 vital capacity, 287  
 vitamin K for, 303  
 vomiting, 315, **330**, 648  
 water balance in, 291  
 Newcastle disease, tests, 394  
 Niacin. See *Nicotinic acid*.  
 Niacinamide. See *Nicotinamide*.  
 Nickel in nutrition, 107  
 Nickerson-Kveim test, 1346  
 Nicotinamide, 366  
   in Hartnup disease, 267  
   requirement, 110  
 Nicotine poisoning, 1390  
 Nicotinic acid, 266, 366  
   deficiency, 366-7  
   effects of, 108  
   excess, effects of, 108  
   function, 108  
   in milk, 121  
   metabolism, 110  
   requirements, 107, 108, 111  
   sources, 108



- Niemann-Pick disease, **1000**  
vs. Tay-Sachs disease, 1094
- Night blindness, 361  
congenital, 245
- Night terrors, 90
- Nightmares, 90
- Nikethamide, dose, 221
- Nikolsky's sign, 1285
- Nipples, fissures, 114
- Nisentil. See *Alphaprodine*.
- Nitrites, poisoning, 1390
- Nitroaniline poisoning, 1383
- Nitrobenzene poisoning, 1383
- Nitrofurantoin, 1034  
dose, 217  
hemolytic anemia with, 264-5
- Nitrofurazone re hemolytic anemia, 953
- Nitrogen, retention in adolescence, 151, 153
- Nitrogen mustard, 969  
dose, 221  
in lymphosarcoma, 994  
in nephrosis, 1049  
therapy, 994
- Nivaquine. See *Chloroquine*.
- Nocardiosis, **565**
- Nodular nonsuppurative panniculitis, 1279
- Nodules, subcutaneous, in rheumatic fever, 907
- Noma, **634**
- Nonprotein nitrogen, blood, 1404
- Norepinephrine. See *Arterenol*.
- Normals, statistical concept, **47-61**
- Nose. See also *Nasopharynx*.  
absence, 744  
accessory, 744  
adenoma, 1348  
foreign bodies in, 745, 756  
fracture, in newborn, 321  
glioma, 1348  
hemorrhage, 745, 746  
in influenza, 511  
in rheumatic fever, 908  
in typhoid fever, 440  
malformation, 744  
obstruction, in leontiasis ossea, 1247  
papilloma, 1348  
passages, in newborn, 32  
polyps, 756  
septum, deviation, 745  
sinuses, development, 754  
tumor, **1347**
- Nose drops, as cause of pneumonia, 800  
in nasal pharyngitis, 750
- Nosebleed. See *Nose, hemorrhage*.
- Novobiocin, antimicrobial properties, 397  
dose, 221
- Nuchal-spinal signs in poliomyelitis, 537
- Nupercaine. See *Dibucaine*.
- Nursery school, effects on development, 63
- Nutmeg poisoning, 1391
- Nutramigen, 125
- Nutrition. See also *Diet; Food*.  
and menstruation, 155  
calories, 98-100  
carbohydrates, 101  
deficiency, and shock, 181  
convalescence, 233  
digestibility in, 111
- Nutrition, disorders, prevention, 142  
disturbances, **352-80**  
fat, 102  
maternal, effect on fetus, 242  
minerals, 102-107  
of embryo re congenital anomalies, 244  
protein, 101  
requirements, **97-112**  
infant, 31  
school period (6-12 years), 36  
roughage in, 111  
satiety in, 111  
socio-economic factors, 111  
vitamins, 107-11  
water, 97, 99, 100
- Nutritional edema, **356**
- Nystagmus, congenital, 1102  
in arachnodactyly, 1243  
in cerebellar disease, 1074
- Nystatin, antimicrobial properties, 397  
dose, 221  
for thrush, 634
- OBEDIENCE in mental and emotional development, 70
- Obesity, **354-6**  
diet calculation, 1409-11  
in adolescence, 37-8, 154, 355  
differential diagnosis, 1162  
in Laurence-Moon-Biedl syndrome, 1232  
prevention, 143
- Obstructive jaundice, 701-702
- Ochronosis, alcaptonuric, 259
- Octamethyl pyrophosphoramide in myasthenia gravis, 1272
- Ocular. See also *Eyes*.  
features, re intracranial pressure, 1083  
formulary, 1331
- Oculoglandular syndrome in cat-scratch fever, 522
- Odontoma, 620
- Ohara's disease, 447
- Oils, poisoning, 1391
- Ointment, anthralin, in alopecia areata, 1281  
hydrocortisone, in infantile eczema, 1316  
Ichthammol, in furunculosis, 1288
- Olac, 124
- Oligocephalon, 1077
- Oliguria. See *Urine, suppression*.
- Ollier's disease, **1245**
- Omental cyst, 1360
- Omphalocele, 340
- Omphalomesenteric duct, anomalies, 670, 671  
patency of, 340
- Onychophagy. See *Nail-biting*.
- Ophthalmia, in meningitis, 428  
sympathetic, 1340
- Ophthalmic astringent solution, 1331
- Ophthalmoscopic. See *Eyes*.
- Opiates, poisoning, 1391
- Opium, camphorated tincture of, dose, 222
- Oppenheim's disease, 1267
- Optic atrophy, 1342  
hereditary, 1101  
in leontiasis ossea, 1247  
in osteopetrosis, 1240  
syphilitic, 477
- Optic chiasm, glioma, 1086
- Optic nerve in filariasis, 588
- Optic neuritis, in typhoid fever, 441  
vs. optic atrophy, 1342
- Oral. See also *Mouth; Teeth*.  
cavity, **619-38**  
tumors, **1347-9**  
fluids, potassium in, 1408  
sodium in, 1408  
hygiene, 619  
moniliasis, 633  
gentian violet, 217  
in newborn, 330  
mucosa, diseases, **633-4**  
solutions, composition, 197  
teratoma, 1347
- Orbit; Orbital. See *Eyes*.
- Orchitis, **1059**  
in mumps, 506, 507  
in pleurodynia, 528  
in smallpox, 499
- Orcin test, 278
- Ordway's solution, composition, 197
- Organic lesions in menstrual irregularities, 156
- Orthodiagraphy of heart, 826
- Orthophoria, 1334
- Orthoptic therapy in strabismus, 1336
- Osgood-Schlatter's disease, 1258
- Osler's nodes, 888
- Osseous. See *Bones*.
- Ossification of epiphyses, 22-4
- Osteitis fibrosa cystica in hyperparathyroidism, 1177-8, 1179-80
- Osteitis fibrosa disseminata, 1246
- Osteoarthropathy, hypertrophic pulmonary, **1248**
- Osteoblastoma, 1366
- Osteochondritis, syphilitic, 474
- Osteochondritis deformans juvenilis, 1258
- Osteochondrodystrophy, hereditary, 1237
- Osteochondroma, 1365  
re multiple exostoses, 1244
- Osteochondrosis, **1258**
- Osteodystrophia fibrosa, 1246
- Osteogenesis imperfecta, **1241-3**  
vs. chondrodystrophy, 1235
- Osteogenesis imperfecta congenita, 1241
- Osteogenesis imperfecta tarda, 1241
- Osteogenic fibroma, 1366
- Osteogenic sarcoma, 1368
- Osteoid osteoma, 1366
- Osteoma, 1366
- Osteomyelitis, **1259-60**  
in brucellosis, 445  
in nocardiosis, 566  
in sporotrichosis, 567  
in typhoid fever, 440  
Salmonella, 444  
vs. acute arthritis, 1257  
vs. cat-scratch fever, 522  
vs. leukemia, 968  
vs. poliomyelitis, 539  
vs. scurvy, 371  
with periapical infection, 626
- Osteopetrosis, **1239-41**
- Osteoporosis in fibrosis of pancreas, 727
- Osteopsathyrosis, **1241-3**
- Osteosarcoma, 1368

- Osteosclerosis, in fluorine poisoning,  
vs. osteopetrosis, 1240  
with hypercalcemia, 1224
- Osteosclerosis fragilis, **1239-41**
- Ostium primum defect, 861-2
- Ostium secundum defect, 860
- Otitis externa, 762
- Otitis media, acute, 763  
chronic, 765  
in bacillary dysentery, 436  
in influenza, 511  
in meningitis, 428  
in nasopharyngitis, 749  
in palatopharyngeal incompetence, 630-31  
in pertussis, 422  
in pneumonia, 791  
re adenoiditis, 760  
re cleft palate, 630  
serous, 764
- Otolith righting reflex, 1067
- Ouabain, dose, 221
- Ovary, agenesis, 1198-1200  
with webbed neck, 1233  
diseases, **1062**  
function, 1193-5  
granulosa cell tumor, 1201  
herniation, 690  
hypofunction, **1198-1201**  
polycystic, 1201  
tumors, 1062, **1358**
- Overfeeding in infant feeding, 130
- Ovum, fertilized, abnormalities, 234
- Owren disease, 255, 982
- Oxalates, poisoning, 1391
- Oxalic acid poisoning, 1391
- Oxalosis, 1054
- OXK agglutination test, 554
- OX2 agglutination test, 554
- OX19 agglutination test, 554
- Oxycephaly, 1227  
in Laurence-Moon-Biedl syndrome, 1232
- Oxygen, deficiency, 740  
cerebral, 1077  
in poliomyelitis, 539  
of newborn, 321-3  
re respiratory center, 733  
saturation, of arterial blood in newborn, 287, 288  
therapy, 742
- Oxytetracycline, in oxyuriasis, 581
- Ophthalmic, 1331
- Oxyuriasis, **579-81**  
epidemiology, 574, 579  
piperazine for, 223  
tests, 388  
treatment, 580
- PABA. See *Para-aminobenzoate*.
- Pachyonychia congenita, **1276**
- Palate, cleft, **628-30**  
hereditary factors, 246  
in palatopharyngeal incompetence, 630-31  
paralysis, in diphtheria, 417  
tumors of salivary gland origin, 1348
- Palatopharyngeal incompetence, 630-31
- Palsy. See *Paralysis*.
- Paludrine. See *Chlorguanide*.
- Pamaquin. See *Primaquine*.
- Pancreas, **717-32**  
absence, 718  
annular, 665, 718  
anomalies, 718, 730  
congenital hypoplasia, 718  
cyst, **731**  
dysplasias, re fibrosis of pancreas, 730  
enzymes of, 718  
in blood, 720  
in duodenal juice, 719  
in fibrosis of pancreas, 728  
in urine, 720  
tests for, 719-20  
extract, in fibrosis of pancreas, 729  
fibrosis, acidosis in, 179, 180  
cystic, **726-30**  
atelectasis in, 803  
etiology, 726  
pathology, 726  
pulmonary function in, 736  
re bronchiectasis, 809  
sweat electrolytes, 195  
treatment, 729-30  
vs. megacolon, 675  
vs. nocardiosis, 566  
fluid, composition, 195  
function, of secretory glands, 718  
tests, 719-20  
in newborn, 292, 718  
in systemic diseases, **731**  
neoplasms, **731**  
pseudocysts, 731  
size, 718  
traumatic lesions, 731  
tumor, **1353**  
re hypoglycemia, 1217
- Pancreatin, dose, 222  
in fibrosis of pancreas, 729
- Pancreatitis, acute, **730**  
mumps, 507, 730
- Pancreozymin, 718
- Panhematopenia, splenic, 989
- Panhypopituitarism, 1154
- Panniculitis, nodular nonsuppurative, **1279**
- Panophthalmitis, 1339
- Pantheric granules, dose, 222
- Pantothenic acid in nutrition, 110
- Papaverine, dose, 222
- Para-aminobenzoate in lupus erythematosus, 1290
- Para-aminobenzoic acid, in nutrition, 110
- Para-aminohippuric acid, renal clearance, 1008
- Para-aminosalicylic acid, dose, 222  
in tuberculosis, 464, 470
- Paradione. See *Paramethadione*.
- Paraganglioma, nonchromaffin, 1348
- Parahemophilia, 255, 982
- Paraldehyde, 206  
dose, 222  
in acrodynia, 1400  
poisoning, 1387
- Paralysis. See also *Paraplegia*.  
Bell's. See *Paralysis, facial*.  
brachial, in newborn, 318-20  
vs. pseudoparalysis of syphilis, 474  
cerebral, **1138-42**  
classification, 1139  
diagnosis, 1138  
drug therapy in, 1142  
prognosis, 1141  
re strabismus, 1336
- Paralysis, cerebral, re toxoplasmosis, 616  
treatment, 1141
- Duchenne-Erb's, 318-20  
due to injections, 1108  
due to meningitis, 428
- Erb's, 318-20  
facial, 1108  
familial, periodic, **1272**  
vs. poliomyelitis, 539  
hysterical, 1068  
in aldosteronism, 1191  
in beta-2-globulin deficiency, 256  
in Cocksackie meningitis, 529  
in diphtheria, 413, 417, 418  
in ECHO virus infections, 531  
in infectious neuronitis, 525  
in meningoencephalitis, 547  
in mumps, 507  
in pertussis, 422  
in poliomyelitis, 539-41  
in porphyria, 281  
in syphilis, 474, 476  
of facial nerve, 320  
re rabies vaccination, 515  
recurrent laryngeal, 772  
traumatic, 1108
- Paralytic ileus, 666
- Paramethadione, dose, 222  
in epilepsy, 1125
- Paranoid dementia praecox, 1149
- Parapertussis, **424**  
tests, 387  
vs. pertussis, 422
- Paraphimosis, 1056
- Paraplegia, hereditary, spastic, 1097  
hysterical, 1068
- Parasitic diseases, epidemiology, **574**  
myocarditis in, 893  
of skin, **1294-6**
- Parathyroid, disorders, **1175-80**  
function, 1175  
hormone, in tetany of vitamin D deficiency, 378  
of newborn, 292
- Paratyphoid fever, immunization, 142  
re Salmonella, 442, 443
- Paregoric, dose, 222
- Parenteral fluids, administration, **198-202**  
intramedullary infusions, 200  
intravenous infusions, 199-200  
solutions, composition, 197  
subcutaneous infusions, 200  
therapy, **183-202**  
deficit, 183-92, 195  
general considerations, 183-6  
historical data in, 183  
in specific conditions, 186-90  
laboratory data in, 184  
in poisoning, 1382  
maintenance, 192-5  
in surgical conditions, 195  
supplemental, **196, 198**
- Parenteral infections re diarrhea, 656
- Parenteral solutions, composition, **197**
- Parenthood, advisability, 4, **247**
- Parents, effect on emotional development, 65, 66  
interview with, 165-6  
observation of, 166-7  
role in mental and emotional development, 69



- Paresis, juvenile, 476  
 Parietal foramina, **1229**  
 Parinaud's oculoglandular syndrome, 518  
 Paronychia, in newborn, **339**  
   in scarlet fever, 409  
 Parotid, hemangioma, 1349  
 Parotitis, epidemic. See *Mumps*.  
   in herpangina, 528  
   in newborn, 637  
   recurrent, 638  
   suppurative, 637  
 Paroxysmal cold hemoglobinuria, 954  
 Paroxysmal tachycardia, **884**  
 Parrot's pseudoparalysis, 474  
 Parturient period, factors, 26, 27  
 PAS. See *Para-aminosalicylic acid*.  
 Passive transfer test, 1308  
*Pasteurella tularensis*, 447  
 Pastia's sign, 406  
 Patellar reflex, 300  
 Pathologic traits, dominant, 235-8  
   genetic factors, 235-41  
   recessive, 238-40  
 Paul-Bunnell test, 519  
 Paul's test, 499  
 PBI. See *Iodine, protein-bound*.  
 Pectus excavatum. See *Thorax, funnel chest*.  
 Pediatrician, and child, 10, 166  
   and parent, 165  
   in psychotherapy, 74  
   re mental and emotional development, 67-72  
 Pediatrics, introduction, **1-11**  
   preventive, **138-47**  
 Pediculosis, **1295-6**  
   Pediculosis capitis, 1295  
   Pediculosis corporis, 1296  
   Pediculosis pubis, 1296  
 Pedigree, chart, 237  
   deaf-mutism, 240  
   muscular atrophy, 239  
   muscular dystrophy, 241  
 Pel-Ebstein syndrome, 995  
 Pellagra, 366-7  
   vs. Hartnup disease, 267  
 Pellizzi's syndrome, 1160  
 Pelvis, breadth, annual increments, 14  
   birth to 5 years, 56-7  
   5-18 years, 58-9  
   measuring technique, 48, 56-9  
   deformities, in rickets, 375  
 Pemphigus neonatorum, **339**  
 Penicillin, antimicrobial properties, 397  
   dose, 222  
   in acute secondary diffuse peritonitis, 688  
   in congenital syphilis, 478, 479  
   in diphtheria, 418  
   in gonorrheal vulvovaginitis, 1061  
   in hyaline membrane disease, 325  
   in meningococcal meningitis, 428  
   in meningococcemia, 428  
   in pneumococcal meningitis, 430  
   in pneumonia in newborn, 328  
   in prevention of pulmonary infection in cystic fibrosis of pancreas, 730  
   in scarlet fever, 409  
   in staphylococcal meningitis, 431  
   in subacute bacterial endocarditis, 889  
 Penicillin, ophthalmic, 1331  
   renal clearance, 1008  
   skin rash, 1282  
 Penicillin benzathine, dose, 222  
 Penicillin V, dose, 222  
 Penis, abnormal size, **1057**  
   in herpes simplex, 492  
   strangulation, 1056  
   tuberculosis, 1059  
 Pentaquin. See *Primaquine*.  
 Pentobarbital sodium, as preanesthetic, 229  
   dose, 221, 222  
 Pentolinium tartrate, dose, 211  
 Pentose, metabolism, 277  
   defective, **276-8**  
 Pentosuria, **1020**  
   essential, **277**  
 Pentylene tetrazol, 206  
   dose, 220  
 Peptic ulcer, 671  
   in Meckel's diverticulum, 670  
   vs. bacillary dysentery, 436  
 Percentile method of tabulation, 43, 47  
 Perchlorperazine, dose, 213  
 Periarthritis nodosa, **927**  
 Pericardial effusion vs. pleural effusion, 814  
 Pericarditis, **899-901**  
   acute, benign, 901  
   adhesive, ascites in, 686  
   cardiac catheterization in, 900  
   chronic, constrictive, 901  
   due to Coxsackie virus, 529  
   idiopathic, 901  
   in acute renal failure, 1050-51  
   in brucellosis, 446  
   in infectious mononucleosis, 519  
   in mumps, 507  
   in rheumatoid arthritis, 901  
   in scarlet fever, 409  
   in uremia, 901  
   postoperative, 901  
   rheumatic, 900, 907  
   septic, 900  
   tuberculous, 901  
   viral, 901  
 Pericardium, cysts, 899  
   diseases, **899-901**  
 Perinatal factors in neonatal disturbances, 138-9  
 Perinatal mortality, **306**  
 Perinephritis, **1034**  
   abscess in, 1034  
 Periostitis in syphilis, 475  
 Periostium, elevation, in scurvy, 368-70  
 Peritoneum, abscess, 688-9  
   drainage, in nephrosis, 1049  
   malformations, **686**  
   tumors, 689  
 Peritonitis, **686-9**  
   acute, localized, 688-9  
   primary, 687  
   secondary diffuse, 687-8  
   chronic, 689  
   in brucellosis, 446  
   in coccidioidomycosis, 572  
   in erysipelas, 411  
   in newborn, 687  
   meconium, 332  
   tuberculosis, 468  
 Peritonsillar abscess, **754**  
 Perlèche, 365, 634  
 Permapen. See *Penicillin benzathine*.  
 Pernicious juvenile anemia, 939  
 Peroneal muscular atrophy, 1100  
 Perspiration, excessive, in acrodynia, 1399  
 Perthes' disease, 1257  
   re congenital hip, 1255  
   vs. tuberculosis of hip, 1263  
 Pertussis, **420-23**  
   clinical manifestations, 421  
   complications, 422  
   death rates, 3  
   diagnosis, 421  
   epidemiology, 420  
   etiology, 420  
   hemorrhage in, 422  
   immunity, 420  
   in newborn, 292  
   immunization, active, 139-41  
   pathology, 421  
   prevention, 423  
   prognosis, 423  
   quarantine for, 398  
   tests, 387  
   treatment, 423  
   vaccination, encephalitis in, 551  
   vaccine, 139-40, 141  
   vs. infectious lymphocytosis, 521  
 Pet Instant milk, 124  
 Petechiae, in newborn, 289, 337  
   in smallpox, 500  
 Petit mal epilepsy, 1119  
 Petroleum oil in pediculosis capitis, 1296  
 pH, nomogram, 176  
   of blood, 1402  
 Pharyngitis, acute, **750-53**  
   chronic, 757  
   in herpangina, 528  
   streptococcal, 751  
   with agranulocytosis, 965  
 Pharyngoconjunctival fever, 747, 751  
   tests, 394  
 Pharynx, in palatopharyngeal incompetence, 630  
   teratoma, 1348  
   tumors, **1347**  
 Phenacetin. See *Acetophenetidin*.  
 Phenergan hydrochloride. See *Promethazine hydrochloride*.  
 Phenobarbital, dose, 223  
   in convulsions, 1116, 1122, 1123, 1124  
   in pylorospasm, 661  
   in tetanus, 434  
 Phenobarbital sodium in status epilepticus, 1122  
 Phenol poisoning, 1391  
 Phenol red, renal clearance, 1008, 1013  
   test, 1008, 1013  
 Phenolphthalein, poisoning, 1391  
   skin rash, 1282  
 Phenolsulfonphthalein, renal clearance, 1008, 1013  
   test, 1008, 1013  
 Phenotype, 235  
 Phenolamine in pheochromocytoma, 1192  
 Phenylalanine, and ascorbic acid, in premature, 311  
   metabolism, defective, 258-61  
   requirements, 101  
 Phenylalanine-tyrosine metabolism, 258  
 Phenylephrine as mydriatic, 1331  
 Phenylketonuria, 259-60, 1131

- Phenylpyruvic oligophrenia. See *Phenylketonuria*.
- Phenytoin. See *Diphenylhydantoin sodium*.
- Pheochromocytoma, **1191**  
vs. hyperthyroidism, 1172
- Phimosis, **1056**  
obstructive, 1026, 1028
- Phlebitis in typhoid fever, 440
- Phlebogram, 823-5, 837  
jugular, 823-5
- Phlyctenular conjunctivitis, 1339
- Phobias, 81
- Phocomelia, 1231
- Phonocardiography, 837
- Phoria, 1334  
test, 146
- Phosphatase, alkaline, re jaundice, 702  
blood, 1404  
in bile, 695  
in rickets, 373  
low, rickets, 1224  
re liver function, 700  
serum, in hepatitis, 705  
in hypothyroidism, 1167
- Phosphate, renal reabsorption, 1007  
defective, 261
- Phosphate tetany, 1111
- Phosphaturia, and amino-aciduria, 262  
and glycosuria, 262, 264
- Phosphorus, deficiency, effects of, 103  
excess, effects of, 103  
function, 103  
in milk, 121  
in oral and parenteral solutions, 197  
inorganic, poisoning, 1391  
metabolism, 105  
organic, poisoning, 1392  
requirements, 103, 105, 107, 111  
serum level, 106  
sources, 103
- Phosphorylethanolamine in urine, 1224
- Photophobia, hysterical, 1068  
in acrodynia, 1399  
in vitamin A deficiency, 362
- Phrenic nerve paralysis, 320  
in diphtheria, 417
- Physical examination, 42  
approach to child, 167-8  
approach to parent, 168-9  
in neurologic disease, **1063-73**  
of newborn, **295-300**  
technique, **167-70**
- Physical growth and development, **12-56**
- Physical health, problems of, 157-8
- Physical status, evaluation, 42-61  
normal distribution curve for, 42
- Physician re mental and emotional development, 62, 63
- Physiologic jaundice, 333
- Phytobezoar, 664
- Pica, 88  
re anemia, 941
- Picking habit, **78**
- Pick's syndrome, 686, 689
- Picrotoxin, 206  
dose, 223
- Piebaldness, 260
- Pierre Robin syndrome, 629, 631, 632
- Pigeon breast, deformity, 1233
- Pigeon toe, 1253
- Pigment metabolism, inborn errors, **279-83**  
classification, 252
- Pilocarpine hydrochloride as miotic, 1331
- Pilonidal dimple, 685
- Pilonidal sinus, 685
- Pineal tumor re precocious puberty, 1159
- Pink disease, **1398-1401**
- Pinworm infection. See *Oxyuriasis*.
- Piperazine, dose, 223
- Piperazine citrate, in ascariasis, 578  
in oxyuriasis, 581
- Piperoxan, dose, 212
- Pitressin, 1155-7  
dose, 223  
in diabetes insipidus, 1156
- Pitressin tannate in oil, 1156
- Pituitary. See also *Diabetes mellitus*.  
adenoma, re Cushing's syndrome, 1190  
deficiency, hypoglycemia in, 1217  
disorders, **1150-57**  
dwarfism, 343, **1151-4**  
differential diagnosis, 1153  
idiopathic, 1151  
prognosis, 1153  
treatment, 1153  
vs. gonadal dysgenesis, 1199  
vs. hypothyroidism, 1167  
with organic lesion, 1152  
extract, posterior, dose, 223  
function, 1150-51  
gigantism, **1154-5**  
growth hormone, 1150  
neoplasms, 1151  
of newborn, 292  
posterior lobe, functions, 1151  
re obesity, 1162
- Pityriasis rosea, **1286**
- Pityriasis versicolor, **1293**
- Placental dysfunction syndrome, **313-14**
- Plagiocephaly, 1227
- Plague, immunization, 142
- Plantar warts, 1296
- Plasma. See also *Blood*.  
albumin, 1403  
composition, 197  
distribution, in body, 172  
electrolytes, 174  
in disease, 179  
fibrinogen, 1403  
globulin, 1404  
in shock, 181  
protein, 1404  
congenital defects of, in hemorrhagic diatheses, 253-5  
defective synthesis of, 251-2, 253  
level, 101  
specific gravity, 1405  
therapy, in nephrosis, 1048  
thromboplastin antecedent (PTA), 252-5 *passim*, 971, 972, 977, 980  
deficiency, 980  
thromboplastin component (PTC), 252-5 *passim*, 971, 972, 977, 980  
deficiency, 980  
volume, 1405
- Plasma cell hepatitis, 710
- Plasma cell pneumonia, 798
- Plasmochin. See *Primaquine*.
- Plasmodia*, 604
- Platelet factor, 253, 254
- Platelets. See under *Blood*.
- Platybasia, **1228**  
in Morquio's disease, 1237  
secondary, 1229
- Play, development, in infant, 34  
in mental and emotional development, 70, **71**
- Pleural effusion, 813-16  
in actinomycosis, 562  
in coccidioidomycosis, 571  
in tularemia, 448
- Pleurideficiency syndrome, 357-60
- Pleurisy, **812-16**  
dry, 812  
in brucellosis, 446  
in Caffey's disease, 1260  
in diphtheria, 417  
in pneumonia, 789  
plastic, 812  
purulent, 815-16  
rheumatic, 908  
serofibrinous, 813-15  
serous, 813-15  
vs. pleurodynia, 528
- Pleuritis, tuberculous, 459
- Pleurodynia, epidemic, 528  
tests, 391  
vs. pleurisy, 813
- Pneumatocoele, 807
- Pneumatosis intestinalis, **672**
- Pneumococcal meningitis, 429-30
- Pneumococcal pneumonia, **787-92**
- Pneumococcus, tests, 387, 389, 393
- Pneumocystis carinii* in pneumonia, 798
- Pneumoencephalography, 1071
- Pneumomediastinum in newborn, **328**
- Pneumonia, **786-801**  
abdominal distention in, 791, 792  
aspiration, **799-801**  
in newborn, 327  
bacterial, **787-94**  
classification, 787  
cryptococcosis, 564  
death rates, 3, 9  
due to *Salmonella*, 444  
eosinophilic, 801  
Friedländer's bacillus, 793  
giant cell, 797  
*H. influenzae*, 793  
hydrocarbon, 799-800  
hypostatic, **801**  
in bacillary dysentery, 436  
in diphtheria, 416  
in erysipelas, 411  
in influenza, 510, 511  
in measles, 486  
in meningitis, 428  
in newborn, **326-8**  
in nocardiosis, 566  
in pertussis, 422  
in Rocky Mountain spotted fever, 559  
in scarlet fever, 409  
in strongyloidiasis, 586  
in toxoplasmosis, 617  
in tracheo-esophageal fistula, 641  
in tularemia, 448  
in typhoid fever, 440  
kerosene, 799-800  
lipoid, 800  
mucormycosis, 565  
plasma cell, 798



- Pneumonia, pneumococcal, 787-92**  
 bronchopneumonic, 790  
 clinical manifestations, 788-90  
 epidemiology, 788  
 lobar, 790  
 meningitis with, 791  
 pathology, 788  
 treatment, 791-2  
 primary atypical, 796-7  
 Q fever, 560  
 sporotrichosis, 567  
 staphylococcal, **792-3**  
 streptococcal, 792  
 thrush, 798  
 tuberculous, 457  
 viral, **794-8**  
 vs. appendicitis, 677  
 vs. diphtheria, 416  
 with nasal pharyngitis, 749
- Pneumonitis, dust, 799**  
 in histoplasmosis, 568  
 in rheumatic fever, 908  
 in thrush, 634  
 interstitial, 794-7
- Pneumothorax, 816**  
 in newborn, **328**  
 tension, 817
- Podophyllin for warts, 1297**
- Poison ivy, 1283**
- Poison oak, 1283**  
 re nephrosis, 1044
- Poisoning, acid burns of esophagus, 643**  
 ammonia, 643  
 antidotes, 1380  
   universal, 1381  
 BAL in, 1381  
 chemical, **1382-97**  
   general considerations, 1378-83  
 Clorox, 643  
 diagnosis, 1379  
 digitalis, 898  
 Drano, 643  
 drug, **1382-97**  
   general considerations, 1378-83  
 esophageal stricture from, 643  
 fluid therapy, 1382  
 food, **1374-5**  
 from vitamin A, 363  
 identification of agent, 1380  
 incidence, 1378  
 lead, **1375-8**  
 lye, 643  
 mercury, 1379  
 mortality rate, 144  
 of liver, 712  
   re hypoglycemia, 1218  
 porphyrinuria in, 279  
 prevention, 1379  
 ragwort, 711  
 re unexpected death, 351  
 salicylate, treatment, parenteral  
   fluid, 196, 198  
 Senecio, 711  
 treatment, general, 1380  
   supportive, 1381
- Poisons, chemical, 1394-8. See also specific chemicals.**  
 drug, **1394-8. See also specific drugs.**
- Poliomyelitis, 531-44**  
 abortive, 535-7  
 bulbar, 539-41, 543-4  
 clinical manifestations, 535-41  
 complications, 541  
 death rates, 3
- Poliomyelitis, epidemiology, 532**  
 hot packs for, 542  
 immunity, active, 533, 534  
   passive, 533  
 immunization, 140, 141  
 in newborn, 292  
 incubation period, 533  
 infection vs. disease, 532  
 lumbar puncture in, 541  
 nonparalytic, 537  
 paralytic, 539-41  
 pathogenesis, 534  
 pathology, 534  
 prognosis, 541-2  
 public health measures, 532  
 pulmonary function in, 736  
 quarantine for, 398  
 re encephalitis, 549  
 re intramuscular injections, 533  
 re tonsillectomy, 533  
 respiratory failure, management,  
   543, 544  
 respiratory paralysis in, 539-41,  
   543-4  
 schema of major features, 536  
 tests, 388, 390, 391  
 tracheotomy for, 544  
 treatment, 542-4  
 vaccination, 141  
   encephalitis due to, 551  
 vaccine, 533, 534  
 vs. bacillary dysentery, 436  
 vs. Cocksackie infections, 529  
 vs. ECHO virus infections, 530,  
   531  
 vs. lead poisoning, 1376  
 vs. pseudoparalysis of syphilis, 474  
 vs. rheumatic fever, 909  
 vs. scurvy, 371  
 vs. Werdnig-Hoffmann disease,  
   1100  
   with respiratory insufficiency, 540
- Poliovirus, diseases due to, 526**  
 types, 532
- Pollakiuria, 1015**
- Pollen, hyposensitization, 1310**
- Pollinosis, hyposensitization, 1310**
- Polyarteritis, 927**
- Polycystic disease, of kidneys, 1024**
- Polycythemia, 962**
- Polycythemia vera, 962**
- Polydactyly, 1231**  
 in Laurence-Moon-Biedl syn-  
   drome, 1232
- Polymorphonuclear white cells, 963**
- Polymyositis, chronic, 1265**  
 vs. Werdnig-Hoffmann disease,  
   1100
- Polymyxin B, antimicrobial proper-  
 ties, 397**
- Polymyxin B sulfate, dose, 223**
- Polyneuritis, chronic, 1107**  
 vs. Werdnig-Hoffmann disease,  
   1100
- Polyorchism, 1059**
- Polyostotic fibrous dysplasia, 1223,  
 1246**  
 with precocious puberty, 1159
- Polyp, nasal, 756**
- umbilical, 341**
- Polyposis, intestinal, 1351**
- Polyserositis, 689**
- Polyuria, 1015. See also Diabetes in-  
 sipidus.**  
 in hypercalcemia, 1224
- Pontocaine. See Tetracaine.**
- Porencephaly, 1075**
- Porphyrin, 279-81**  
 acute, intermittent, 280-81  
   vs. poliomyelitis, 539  
 congenital, 279-80  
 cutanea tarda type, 281  
 erythropoietic, 279-80  
 hereditary, 280-81
- Porphyrins, in bile, 695**  
 in lead poisoning, 1376  
 metabolism, 279
- Porphyrinuria, acquired, causes, 279**
- Positions of comfort, 1250-52**
- Posthitis, 1057**
- Postinfectious encephalitis, 550**
- Postmaturity, 313**
- Postural reflexes, in newborn, 1067**
- Posture, development, 17, 18**  
 preschool period (2-6 years), 36  
 school period (6-12 years), 37
- Postvaccinal encephalitis, 551**
- Potassium, deficiency, effects of, 103**  
 electrocardiogram in, 830  
 in dehydration, 185, 187  
 in periodic paralysis, 1272  
 excess, effects of, 103  
 function, 103  
 in aldosteronism, 1191  
 in diabetes mellitus, 1209  
 in fluid therapy, 197  
 in hypokalemia, 192  
 in hypopotassemia, 192  
 in milk, 121  
 in nephrotic syndrome, 1049  
 in oral and parenteral solutions,  
   197  
 in oral fluids, **1408**  
 intoxication, in acute renal failure,  
   1050-51  
   treatment, 198  
 loss from body fluids, 195  
 metabolism, 105  
 plasma level, 105, 106  
 requirements, 103, 105  
 serum level, high, electrocardio-  
   gram in, 827, 830  
 sources, 103
- Potassium antimony tartrate in schis-  
 tosomiasis, 595**
- Potassium chloride in familial peri-  
 odic paralysis, 1273**
- Potassium iodide in asthma, 1324**  
 in sporotrichosis, 567
- Potassium permanganate, in derma-  
 titis venenata, 1283**  
 in larkspur poisoning, 1390  
 in monk's hood root poisoning,  
   1390  
 in oxalate and oxalic acid poi-  
   soning, 1391  
 in phosphorus poisoning, 1392  
 in ringworm of foot, 1292  
 in smallpox, 501
- Pott's disease 1262**
- PPD. See under Tuberculin.**
- Prausnitz-Küstner reaction, 1308**
- Preanesthetic medication, 229-30**
- Prauricular fistula, 762**
- Precocious puberty. See under Pu-  
 berty.**
- Prednisolone, 1181**  
 dose, 224
- Prednisone, 1181**  
 dose, 224  
 in dermatomyositis, 925  
 in nephrotic syndrome, 1048

- Prednisone, in rheumatic fever, 912  
in rheumatoid arthritis, 919
- Pregnancies, multiple, **304-306**
- Pregnanediol, 1194
- Premature birth re kernicterus, 959
- Premature infant, caloric requirements, 290  
capillary fragility in, 337  
care, **308-12**  
drugs in, 311  
feeding, 309-11  
gamma globulin in, 312  
hemorrhage in, 289  
incubator care, 308  
intracranial hemorrhage in, 316-18  
iron for, 932  
plasma cell pneumonia in, 798  
prevention of infection, 311  
retrolental fibroplasia in, 1343  
tyrosyluria in, 260  
vitamins in, 310
- Premature senility, 1153
- Prematurity, **306-12**  
causes, 307  
causes of death, 307  
definition, 307  
effect on growth and development, 40  
incidence, 307  
mortality, 307  
prevention, 307  
preventive aspects, 139  
prognosis, 312  
re neurologic disease, 1077
- Prenatal disturbances, **234-85**  
metabolic, **250-85**
- Prenatal factors, 4, **234-43**
- Prenatal period, age factors, 4, 26, 27  
preventive pediatrics in, 138
- Prepuce, adherent, **1056**  
of newborn, 30  
redundant, 1056
- Preschool period, age factors, 7, 26  
behavior, 36  
characteristics, 33, 35-6  
dental care, 33, 36  
growth, 33  
posture, 36
- Preventive pediatrics, **138-47**  
accidents, 143  
detection of disease, **145-7**  
health education, **145-7**  
immunization, 139-42  
neonatal period, 139  
nutritional disorders, 142  
perinatal factors, 138  
prenatal disturbances, 138  
primary factors, 138-44  
secondary factors, 144
- Preventriculosis, 644
- Prickly heat, 1298
- Primaquine, 608  
hemolytic anemia with, 264-5  
re hemolytic anemia, 953
- Primary atypical pneumonia, 796-7
- Primidone, dose, 220  
in epilepsy, 1124, 1125  
in infantile myoclonic seizures, 1120
- Primordial dwarfism, 1152
- Priscoline. See *Tolazoline*.
- Privine. See *Nephazoline*.
- Probanda, 125
- Probanthine. See *Propantheline*.
- Procaine, dose, 222
- Procaine amide hydrochloride, dose, 224
- Prochlorperazine, dose, 213
- Procidencia, **683**
- Proconvertin deficiency, 255
- Progeria, 1153  
vs. Simmonds' disease, 1154
- Progesterone, 1193
- Proguanil. See *Chlorguanide*.
- Prolapse of rectum, **683**
- Proline absorption, test for, 720
- Promethazine hydrochloride, dose, 223
- Promin in tuberculosis, 464
- Promizole in tuberculosis, 464
- Pronestyl. See *Procaine amide hydrochloride*.
- Propantheline, dose, 224
- Proportions, body, changes in, 16-18
- Propylthiouracil, dose, 224  
in hyperthyroidism, 1173  
re goiter, 1171
- Prostate, tumors, **1357**
- Prostigmin bromide, dose, 221
- Prostigmin methylsulfate, dose, 221
- Protein, Bence-Jones, in urine, 1019  
conversion, 101  
deficiency, 356  
function, 99, 101  
in diet in epilepsy, 1125  
in milk, 120, 121  
in oral and parenteral solutions, 197  
in proprietary milks, 124-5  
in urine, 1012, 1018  
loss, from body fluids, 195  
metabolism, hepatic, 698  
inborn errors of, **253-68**  
plasma, 1404  
defective synthesis, 251-2, 253  
re hypoglycemia, 1220  
requirements, 99, 100, 101, 111  
serum, 1403  
levels, 698  
SMA, 124  
source, 99
- Protein-base binding power (serum), 1402
- Protein-bound iodine. See under *Iodine*.
- Proteus, tests, 387, 388, 389, 392, 393, 394
- Proteus vulgaris* re serologic tests for rickettsia, 554
- Prothrombin. See under *Blood*.
- Protozoa, intestinal, 610
- Protozoan diseases, **604-18**
- Provitamin D, 372
- Prurigo, **1301**
- Pruritus re jaundice, 701
- Pruritus ani, **683**
- Pseudogynecomastia, 1198
- Pseudohermaphroditism, female, 1202  
re Klinefelter's syndrome, 1197  
in adrenal hyperplasia, 1187, 1188  
male, 1203  
re Turner's syndrome, 1199  
re adrenocortical tumor, 1189
- Pseudohypoparathyroidism, 261, 1176  
tetany in, 1111
- Pseudomonas, tests, 387, 388, 389, 392, 393, 394
- Pseudoparalysis, in Caffey's disease, 1260  
syphilitic, 474  
vs. poliomyelitis, 539
- Pseudo - pseudohypoparathyroidism, 1177
- Pseudosclerema, 1278
- Pseudotumor cerebri, 1092
- Psittacosis, tests, 387
- Psoas abscess, tuberculous, 1262
- Psoriasis, **1285-6**
- P.S.P. See *Phenolsulfonphthalein*.
- Psychogenic factors in menstrual irregularities, 155
- Psychogenic megacolon, 654
- Psychologic aspects of adolescence, **156-60**
- Psychologic disorders, **73-91**  
as neurotic traits, **75-83**  
effect on reading, 95  
effect on speech development, 92  
general considerations, 73  
in psychosomatic illness, **87-91**  
in school, 83  
re stuttering, 93
- Psychologic factors, in lactation, 115-16  
re obesity, 355
- Psychomotor seizure, 1119
- Psychoses, **1148**  
in porphyria, 281  
re cranial injury, 1105
- Psychosomatic factors in ulcerative colitis, 679
- Psychosomatic illness, **87-91**
- Psychotherapy, 74-5  
in allergy, 1311  
in asthma, 1325
- PTA. See *Plasma, thromboplastin antecedent*, under *Blood*.
- PTC. See *Plasma, thromboplastin component*, under *Blood*.
- Pteroylglutamic acid, in nutrition, 111
- Pterygium, 1332
- Pterygium colli, 1233
- Ptyalism, 637
- Ptyalorrhea, 637
- Puberty. See also *Adolescence*.  
precocious, **1157-61**  
classification, 1157  
constitutional, 1157-9  
criteria, 1157  
medicational, 1161  
partial, 1161  
true, 1157-9  
vs. pituitary gigantism, 1155  
with brain lesion, 1159-61  
with fibrous dysplasia of bone, 1246  
with polyostotic fibrous dysplasia, 1159
- pseudoprecocious, due to granulosa cell tumor, 1201  
in adrenal hyperplasia, 1186-9  
re adrenocortical tumor, 1189  
re testicular tumors, 1197
- Pubic hair, 38, 39
- Puetz-Jeghers syndrome, 1351
- Pulling habit, **78**
- Pulmonary. See also *Lungs*.  
arteriovenous fistula, 855  
atresia, 833-5, 848  
compliance, 734  
failure, in newborn, **324**



- Pulmonary hyaline membrane, 308  
hypertension, in Eisenmenger syndrome, 849  
primary, **879-80**  
with ventricular septal defect, 856  
resistance, 736  
stenosis, 833-5, 866-70  
classification, 867  
in tetralogy of Fallot, 842-8  
infundibular, 869  
valvular, 867-8  
with arteriovenous shunt, 869-70  
with atrial septal defect, 869, 870  
with patent ductus arteriosus, 870  
with transposition of vessels, 852  
with veno-arterial shunt, 870  
with ventricular septal defect, 870  
valve, disease, acquired, 892  
venous return, anomalous, **874-5**  
ventilation, 737-9
- Pulse, arterial, 821-2  
Corrigan, 822  
rate, by age, 821  
in anesthesia, 230  
in newborn, 288, 298  
venous, 823
- Pulsus bigeminus, 884  
Pulsus paradoxus, 899  
Pulsus trigeminus, 884
- Pupil, dilatation, drugs for, 1330, 1331  
disturbances, 1333
- Pupillary light reflex, 300
- Purines, defective reabsorption, 261
- Purinethol. See *Mercaptopurine*.
- Purpura, anaphylactoid, **920-22**  
with nephritis, 1042  
congenital, thrombocytopenic, 337  
fibrinolytic, 982  
in adrenal crisis, 1183  
in brucellosis, 446  
in cytomegalic inclusion disease, 524  
in kala-azar, 609  
nonthrombocytopenic, due to drugs, 974  
Schönlein-Henoch, 920-22  
thrombocytopenic, congenital, 337, 976  
etiology, 975, 976, 977  
idiopathic, 974-6  
in newborn, 976  
thrombotic, 976  
with giant hemangioma, 977  
toxic vascular, 974
- Pyelitis, **1030-34**. See also *Pyelonephritis*.
- Pyelonephritis, **1030-34**  
acute, 1031-4  
chronic, 1028, 1031-4  
clinical manifestations, 1032  
diagnosis, 1032  
etiology, 1031  
in bacillary dysentery, 436  
pathology, 1031
- Pyknolepsy, 1119
- Pylorospasm, 660, 661
- Pylorus, stenosis, 658-62  
alkalosis in, 179, 180  
clinical manifestations, 659  
deficit therapy, 186, 189
- Pylorus, stenosis, diagnosis, 660  
re prognosis, 660  
treatment, 661-2  
vs. adrenal hyperplasia, 1188  
vs. adrenal insufficiency, 660  
vs. intestinal obstruction, 666  
water and electrolyte deficits in, 185
- Pyopneumothorax, 816
- Pyribenzamine. See *Tripelethamine hydrochloride*.
- Pyridostigmine in myasthenia gravis, 1272
- Pyridoxine, deficiency, tryptophane in, 265  
in nutrition, 110
- Pyrimethamine in toxoplasmosis, 617, 618
- Pyrogallol poisoning, 1391
- Pyruvic acid, blood level, 1403
- Q FEVER**, **553, 561**  
general considerations, 553-5  
tests, 387, 392  
transmission, 600
- Quadruplets, 304-306
- Quarantine, 142  
regulations, 398
- Quinacrine, in giardiasis, 614  
in lupus erythematosus, 1290  
in malaria, 608  
in teniasis, 590, 591
- Quincke's meningitis, 1092
- Quinidine sulfate, dose, 224  
in digitalis poisoning, 1387
- Quinine, in malaria, 607  
in myotonia congenita, 1267  
skin rash, 1282
- RABBIT fever**, **447-9**
- Rabies, **512-15**  
hyperimmune serum, 514, 515  
in dog, 513  
in man, 513  
indications for prophylaxis, 514  
passive immunization, 514, 515  
pathology, 547  
tests, 390  
vs. poliomyelitis, 539
- Race re growth and development, 40
- Rachitic-like lesions, **1221-5**
- Rachitic rosary, 374
- Radiation injury, **1371-3**
- Radioactive iodine. See under *Iodine*.
- Radioisotopes, dangers of, 1372
- Radius, subluxation of head, **1259**
- Ragwort poisoning, 711
- Ramsay Hunt syndrome, 498, 763
- Ranula, **638**
- Rat-bite fever, **481**
- Rate of heart, disturbances, **883**
- Reading disorders, **95-7**
- Reagent, Bial's, 278
- Reagin, 1304
- Recessive traits, in inheritance, 238-40  
sex-linked, 240  
symbols, 235
- Recreation re mental and emotional development, 63
- Rectal administration of drugs, 227
- Rectovaginal fistula, 681
- Rectum. See also *Anorectum*; *Anus*.  
absence, 681  
disorders, **680, 681**  
fistula, 681, 684  
prolapse, **683**  
in fibrosis of pancreas, 728  
in nephrosis, 1046  
in trichocephaliasis, 582  
in ulcerative colitis, 679  
re phimosis, 1056  
tumors, **684-5**
- Red blood cells. See *Erythrocytes*.
- Reflex actions, **63**
- Reflexes, 1065-6  
abdominal, 1066  
anal, 1066  
feeding, 118  
grasp, 299, 1066  
in newborn, 299, 300, 1067  
in poliomyelitis, 537  
infant, 32  
Landau, 1067  
Moro, 299, 1067  
myotatic, 1065  
otolith righting, 1067  
patellar, in newborn, 300  
plantar, 1066  
postural, in newborn, 1067  
retrobulbar pupillary, 1333  
rooting, 1068  
stretch, 1065  
sucking, 1068  
tonic neck, 299, 1067
- Refractive errors, **1331-2**
- Regional enteritis, **671-2**
- Regitine. See *Phentolamine*.
- Regurgitation in infant feeding, 130
- Reilly bodies in gargoylism, 1239
- Religion re mental and emotional development, 63
- Renal. See also *Kidneys*.  
dwarfism, 1179-80  
glycosuria, 261, 1020  
re hypoglycemia, 1217  
hyperparathyroidism, and bone disease, 1179-80, 1223  
manifestations, in anaphylactoid purpura, 921  
rickets, **1179-80**, 1223  
vein thrombosis, 1050, 1051, 1053
- Rendu-Osler-Weber disease, 1359
- Rennin in urine, 1012
- Reserpine, 206  
dose, 225  
in behavior problems, 1144  
in hypertensive encephalopathy, 1040, 1041, 1042
- Resins, cation exchange, in acute glomerulonephritis, 1042
- Resorcin. See *Chloroquine*.
- Resorcinol poisoning, 1391
- Respiration, artificial, **740-42**. See also *Respirator*; *Resuscitation*.  
measurements of ventilation, 737-9  
nomogram for regulation of, 738  
in fetus, 28  
in newborn, 28, 297  
initiation, 740  
mechanics, **734-6**  
muscles of, **733**  
nervous control, **733**  
ventilation in, **737-9**  
measurements, 737-9

- Respirator, for diphtheritic paralysis, 419  
for poliomyelitis, 543, 544  
Respiratory acidosis, 178  
Respiratory alkalosis, 179  
Respiratory distress in newborn, **320-23**  
Respiratory factors in anesthesia, 230  
Respiratory insufficiency in poliomyelitis, 540  
Respiratory quotient of newborn, 290  
Respiratory system, disorders, in childhood, 744  
in infants, 743, 744  
in newborn, **323-9**  
re age, **743-4**  
infections, in breast-fed vs. artificially fed infants, 114  
re unexpected death, 350  
tests for, 387  
obstruction, re thymus, 998  
physiology, **733-43**  
upper, infections of, **746-61**  
viruses of, **746-8**  
Rest in convalescent care, 232  
Resuscitation of newborn, 301-303, 741  
Reticuloendotheliosis, **1002-1004**  
Reticulum cell sarcoma of bone, 1369  
Retina, **1342**  
angioma, 1359  
changes, in chronic nephritis, 1050  
in pheochromocytoma, 1191  
detachment, 1342  
in retrolental fibroplasia, 1343  
vs. retinoblastoma, 1341  
examination, 1330  
fibrosis, vs. retinoblastoma, 1342  
hemorrhage, in blood dyscrasias, 1342  
in newborn, 1329, 1342  
in Tay-Sachs disease, 1342  
of newborn, 1329  
Retinitis, syphilitic, 477  
vs. retinoblastoma, 1342  
Retinitis pigmentosa, 1342  
in Laurence-Moon-Biedl syndrome, 1232  
Retinoblastoma, 1341  
Retinopathy of prematurity. See *Retrolental fibroplasia*.  
Retrolental hemorrhage, 1332  
Retrolental pupillary reflex, 1333  
Retrosophageal abscess, 645  
Retrolental fibroplasia, 308, **1343**  
vs. retinoblastoma, 1342  
Retropertitoneal lipoma, 1362  
Retropertitoneal teratoma, 1356  
Retropertitoneal tumors, **1356**  
Retropharyngeal abscess, **753**  
tuberculous, 1262  
vs. acute laryngitis, 779  
vs. diphtheria, 416  
Retrotonsillar abscess, **754**  
Rh factor. See also *Hemolytic disease of newborn*.  
incompatibility, genetics, 956  
inheritance, 238  
iso-immunization, 956-61  
pathogenesis, 956  
re transfusions, 201, 202  
Rhabdomyoma of heart, 1350  
Rhabdomyosarcoma of soft tissue, 1364  
Rhagades, syphilitic, 475  
Rheumatic carditis vs. patent ductus arteriosus, 865  
Rheumatic endocarditis, **889-92**  
Rheumatic fever, **903-14**  
aortic insufficiency, 891  
aortic stenosis, 892  
arthritis in, 906  
C-reactive protein in, 910  
carditis in, 907  
chorea in, 906  
clinical pattern, 905  
convalescent care, 233  
corticosteroids in, 912  
differential diagnosis, 909  
electrocardiogram in, 910  
epidemiology, 904  
erythema nodosum in, 1300  
etiology, 904  
evaluation of clinical status, 909  
mitral insufficiency, 890  
mitral stenosis, 890  
pathology, 905  
penicillin for, 222  
pericarditis in, 907  
prevention, 142  
of bacterial endocarditis, 911  
of initial attacks, 910  
of recurrent attacks, 911  
prognosis, 910  
sedimentation rate in, 910  
serologic test, 392  
sulfadiazine for, 225  
treatment, 911-12  
tricuspid valvular disease, 892  
vs. leukemia, 968  
vs. osteomyelitis, 1260  
vs. poliomyelitis, 539  
vs. scurvy, 371  
vs. sickle cell disease, 951  
Rheumatic nodules, 907  
Rheumatic pericarditis, 900  
Rheumatic pleuritis, 908  
Rheumatic pneumonitis, 908  
Rheumatoid arthritis, **915-20**  
pericarditis in, 901  
vs. rheumatic fever, 909  
Rhinitis, allergic, **1319-21**  
vs. common cold, 749  
atrophic, 756  
chronic, **756**  
hypertrophic, 756  
syphilitic, 473  
vasomotor, **1319-21**  
Rhythm of heart, disturbances, **883**  
Rhythmic movements, neurotic trait, **78**  
Riboflavin, 109, 365-6  
deficiency, 365  
effects of, 108  
excess, effects of, 108  
function, 108  
in milk, 121  
metabolism, 110  
requirements, 107, 108, 111  
sources, 108  
Ribs, notching, with coarctation of aorta, 871  
Rickets, chemical pathology, 373-4  
in celiac disease, **1224**  
of vitamin D deficiency, **351-77**  
osseous, pathology, 372-3  
prognosis, 377  
refractory, with hydrophthalmos, **1223**  
renal, 1179-80, 1223  
treatment, 377  
Rickets, vitamin D-refractory, **1221**  
in craniosynostosis, 1227  
vs. chondrodystrophy, 1235  
vs. Morquio's disease, 1237  
vs. osteogenesis imperfecta, 1243  
vs. scurvy, 377  
vs. Werdnig-Hoffmann disease, 1100  
with amino-aciduria, **1222**  
with "base-losing nephritis," 1223  
Rickettsiae, culture, 554  
tests, 387, 392, 554  
Rickettsial diseases, **553-61**  
control measures, 556-61 *passim*  
diagnosis, 553, 554  
general considerations, 553-5  
pathology, 555  
summary, 553  
Rickettsialpox, **559-60**  
general considerations, 553-5  
tests, 392  
Riley-Day syndrome, 1107  
Ringer's lactate solution, composition, 186, 197  
Ringworm, **1291-3**  
hands and feet, 1291  
scalp, 1292  
smooth skin, 1291  
tests, 393  
*Risus sardonius*, 433  
Ritter's disease, **1285**  
Rocky mountain spotted fever, **553**, 558  
general considerations, 553-5  
laboratory tests, 392  
Roentgen doses, 1371  
Roentgen examinations re convulsions, 1121  
Roentgen radiation injury, **1371-3**  
prevention, 1372  
Roentgen rays re congenital anomalies, 244  
Roentgen therapy in leukemia, 969  
Roentgenogram, bones in syphilis, 474  
in rickets, 376  
in scurvy, 369  
normal chest, 783  
skull, 1071  
Roentgenokymograms in cardiac examination, 837  
Rokitansky-Cushing ulcer, 671  
Rooting reflex, 118  
Rose spots in typhoid fever, 439, 440  
Roseola infantum, **489-90**. See also *Exanthema subitum*.  
Rotenone poisoning, 1392  
Roughage in nutrition, 111  
Roundworms, infections by, **575-89**  
piperazine for, 223  
Rubbing habits, 78  
Rubella, **487-9**  
cataracts in, 1333  
encephalitis, 550  
in pregnancy, 488  
mental deficiency in, 1132  
quarantine for, 398  
re congenital anomalies, 243, 244  
résumé, 400  
vs. Boston exanthem, 531  
vs. measles, 485  
vs. scarlet fever, 408  
Rubeola. See *Measles*.  
Rumination, 649



- SACRAL hygroma, 1360
- Sacroccygeal region, anomalies, 685
- Sacroccygeal tumors, 685
- Saffron, meadow, poisoning, 1389
- St. Anthony's fire, 410
- St. Vitus' dance, 906
- Salicylates, in rheumatic fever, 912  
in rheumatoid arthritis, 920  
intoxication, alkalosis in, 179, 180  
poisoning, 1392  
treatment, parenteral fluid, 196, 198  
skin rash, 1282
- Salicylic acid, in ichthyosis, 1275  
in keratosis palmaris et plantaris, 1275  
in plantar warts, 1297  
in ringworm of foot, 1292  
in seborrheic dermatitis of scalp, 1315  
poisoning, 1392  
re hypoprote thrombinemia, 379  
renal clearance, 1008
- Saline solution. See also *Sodium chloride*.  
composition, 197
- Salivary glands, disorders, 637  
enlargement, 637  
mucoepidermoid, 1349  
tumors, mixed, 1349
- Salivation, 637
- Salk vaccine, 533
- Salmonella, carriers, 443  
food poisoning, 1375  
infection, 442-4  
bacteriologic diagnosis, 444  
pathology, 443  
vs. bacillary dysentery, 436  
tests, 387-90 *passim*
- Salmonella typhosa*, 437, 438
- Salt. See also *Sodium chloride*.  
dietary, 135
- "Salt-losing" in adrenal hyperplasia, 1188
- Salzer technique for esophageal stricture, 644
- San Joaquin fever. See *Coccidioidomycosis*.
- Sandflies, vectors of disease, 600
- Santonin poisoning, 1393
- Sarcoidosis, 1346
- Sarcoma, alveolar, of soft tissues, 1364  
botryoides, of vagina, 1358  
of soft tissues, 1364
- Satiety in nutrition, 111
- Scabies, 599, 1294  
vs. eczema, 1314
- Scalp, ringworm, 1292  
seborrhea, in newborn, 1283
- Scaphocephaly, 1227
- Scapula, anomalies, 1233  
winged, 1233
- Scarlatina. See *Scarlet fever*.
- Scarlet fever, 404-10  
clinical manifestations, 406-408  
complications, 408  
death rates, 3  
differential diagnosis, 408  
epidemiology, 404  
etiology, 404  
immunity to, 405  
of fetus, 243  
prevention, 409  
quarantine, 398
- Scarlet fever, résumé, 400  
surgical, 410  
treatment, 409  
vs. diphtheria, 416  
vs. smallpox, 500
- Schick test, 140, 141, 412, 414
- Schilder's disease, 1096
- Schistosomiasis, 574, 593-6  
re congestive splenomegaly, 987  
treatment, 595
- Schizophrenia, 1148
- Schönlein-Henoch syndrome, 920-22  
vs. allergy, gastrointestinal, 1327  
with nephritis, 1042
- School, age factors 7, 26  
difficulties, 83  
for blind, 1343  
health program, 145-6  
problems, in adolescence, 159  
re development, 63
- School period, nutritional requirements, 36  
6-12 years, characteristics, 36  
growth, 36
- Schultz-Charlton phenomenon, 406
- Schwannoma, 1363
- Sclera, 1333  
blue, in osteogenesis imperfecta, 1241  
inheritance, 238  
disturbances, 1333  
examination, 1330
- Scleredema, 1278
- Sclerema adiposum, 1278
- Sclerema edematosum, 1278
- Sclerema neonatorum, 1278
- Sclerodactylia, 928
- Scleroderma, 928
- Scoliosis, 1257  
in rickets, 375  
in Sprengel's deformity, 1233
- Scopolamine, as preanesthetic, 229  
dose, 225
- Scorpion bite, 598
- Scrofuloderma, 1289
- Scrotum, inflammation, 1058
- Scrub typhus, 553, 557
- Scurvy, 368-71  
vs. osteomyelitis, 1260  
vs. poliomyelitis, 539  
vs. pseudoparalysis of syphilis, 474  
vs. rickets, 377  
vs. Werdnig-Hoffmann disease, 1100
- Seabright-bantam syndrome, 261, 1177
- Seborrhea, due to vitamin A, 363  
vs. eczema, 1314
- Seborrheic dermatitis, 1283  
in hepatitis, 705  
salicylic acid ointment for, 1315
- Secobarbital sodium, dose, 225
- Seconal. See *Secobarbital sodium*.
- Secretin, 718
- Sedation in asthma, 1324
- Sedatives, 205-206
- Sedimentation rate, erythrocyte, 1405
- Selenium, in nutrition, 107
- Senecio poisoning, 711
- Senility, premature, 1153
- Senses, special, development of, 64-5
- Sensory loss, hysterical, 1068
- Sensory system, examination, 1066
- Septicemia vs. cytomegalic inclusion disease, 525
- Serologic tests, general considerations, 385-6
- Serotonin, 265-6  
in carcinoid of intestine, 894  
re bleeding, 970
- Serous meningitis, 1092
- Serous otitis media, 770
- Serum. See also under *Blood*.  
hepatitis, 704-707  
sickness, 1325-6  
prevention, 1326
- Sex, characters, development, 38, 39  
in adolescence, 154  
chromosomal, 1202  
chromosomes in fertilized ovum, 234  
differentiation, embryonic, 1202  
education, 71  
in adolescence, 158  
effect on growth and development, 40  
hormones in adolescence, 154  
organs, development, 38, 39  
problems, in adolescence, 158
- Sex-linked recessive traits, 240
- Sexual hair, premature, 1161
- Shellfish poisoning, 1393
- Shigellosis, 434-7  
tests, 388
- Shingles. See *Herpes zoster*.
- Shock, 181-2  
in acute renal failure, 1050-51  
therapy, in psychoses, 1149  
treatment, 182
- Shoes, 1253
- Sickle cell disease, 949-52
- Sickle cell trait, 949
- Sickle cell-thalassemia disease, 952
- Sickling, test for, 950
- Siderotic cirrhosis, 711
- Sight. See *Vision*.
- Sigmoid, prolapse, 683  
tumors, 684-5
- Sign, Babinski's, 299
- Chvostek's, 299, 111
- de Lange's, 1067
- d'Espine's, 456
- Duroziez's, 891
- Erb's, 1111
- Eustace Smith's, 456
- Ewart's, 899
- Gill's, 1257
- Graefe's, 1172
- Grocco's triangle, 814
- Macewen's, 1066
- Moebius', 1172
- Nikolsky's, 1285
- Pastia's, 406
- Stellwag's, 1172
- Trendelenburg's, 1255
- Trousseau's, 111
- Silicon in nutrition, 107
- Silver nitrate, in acute catarrhal conjunctivitis, 1338  
in fissure in ano, 683
- Similac, 124
- Simmonds' disease, 1154
- Sino-atrial block, 886
- Sinus, nasal, development, 754  
newborn, 29  
of Valsalva, rupture, 866  
paranasal, adenoma, 1348  
papilloma, 1348  
tumors, 1347
- Sinus arrhythmia, 822, 883

- Sinusitis, 754-6**  
 acute, 755  
 and bronchiectasis, 809  
 chronic, 755, 756  
 from periapical infection, 626  
 in erysipelas, 411  
 in influenza, 511  
 in mucormycosis, 565  
 in nasopharyngitis, 749  
 in scarlet fever, 408  
 tonsillectomy for, 758
- Sitting height.** See under *Height.*
- Situs inversus, and bronchiectasis, 809**  
 with dextrocardia, 855
- Skatole, 266**
- Skeletal.** See *Bones.*
- Skin, aneurysms, 1359**  
 anomalies, **1274-7**  
 blastomycosis, 563  
 care, in newborn, 303  
 defects, congenital, **1274-7**  
   localized, 338  
 diphtheria of, 415  
 diseases, formulary, **1301**  
 disturbances, **1274-1301**  
   in sebaceous glands, **1280**  
   in subcutaneous fat, **1278**  
 drug rashes, **1282**  
 glomus tumor, 1359  
 herpes simplex, 490  
 in acrodynia, 1399  
 in cat-scratch fever, 522  
 in coccidioidomycosis, 571, 572  
 in congenital syphilis, 473  
 in cryptococcosis, 564  
 in dermatomyositis, 923  
 in Gaucher's disease, 1000  
 in infectious lymphocytosis, 521  
 in infectious mononucleosis, 519  
 in kwashiorkor, 359  
 in Letterer-Siwe disease, 1003  
 in lupus erythematosus, systemic, 926  
 in neurofibromatosis, 1079  
 in newborn, **338**  
 in nocardiosis, 566  
 in pellagra, 366-7  
 in rheumatic fever, 908  
 in schistosomiasis, 593  
 infections, bacterial, **1287-90**  
   fungus, **1291-4**  
   tests, 393, 394  
   viral, **1296-7**  
 lesions, in porphyria, 280, 281  
   in typhoid fever, 440  
 leukemic infiltrations, 966  
 lupus erythematosus, 1290  
 moniliasis of, **1293**  
 of newborn, 295  
 parasitic infestations, **1294-6**  
 pigmentary changes, **1277**  
 port-wine mark, 1274  
 rash, due to drugs, **1282**  
   due to smallpox vaccination, 504  
   in ECHO virus infections, 526, 530, 531  
   in hepatitis, 705  
   in toxoplasmosis, 616, 617  
 scars, 1277  
 test, allergy, 1307-1309  
   toxoplasmosis, 617  
   trichinosis, 587  
 tuberculosis, **1289-90**  
   primary, 1289  
 tuberos sclerosus, 1079
- Skin, tumors, 1358-62**  
 xanthomas, 1001-1002
- Skull.** See *Cranium.*
- Sleep, disorders, 89**  
 patterns, 136
- Slipped epiphysis, 1257**
- SMA, 124**
- Smallpox, 499-501**  
 epidemiology, 499  
 esophagitis in, 643  
 immunity, in newborn, 292  
 immunization, 141  
 of fetus, 243  
 pathology, 499  
 quarantine for, 398  
 résumé, 400  
 tests, 393, 394  
 vaccination, 501-505  
   age of initial vaccination, 502  
   complications, 504  
   encephalitis in, 504, 551  
   method, 502  
   re eczema, 504  
   revaccination, 503  
   site, 502  
   care of, 503  
   types of reaction, 502  
 Smallpox encephalitis, 550
- Smell, 64**
- Snellen E chart, 1330, 1331**
- Snuffles, syphilitic, 473**
- Sobee, 125**
- Social development, infant, 34**
- Sodium, deficiency, effects of, 103**  
 in dehydration, 185, 187  
 excess, effects of, 103  
 function, 103  
 in milk, 121  
 in oral fluids, **1408**  
 in oral and parenteral solutions, 197  
 loss, from body fluids, 195  
 metabolism, 105  
 plasma level, 105  
 requirements, 103, 105  
 sources, 103
- Sodium antimony tartrate in schistosomiasis, 595**
- Sodium bicarbonate solution, composition, 197**  
 in acidosis, 191  
 in diabetes mellitus, 1209  
 in potassium intoxication, 198  
 in salicylate poisoning, 196, 198
- Sodium chloride.** See also *Saline solution; Salt.*  
 as additive in fluid therapy, 197  
 in Addison's disease, 1185  
 in adrenal hyperplasia, 1189
- Sodium citrate in chronic lead poisoning, 1378**
- Sodium formaldehyde sulfoxalate in mercury poisoning, 1390**
- Sodium hypochlorite, poisoning, 1393**
- Sodium hypophosphate in mercury poisoning, 1390**
- Sodium lactate, as additive in fluid therapy, 197**  
 solution, composition, 197  
 in acidosis, 191
- Sodium nitrite in cyanide poisoning, 1386**
- Sodium phenobarbital in intracranial hemorrhage, 318**
- Sodium salicylate, in rheumatic fever, 912**  
 poisoning, 1392
- Sodium sulfate in barium salts poisoning, 1385**
- Sodium thiosulfate, in bromate poisoning, 1385**  
 in cyanide poisoning, 1386  
 in iodine poisoning, 1389
- Sodium-l-thyroxine in congenital hypothyroidism, 1168**
- Sudoku, 481**
- Soft tissue tumors, 1362-5**
- Solanine poisoning, 1393**
- Solution.** See also *Fluids; and specific solutions.*  
 common, composition, 197  
 physiologic anions and cations in, 1407
- Somatotropin, 1150**
- Somnambulism, 90**
- Spasm, carpopedal, 1113**  
 habit. See *Tics.*
- Spasmodic croup, 777**
- Spasmus nutans, 1102**
- Spasticity in cerebral palsy, 1138**
- Specific dynamic action, 99**
- Specific gravity, blood, 1405**  
 plasma, 1405
- Specimens, collection, 203-204**
- Speech, defective, 93**  
 development, 65, 91  
 disorders, **91-3**  
 in mental development, 65  
 in palatopharyngeal incompetence, 630-31  
 infant, 34  
 re cleft palate, 630
- Spermatic cord, torsion, 1059**
- Spermatogenesis, 1193**
- Spherocytosis, hereditary, 237, 944-6**  
 crises in, 945
- Spider bites, 598**
- Spina bifida, 1076, 1079**
- Spinal cord, defects, 1076, 1079**  
 diseases, **1105-1106**  
 injury, 1105  
 in newborn, 318  
 lesion, vs. Werdnig-Hoffmann disease, 1100  
 neoplasms, vs. poliomyelitis, 539  
 tumor, 1106
- Spinal fluid.** See *Cerebrospinal fluid.*
- Spinal puncture, 1069-71**  
 re intracranial pressure, 1084
- Spine, 1257**  
 injuries, in newborn, 318  
 tuberculosis, 1262
- Spirillum minus, 481**
- Spleen, 985-9**  
 anomalies, 986  
 function, 985  
 infarction, 989  
 rupture, 986  
 structure, 985  
 supernumerary, 986  
 tuberos sclerosus, 1079  
 weights, 986
- Splenectomy in spherocytosis, hereditary, 946**
- Splenic cytopenia, 988**
- Splenic panhematopenia, 989**
- Splenomegaly, 988**  
 causes, 987



- Splenomegaly, congestive, **986-8**  
 esophageal varices in, 645  
 re cirrhosis, 709  
 vs. kala-azar, 609  
 vs. purpura, thrombocytopenic, idiopathic, 975
- Splenoportal hypertension, 986-8
- Splint, Fredjka, 1255
- Split foot, 1231
- Split hand, 1231
- Spondylitis, in brucellosis, 445, 446  
 tuberculous, 1262
- Spondylolisthesis, 1257
- Sporotrichosis, **566**  
 laboratory tests, 393
- Sprengel's deformity, **1233**
- Sprue, 722
- Squamous cell carcinoma, 1362
- Squint. See *Strabismus*.
- Stable factor, 253, 254, 255, 971, 973  
 deficiency, 255, 981
- Staphylococcal food poisoning, **1374**
- Staphylococcal infections, in newborn, **344-6**  
 vs. nocardiosis, 566
- Staphylococcal meningitis, 431
- Staphylococcal pneumonia, 792-3  
 in newborn, 328  
 with thrush, 798
- Staphylococcus, in pulmonary abscess, 810  
 re diarrhea, 655, 656  
 re osteomyelitis, 1259, 1260  
 tests, 387, 388, 389, 392, 393, 394
- Staphyloma, of cornea, 1333  
 of sclera 1333
- Starch, in stool, test for, 720  
 intolerance, in celiac disease, 724  
 poultice, 1301
- Starchy foods in infant feeding, 129
- Starlac, 124
- Status asthmaticus, 1322
- Status epilepticus, treatment, 1122
- Status thymicolymphaticus, 998  
 re unexpected death, 351
- Stealing, in emotional development, 68
- Steatorrhea, causes, 720-21  
 idiopathic, 721-6
- Stein-Leventhal syndrome, **1201**
- Stellwag's sign, 1172
- Stem length. See *Height, sitting*.
- Stenocephaly, **1226-8**
- Stenosis, laryngeal, **772**  
 mitral, congenital, **876**
- Sterane. See *Prednisolone*.
- Sterilization, bacterial, terminal, in milk formulas, 127-8  
 sexual, re mental deficiency, 1136
- Sternberg cell, 994
- Sternocleidomastoid, fibroma, 1265  
 hematoma, 1265  
 injury, in newborn, 320
- Sternum, deformity, **1233**  
 fissure, 1233
- Stevens-Johnson syndrome, 1299
- Stibophen in schistosomiasis, 595
- Stilbamidine, 564
- Stilbestrol, 1193  
 in gonadal dysgenesis, 1200
- Still's disease. See *Rheumatoid arthritis*.
- Stimulants, central nervous system, 206
- Stokes-Adams syndrome, 1127
- Stomach, acidity, in newborn, 289  
 aspiration, in newborn, 301  
 atresia, 658  
 bezoar, 664  
 dilatation, 662  
 acute, 662  
 disorders, **658**  
 duplication, 658  
 fluid, composition, 195  
 solution for replacement of losses, 197  
 foreign bodies, 663  
 gavage, 204  
 hemorrhage, 663  
 "hourglass," 658  
 lavage, 204  
 in poisoning, 1381  
 malformations, 658  
 malpositions, 658  
 neoplasms, 663  
 perforation, 663  
 tetany, 1112  
 tumors, 1351
- Stomatitis, aphthous, 491-2  
 gangrenous, 634  
 herpetic, **491-2**, 633  
 recurrent, 492
- Stools. See *Feces*.
- Strabismus, **1334-7**  
 accommodative, 1336  
 alternating, 1336  
 amblyopia in, 1336  
 and cerebral palsy, 1336  
 comitant, 1335  
 in mental deficiency, 1133  
 noncomitant, 1335  
 nonparalytic, 1335  
 orthoptic therapy, 1336  
 paralytic, 1335  
 tests for, 1335
- Streptobacillus moniliformis*, 481
- Streptococcal food poisoning, 1375
- Streptococcal infections, erythema nodosum in, 1300  
 general considerations, **401-404**
- Streptococcal meningitis, 429
- Streptococcal pneumonia, 792
- Streptococcosis, 751
- Streptococcus, anaerobic, laboratory tests for, 394  
 antibiotic susceptibility, 402  
 antigens of group A, 401-402  
 beta hemolytic, 751  
 control measures, 403  
 epidemiologic aspects, 402  
 hemolytic, in glomerulonephritis, 1035  
 in erysipelas, 410  
 in scarlet fever, 404  
 serologic group, 401  
 tests, 387, 388, 389, 391, 393, 394
- Streptomycin, antimicrobial properties, **397**  
 dose, 225  
 in acute secondary diffuse peritonitis, 688  
 in hyaline membrane disease, 325  
 in influenzal meningitis, 431  
 in pneumonia in newborn, 328  
 in prevention of pulmonary infection in cystic fibrosis of pancreas, 730  
 in tuberculosis, 464, 467, 470  
 in tularemia, 448  
 ophthalmic, 1331
- Streptomycin, skin rash, 1282  
 toxic effects, 765, 767
- Stridor, laryngeal, 771
- Strongyloides stercoralis*, 585
- Strongyloidiasis, **585-7**  
 epidemiology, 574, 586  
 g-Strophanthin, dose, 221
- Struma, Hashimoto's, 1171
- Struma lymphomatosa, 1171
- Strychnine poisoning, 1393
- Stuart factor, 254, 255
- Sturge-Weber syndrome, 1080  
 mental deficiency in, 1131
- Stuttering, **93-5**
- Sty, 1337
- Subacute inclusion encephalitis, 550, 552
- Subacute sclerosing leukoencephalitis, 552
- Subcutaneous fat necrosis, 316
- Subcutaneous infusions for parenteral fluids, 200
- Subcutaneous tissue, growth, 15, 16  
 infant, 31
- Subdural effusion, 1089
- Subdural fluid, 1071
- Subdural hematoma, acute, 1089  
 chronic, in children, 1089  
 in infants, 1087-9
- Subdural hygroma, 1089
- Subdural puncture, 1071
- Sublingual administration of drugs, 227
- Succinylcholine, sensitivity to, 265
- Sucrosuria, 273
- Suffocation, mortality rate, 144  
 re unexpected death, 351
- Sugar, blood, galactose in, 275  
 level, 1403  
 dietary, 135  
 in formulas, 126, 127  
 in urine, 1012. See also *Diabetes mellitus*.
- Sulfadiazine, dose, 225  
 in influenzal meningitis, 431  
 in meningococcal meningitis, 428  
 in meningococcemia, 428  
 in pneumococcal meningitis, 430  
 in toxoplasmosis, 617, 618
- Sulfaethylthiadiazole, dose, 226
- Sulfamethoxypyridazine, dose, 225
- Sulfanilamide, hemolytic anemia with, 264-5
- Sulfates, blood, 1402  
 renal reabsorption, 1007
- Sulfhemoglobinemia, congenital, 283
- Sulfisoxazole, dose, 217  
 re hyperbilirubinemia, 334
- Sulfonamide, ophthalmic, 1331
- Sulfonamides, antimicrobial properties, 397  
 dose, 225  
 in bacillary dysentery, 437  
 in histoplasmosis, 571  
 in periarteritis nodosa, 927  
 in pyelonephritis, 1034  
 re hemolytic anemia, 953  
 re renal damage, 1051  
 renal clearance, 1008  
 skin rash, 1282  
 use, 207
- Sulfur, blood, 1402  
 deficiency, effects of, 104  
 excess, effects of, 104  
 function, 104, 106

- Sulfur, in body, 106  
 in milk, 121  
 requirements, 104, 106  
 sources, 103, 104  
 Sulkowitch's reagent (test), 1221  
 Sul-Spansion. See *Sulfaethylthiadiazole*.  
 Summer eruption, recurrent, 1301  
 Sunlight for infants, 137  
 Suppurative lesions in salmonellosis, 443  
 Suppurative pancreatitis, 730  
 Supratentorial tumor, 1086  
 Suramin, 589  
 Surface area, nomogram, 209  
 Surgical scarlet fever, 410  
 Suvren. See *Captodiamine*.  
 Swallowed blood syndrome, 336  
 Swallowing dysfunction, neurogenic, 642  
 Sweat, composition of external loss of, 195  
 electrolytes, in fibrosis of pancreas, 729  
 in cystic fibrosis of pancreas, 727, 729  
 Sweat glands, infant, 32  
 Swift's disease, 1398-1401  
 Swimmer's itch. See *Dermatitis, cercarial*.  
 Symblepharon, 1333  
 Sympathetic ophthalmia, 1340  
 Syncope, 181, 1127  
 with congenital heart block, 887  
 Syndactyly, 1231  
 hereditary factors, 246  
 in Laurence-Moon-Biedl syndrome, 1232  
 Syndrome, Adie, 1333  
 Albright, 1223  
 amyotonia congenita, 1099-1100, 1267  
 aseptic meningitis, 545-6  
 Banti's, 986-8  
 Bonnevie-Ullrich, 1198-1200  
 celiac, 721-30  
 Chediak-Higashi, 965  
 crush, 1050-51  
 Cushing's, 1189-90  
 diabetes mellitus, in newborn, 1213  
 Dubin-Johnson, 703  
 Ehlers-Danlos, 974, 1277  
 Eisenmenger, 833-5, 849-51  
 Ellis-van Creveld, 1237  
 epilepsy, and cerebral degeneration, 1101  
 eunuchoid, 1195-7  
 Fanconi-de Toni-Debré, 262, 263-4, 1222  
 Franceschetti-Klein, 632  
 Frölich's, 355, 1162  
 Guillain-Barré, 525  
 Hand-Schüller-Christian, 1002  
 Horner's, 1333  
 Hurler's, 268, 1238  
 Hutchinson-Gilford, 1153  
 inspissated bile, 334  
 Kartagener's, 809, 855  
 Kimmelstiel-Wilson, 1208  
 Klinefelter, 1197  
 Klippel-Feil, 1233  
 Kunkel's, 710  
 Laurence-Moon-Biedl, 1162, 1232  
 Libman-Sacks, 926  
 Lightwood, 1223  
 Loeffler's, 801  
 Syndrome, Lowe's, 1223  
 Lutembacher, 860  
 McCune-Albright, 1159  
 Marfan's, 1243  
 cardiovascular lesions, 880  
 Mauriac, 1208  
 Mikulicz's, 638  
 Moebius, 1065  
 nephrotic 1044-9. See also *Nephrosis*.  
 Parinaud's oculoglandular, 518  
 Pel-Ebstein, 995  
 Pellizzi's, 1160  
 Pick's, 686, 689  
 Pierre Robin, 629, 631, 632  
 placental dysfunction, 313-14  
 pleurideficiency, 357-60  
 Puetz-Jeghers, 1351  
 Ramsay Hunt, 498, 763  
 Riley-Day, 1107  
 Seabright-bantam, 261, 1177  
 Stein-Leventhal, 1201  
 Stevens-Johnson, 1299  
 Stokes-Adams, 1127  
 Sturge-Weber, 1080  
 mental deficiency in, 1131  
 swallowed blood, 336  
 Takayasu's, 927  
 Taussig-Bing, 852  
 Treacher-Collins, 632  
 Turner's, 1196, 1198-1200, 1233  
 von Willebrand's, 980  
 Waterhouse-Friderichsen, 427-8, 1183-5  
 Weber-Christian, 1279  
 Werdnig-Hoffmann, 1099  
 Wolff-Parkinson-White, 885  
 Synkavite, 379  
 anemia due to, 336  
 Synostoses, premature, of skull, 1226-8  
 Synovitis, of hip, 1256  
 vs. poliomyelitis, 539  
 Syphilis, 472-80  
 acquired, 479  
 chorioretinitis in, 1342  
 congenital, 472-9  
 clinical manifestations, 477  
 diagnosis, 478  
 early, 472-6  
 late, 476-8  
 prevention, 478  
 prognosis, 478  
 treatment, 478-9  
 vs. eczema, 1314  
 falsely positive test, 520  
 hemoglobinuria in, 1022  
 mental deficiency in, 1132  
 re chronic rhinitis, 756  
 re nephrosis, 1044  
 tests, 392  
 vs. cytomegalic inclusion disease, 525  
 vs. faucial diphtheria, 416  
 vs. nasal diphtheria, 416  
 vs. osteogenesis imperfecta, 1243  
 vs. osteopetrosis, 1240  
 vs. scurvy, 371  
 vs. sporotrichosis, 567  
 Syphilitic arthrosis vs. rheumatic fever, 909  
 Syphilitic osteomyelitis vs. poliomyelitis, 539  
 Syringocystadenoma papilliferans, 1361  
 Syringoma, 1362  
 Syringomyelia, 1106  
 Systemic disturbances, shock due to, 182  
 Systemic infections, tests for, 389  
 Systole, duration, on electrocardiogram, 829  
 TABES, juvenile, 476  
 Tache cérébrale, 427  
 Tachycardia, 821  
 paroxysmal, 884  
 syncope in, 1127  
 Taenia saginata, 589  
 Taenia solium, 589  
 Taeniasis. See *Teniasis*.  
 Takayasu's syndrome, 927  
 Talbot's solution, composition, 197  
 Tapazole. See *Methimazole*.  
 Tapeworm infections, 589-93. See also *Teniasis*.  
 tests, 388  
 Taste, infant, 32  
 sense, 64  
 Taussig-Bing syndrome, 852  
 Tay-Sachs disease, 1094  
 vs. Niemann-Pick disease, 1000  
 Teaching re development, 64  
 Tears, overflow of, 1332  
 Technical procedures, 203-204  
 Teeth, aberrations, in apposition, 621, 622  
 in development, classification, 621  
 ameloblastomas, 620  
 attrition, disturbances, 621, 625  
 black, 620  
 brown, 620  
 brushing, 619  
 calcification, 25  
 care, preschool period (2-6 years), 33, 36  
 school period (6-12 years), 37  
 caries, 625-6  
 diet, 625  
 fluorine, 626  
 prevention, 142  
 color, abnormal, 620  
 cysts, 620  
 deciduous, premature loss of, 1224  
 time of eruption, 623  
 defective, in hypoparathyroidism, 1176  
 dentin, interglobular, 621, 622  
 opalescent, 620  
 development, 21, 25-7  
 deficient, 621  
 excessive, 621  
 disturbances, 620-26  
 in calcification, 621, 622  
 in growth, 620, 621  
 structural, re age period, 623  
 effect of mouth-breathing, 627  
 effects of thumb-sucking, 627  
 enamel, hypoplasia, 621, 622  
 re age periods, 623  
 mottled, 621, 622  
 pitted, 621, 622  
 eruption, 25  
 delayed, 621, 624  
 difficult, 621, 624  
 premature, 296, 621, 624  
 exfoliation, effects of, 627  
 premature, 624  
 fluorosis, 622



- Teeth, form, abnormal, 622  
 gray, 620  
 green, 620  
 grinding, 77  
 Hutchinson's, 475  
 hypoplasia, re age periods, 623  
 in acrodynia, 1399  
 in dietary deficiencies, 622-3  
 in porphyria, 280  
 in porphyria, 620  
 in rickets, 374  
 in syphilis, 475  
 in vitamin deficiencies, 623  
 incisors, fractured, 628  
 infant, 32  
 infections, periapical, 626  
   re systemic disease, 626  
 jaundice, 620  
 large, 622  
 life cycles, 620, 621  
 malocclusions, 621, 627  
 Moon, 476  
 mulberry, 476  
 night-grinding, 621, 625  
 number, deficient, 620  
 odontomas, 620  
 pain, diagnosis, 624  
   treatment, 624  
 peg, 622  
 permanent, time of eruption, 624  
 physiologic spacing, 627  
 pink, 620  
 preschool period (2-6 years), 33, 36  
 primary. See *Teeth, deciduous*.  
 proliferation, 620, 621  
 school period (6-12 years), 37  
 secondary. See *Teeth, permanent*.  
 shedding, 25  
 size, abnormal, 622  
 small, 622  
 stains, intrinsic, 620  
 supernumerary, 620  
 tumor, 1369
- Teething, 624
- Telangiectases, cerebral, 1081  
   in xeroderma pigmentosum, 1276
- Telangiectasia, hereditary, 974, 1359
- Television re eyestrain, 1343
- TEM. See *Triethylene melamine*.
- Temper re emotional development, 68
- Temperature, C. and F. equivalents, 1413  
   in anesthesia, 230  
   taking of, 169
- Temporal mandibular joint, ankylosis, 628
- Tempra. See *Acetaminophen*.
- Tendon, giant cell tumor, 1364
- Teniasis, 589-91  
   epidemiology, 574, 589  
   tests, 388
- Teratoma, ovary, 1358  
   pharyngeal, 1348  
   retroperitoneal, 1356  
   sacrococcygeal, 685  
   testis, 1357
- Terramycin. See *Oxytetracycline*.
- Terrors, day or night, 90, 91
- Test, Addis count, 1012  
   adenovirus, 387, 394  
   Aerobacter infections, 388  
   agglutination, for rickettsiae, 554  
   allergy, 1306-1309. See also under *Allergy*.
- Test, amino acid absorption, 720  
   antibiotic susceptibility, 396  
   Apt, 337  
   Arakawa, 365  
   bacterial, 384-97  
   bilirubin clearance, 699  
   blastomycosis, 393  
   bleeding disorders, 972  
   bromsulphalein, 700  
     in hepatitis, 705  
   brucellin, 446  
   brucellosis, 391  
   *Candida albicans*, 387, 388, 393  
   carbohydrate tolerance, 697-8  
   CCA virus, 387  
   cephalin flocculation, 697, 702  
   chloride in sweat, 729  
   coccioidin, 572  
   "cold viruses," 387  
   colloidal gold reaction of blood serum, 697  
   color blindness, 1330  
   Colorado tick fever, 391  
   Congo red, 1345  
   Coombs', direct and indirect, 201, 202  
   Coxsackie virus, 388, 390, 391, 393  
   cryptococcosis, 389  
   cytomegalic inclusion disease, 390, 391, 392  
   dark adaptation, 362  
   dengue, 391  
   Dick, 405  
   diphtheria, 387  
   Donath-Landsteiner, 1022  
   dye, for hydrocephalus, 1071  
     for toxoplasmosis, 617  
     for ventricular-spinal obstruction, 1071  
   ECHO virus, 387, 388, 390  
   Ellsworth-Howard, 1177  
   encephalitic viruses, 390  
   enterococcus infection, 392  
   enterovirus, 388  
   epinephrine tolerance, 1219  
   erythrocyte sedimentation rate, 697  
   *E. coli*, 387, 388, 389, 392, 393, 394  
   exercise, in cardiac disease, 838  
   eye infection, 393  
   Farber, 665  
   farsightedness, 146  
   fat, in stool, 720  
     tolerance, 720  
   Frei, 518  
   fungal infection, 384-97  
   fusospirochetal infections, 393  
   galactose tolerance, 698  
   gas gangrene, 394  
   gastrointestinal infection, 388  
   genitourinary infection, 392  
   gliadin tolerance, 722  
   glucose, reabsorption, 1014  
     tolerance, intravenous, 1219  
     oral, 698  
   glutathione stability, 953  
   gonococcal infection, 392, 393  
   Harrison spot, 706  
   hepatic fat metabolism, 698  
   hepatic protein metabolism, 698  
   herpangina, 393  
   herpes simplex, 390-94 *passim*  
   herpes zoster, 390, 393, 394  
   heterophile antibody, 519  
   hippuric acid, 700  
   Hirst and Hare, 509  
   histoplasmin, 570
- Test, histoplasmosis, 391  
   Hoover, 1068  
   hyperopia, 146  
   icterus index, 699  
   inclusion blennorrhoea, 394  
   insulin tolerance, 1219-20  
   intelligence, 66  
   intestinal infection, 388  
   inulin clearance, 1006, 1013  
   Kahn, falsely positive, 520  
   keratoconjunctivitis, epidemic, 394  
   Lipiodol, for fat absorption, 720  
   liver function, 697-700, 702  
   lymphocytic choriomeningitis, 390  
   lymphogranuloma venereum, 392  
   malaria, 391  
   mannitol clearance, 1006, 1013  
   measles, 391  
   Meningococcus, 387, 389  
   meningoencephalitic viruses, 390  
   methylene blue, 706  
   Millon, 259  
   molluscum contagiosum, 393, 394  
   Moloney, 140  
   monilia, 387, 388, 393  
   mumps, 390, 391  
   muscular strength, 1065  
   mycotic infection, 384-97  
   myopia, 146  
   myxoviruses, 387  
   nervous system infection, 389  
   Newcastle disease, 394  
   Nickerson-Kveim, 1346  
   Orcin, 278  
   OXK agglutination, 554  
   OX2 agglutination, 554  
   OX19 agglutination, 554  
   oxyuriasis, 388  
   pancreatic enzymes, 719-20, 728  
   pancreatic function, 719-20  
   parapertussis, 387  
   passive transfer, 1308  
   Paul, 499  
   Paul-Bunnell, 519  
   pertussis, 387  
   pharyngoconjunctival fever, 394  
   phenol red, 1008, 1013  
   phenolsulfonphthalein, 1008, 1013  
   phoria, 146  
   pleurodynia, 391  
   Pneumococcus, 387, 389, 393  
   poliomyelitis, 388, 390, 391  
   proline absorption, 720  
   Proteus, 387, 388, 389, 392, 393, 394  
   prothrombin, consumption, 972  
     one-stage, 972  
     two-stage, 972  
   P.S.P., 1008, 1013  
   Pseudomonas, 387, 388, 389, 392, 393, 394  
   psittacosis, 387  
   Q fever, 387, 392  
   rabies, 390  
   respiratory infection, 387  
   rickettsiae, 387, 392, 554  
   rickettsialpox, 392  
   ringworm, 393  
   Salmonella, 387-90 *passim*  
   Schick, 140, 141, 412, 414  
   serologic, coccidioidomycosis, 572  
     general considerations, 385 6  
     glomerulonephritis, 392  
     rheumatic fever, 392  
   shigellosis, 388  
   sickling, 950

- Test, skin, allergy, 1307-1309  
blastomycin, 563  
cat-scratch fever, 523  
infections, 393, 394  
mumps, 505  
toxoplasmosis, 617  
trichinosis, 587  
tularemia, 448  
smallpox, 393, 394  
Staphylococcus, 387, 388, 389, 392, 393, 394  
starch in stool, 720  
strabismus, 1335  
Streptococcus 387, 388, 389, 391, 393, 394  
Sulkowitch, 1221  
syphilis, 525  
  falsely positive, 520  
  systemic infection, 389  
tapeworm infection, 388  
teniasis, 388  
thromboplastin generation, 972  
thrush, 387, 388, 393  
thymol flocculation, 702  
thymol turbidity, 697, 702  
tinea infection, 393  
toxoid sensitivity, 140  
toxoplasmosis, 390, 617  
trachoma, 394  
trypsin in stool, x-ray film, 728  
tuberculin, 461-2  
tuberculin patch, 462  
tuberculosis, 387, 389  
turbidity, in thyroiditis, 1171  
typhoid fever, 388, 390  
typhus infection, 392  
urea clearance, 1013  
urinary tract infection, 392  
urine, concentration, 1012  
  retention, 1014  
urobilin excretion, 699  
vaccinia, 393  
van den Bergh reaction, 698  
varicella, 391, 392, 394  
viruses, 384-97  
vision, 146  
visual field, 1330  
vitamin A tolerance, 720  
Wassermann, 478  
  falsely positive, 520  
Widal, 438, 440  
Zoeller, 140
- Testes, abnormal number, 1059  
absence, 1059, 1196  
atrophy, 1196  
dysgenesis, 1197  
function, 1193-5  
hypofunction, 1195  
tuberculosis, 1059  
tumor, 1197, **1357**  
  with gynecomastia, 1198  
  undescended, **1058**
- Testosterone in hypogonadism, 1196
- Tetanus, **432-4**  
antitoxin, 433, 434  
immunity, in newborn, 292  
immunization, 139-40, 141  
prevention, 433  
toxoid, 139-40, 141  
treatment, 434  
vs. poliomyelitis, 539  
vs. rabies, 513
- Tetany, **1110-13**  
causes, 1110-11  
clinical manifestations, 1112  
hyperventilation, 1111
- Tetany, hypocalcemia, 1110-13  
  in hypoparathyroidism, 1175-7  
  in nephrosis, 1047  
  in newborn, **342**  
  in pertussis, 422  
  in vitamin D-refractory rickets, 378  
  latent, 1112  
  manifest, 1113  
  of alkalosis, 1110-13  
  of newborn, 342, 1111  
  of vitamin D deficiency, 378  
  surgical, 1175  
  treatment, 1113  
  with renal failure, 1050
- Tetracaine in herpetic infections, 494
- Tetrachloroethane poisoning, 1389
- Tetrachloroethylene, in hookworm infections, 586  
  in trichocephaliasis, 582
- Tetracycline, antimicrobial properties, 397  
  dose, 226  
  in amebiasis, 613  
  in balantidiasis, 614  
  in pertussis, 423  
  in rickettsial diseases, 555  
  skin rash, 1282
- Tetraethylpyrophosphate in myasthenia gravis, 1272
- Tetraiodothyronine, 258
- Tetralogy of Fallot, **842-8**  
  acyanotic, 842  
  cardiac catheterization, 833-5, 844  
  circulation time, 845  
  clinical manifestations, 842  
  electrocardiogram, 844  
  hemodynamics, 842  
  prognosis, 846  
  roentgen examination, 843  
  selective angiocardiography, 845  
  treatment, 846
- Thalassemia, 946-9  
  Thalassemia major, 946-9  
  Thalassemia minor, 946-9  
  Thalassemia-sickle cell disease, 952  
  Thallium poisoning, 1393
- Theophylline with ethylenediamine, dose, 210
- Therapy, drug, **205-27**
- Thiamine, deficiency, 363-5  
  effects of, 108  
  excess, effects of, 108  
  function, 108  
  in beriberi, 365  
  in milk, 121  
  metabolism, 109  
  requirements, 107, 108, 111  
  sources, 108
- Thiocyanate insecticides, poisoning, 1393
- Thiomerin. See *Mercaptomerin*.
- Thirst, treatment, parenteral fluid, 186-7
- Thomsen's disease, 1267
- Thorax, actinomycosis, 562
- Circumference, annual increments, 14  
  birth to 5 years, 56-7  
  5-18 years, 58-9  
  infant, 31  
  measuring technique, 49
- Funnel chest, 1234
- Newborn, 29
- Normal, roentgenogram, 783
- Thorazine. See *Chlorpromazine*.
- Threonine, requirements, 101
- Thrills, cardiac, 819
- Throat cultures, collection, 204
- Thrombocytopenia, and giant hemangioma, **977**  
  in cytomegalic inclusion disease, 524  
  in Letterer-Siwe disease, 1003  
  in lupus erythematosus, 926  
  in newborn, 337, **976**
- Thrombocytopenic purpura. See under *Purpura*.
- Thromboplastin. See under *Blood*.
- Thrombosis, **903**  
  dural sinus, 1091  
  in diphtheria, 417  
  in typhoid fever, 440  
  lateral sinus, 765  
  renal vascular, 1050-51  
  renal vein, 1053  
  re nephrosis, 1044
- Thrush. See also *Moniliasis*.  
  pneumonia, 798
- Thumb-sucking, **77**  
  effect on teeth and jaws, 627
- Thymol flocculation test, 702
- Thymol turbidity, in hepatitis, 705  
  in thyroiditis, 1171  
  test, 697, 702
- Thymoma, 1350
- Thymus, **997-8**  
  anatomy, 997  
  function, 997  
  irradiation, re thyroid carcinoma, 1173, 1174  
  newborn, 30  
  re myasthenia gravis, 997, 1272  
  re unexpected death, 351, 998  
  roentgenographic shadow of, 825  
  tumors, 1349  
  weights, 997
- Thyroglossal duct cyst, 639
- Thyroid, adenoma, 1349  
  aplasia, 1165-8  
  carcinoma, **1173**  
  deficiency, in newborn, 343  
  desiccated, (therapy), 1167  
  in congenital hypothyroidism, 1168  
  in sporadic goiter, 1171
- Disorders, **1163-74**  
  in adolescence, 154  
  in menstrual irregularities, 155-6  
  myocarditis in, 894
- Extract, in carcinoma of thyroid, 1174  
  in Simmonds' disease, 1154
- Function, 1163-5  
  general considerations, 1163-5  
  hypoplasia, 1165-8  
  in newborn, 292  
  lingual, 1349  
  teratoma, 1349
- Thyroid-stimulating hormone, 1164
- Thyroiditis, 1171  
  chronic lymphocytic, 1171  
  suppurative, 1171
- Thyrototoxicosis, 1172
- Electrocardiogram in, 827
- Maternal, re goiter, 1171
- Thyrotropic hormone, 1150, 1151
- Thyrotropin, 1164
- Thyroxine, 258, 1163-4  
  in hypothyroidism, 1168



- Tick, bites, 599  
     vs. poliomyelitis, 539  
     vector of disease, 600  
 Tics, **82**, 83, 1065  
     impulsive, 83  
 Tinea, **1291-3**  
     infections, tests, 393  
 Tinea capitis, 1292  
 Tinea circinata, 1291  
     vs. impetigo, 1287  
 Tinea cruris, 1291  
 Tina favosa, 1293  
 Tinea kerion, 1293  
 Tinea tonsurans, 1292  
 Tinea versicolor, 1293  
 Toes, hypertrophy, 1232  
 Toilet training, re encopresis, 655  
     re enuresis, 1016  
 Tolazoline in acrodynia, 1400  
 Toluidine, poisoning, 1383  
 Tongue, aberrant thyroid in, 1349  
     atrophic, 636  
     black hairy, 635  
     cyst, 636  
     disorders, **635-7**  
     fissured, 635  
     frenum, in newborn, 29  
         ulceration, 637  
     furry, 636  
     geographic, 635  
     glycogen disease, 271  
     hemangioma, 636, 1349  
     hypertrophy, 636  
     in cretinism, 636  
     in herpes simplex, 492  
     in mongolism, 1133  
     in systemic disturbances, 636  
     large, 636  
     lymphangioma, 1348  
     myoblastoma, 1349  
     neurofibroma, 1349  
     raw, red, 636  
     rhabdomyoma, 636  
     strawberry, in scarlet fever, 406  
     trauma, 637  
     white coated, 636  
     white strawberry, 636  
 Tonguetie, **636**  
     in newborn, 29  
 Tonic neck reflex, 299, 1067  
 Tonsillectomy, 758  
     complications, 758  
     in actinomycosis, 562  
     re active infection, 759  
     re age of child, 758  
     re poliomyelitis, 533  
     re season, 759  
     type of operation, 758  
 Tonsillitis, acute, 751, 757  
     chronic, 757-60  
     in tularemia, 448  
     vs. diphtheria, 416  
 Tonsils, and adenoids, **757-61**  
     carcinoma, 1348  
     chronically infected, 757  
     hypertrophic, 757-60  
     in scarlet fever, 408  
     neoplasm, 757  
     school period (6-12 years), 36  
     tuberculosis, 466  
 Tooth. See *Teeth*.  
 Torticollis, **1264**  
     acquired, 1264  
     congenital, 1264  
     in newborn, 320  
 Torulosis, 564  
 Toxin, diphtheria, 412  
*Toxocara canis*, 578  
*Toxocara cati*, 578  
 Toxocariasis, 574, **578**  
 Toxoid, diphtheria, 139-40, 141  
     sensitivity test, 140  
     tetanus, 139-40, 141  
     triple, 139  
*Toxoplasma gondii*, 615  
 Toxoplasmosis, **615-18**  
     acquired, 616  
     congenital, 616  
     diagnosis, 617  
     re congenital anomalies, 244  
     re dwarfism, 1153  
     tests, 390, 617  
     vs. cryptococcosis, 564  
     vs. cytomegalic inclusion disease, 525  
 Trachea, diverticulum, 781  
     esophageal fistula, 640-42  
     foreign body, 773, 774  
     malformations, **781**  
 Tracheobronchitis, acute, 785-6  
 Tracheo-esophageal fistula, 640-42  
     without atresia, 641  
 Tracheotomy, 780  
     for poliomyelitis, 544  
     in hypoplasia of mandible, 631-2  
     in laryngeal diphtheria, 419  
     re laryngeal stenosis, 772  
 Trachoma, 1339  
     tests, 394  
 Training re development, 70  
 Tranquilizers, 206  
     in behavior problems, 1144  
 Transaminase, in hepatitis, 705  
     serum, 702  
     level, 697  
 Transfusion. See under *Blood*.  
 Transitory fever of newborn, 342  
 Transplacental hemorrhage, 335  
 Transposition, of aorta, and over-riding pulmonary artery, 852  
     of great vessels (arteries), 833-5, **851-2**  
         with pulmonary stenosis, 852  
         with single ventricle, 852  
         with tricuspid atresia, 852  
     of tricuspid valve, 852  
 Trauma, birth, re neurologic disease, 1077, 1078  
     effect on growth and development, 42  
     vs. poliomyelitis, 539  
 Traumatic herpes, 491  
 Travel, immunization for, 142  
 Treacher-Collins syndrome, 632  
 Trematodes, infections, **593-8**  
 Tremors, 1065  
     hysterical, 1068  
     in cerebral palsy, 1138  
 Trendelenburg's sign, 1255  
*Treponema pallidum*, 472  
 Triamcinolone, 1181  
     dose, 226  
 Tribromoethanol solution, dose, 211  
     in tetanus, 434  
 Trichiasis of eyelids, 1337  
*Trichinella spiralis*, 587  
 Trichinosis, **587**  
     epidemiology, 574, 587  
     re aseptic meningitis, 546  
     skin test, 587  
 Trichloroethane poisoning, 1389  
 Trichobezoar, 664  
 Trichocephaliasis, **581-3**  
     epidemiology, 574, 581  
     treatment, 582  
 Tricho-epithelioma, 1362  
 Trichomonas vaginitis, 1060  
 Trichuriasis, **581-3**  
     epidemiology, 574, 581  
 Tricuspid atresia, 833-5, 848  
     with transposition of great vessels, 852  
 Tricuspid valve, disease, 892  
     transposition, 852  
 Tridione. See *Trimethadione*.  
 Triethylene melamine, dose, 226  
     in leukemia, 969  
     in lymphosarcoma, 994  
 Triglycerides, 102  
 Triiodothyronine, 1164, 1168  
 Trilogy of Fallot, 870  
 Trimethadione, in epilepsy, 1124  
     re nephrosis, 1044  
 Trimethaphan camphorsulfonate, dose, 226  
 Tri-ortho-cresyl-phosphate poisoning, 1387  
 Tripelennamine hydrochloride, dose, 224  
 Triplets, 304-306  
 Tripod sign in poliomyelitis, 537, 538  
 Trismus, 433  
 Tropia. See *Strabismus*.  
 Tropical eosinophilia, 602  
 Troussseau's sign, 1111  
 Truncus arteriosus, **853**  
 Truss for hernia, 691  
 Trypsin, 718, 719  
     in stool, 719  
     x-ray film test for, 728  
 Tryptophane, in deficiency of vitamin B<sub>6</sub>, 265  
     metabolism, defects of, 265-7  
         disturbed, in anemia, 934  
         in Hartnup disease, 267  
         in mental deficiency, 265-6  
     requirements, 101  
 Tsutsugamushi fever, 553, **557**  
     general considerations, 553-5  
 Tubercle bacilli in milk, 122  
 Tuberculides, **1290**  
 Tuberculin test, 461-2  
     patch test, 462  
     P.P.D., 461 2  
 Tuberculoma, 468  
 Tuberculosis, **449-71**  
     abdominal, 467, 468  
     age factors in, 451  
     allergy re immunity, 451  
     atelectasis in, 456, 457  
     bacteriologic examination for, 462  
     BCG vaccine, 463  
     bronchial lesions, 456-7  
     caseous bronchopneumonia, 457  
     chemoprophylaxis, 464  
     chorioretinitis in, 1342  
     death rates, 3  
     emphysema in, 456  
     epidemiology, 449  
     erythema nodosum in, 1300  
     etiology, 449  
     extrathoracic, **466-70**  
         classification, 466  
         heredity in, 450  
         history in, 460  
         identification of contacts, 463  
     immunity, artificial, 463  
     in adolescence, 152, 153

- Tuberculosis, in pertussis, 422  
 intestinal, 468  
 intra-abdominal, **467**  
 intrathoracic, classification, **453**  
   clinical forms, **453-9**  
 kidney, 1052  
 meningeal, **469-70**  
 miliary, 457  
 mortality rates, 449-50  
 of bones, 1261-3  
 of cervical lymph nodes, **466**  
   vs. cat-scratch fever, 523  
 of female genitalia, 1062  
 of hilar lymph nodes, 454-7  
 of hip, 1262  
 of male genitalia, **1059**  
 of nervous system, **468-70**  
 of peritoneum, 468  
 of skin, **1289-90**  
 of spine, **1262**  
 of superficial lymph nodes, 467  
 of tonsils, **466**  
 pathogenesis, 451  
 pathology, 451  
 pleuritis in, 459  
 prevention, 463  
 primary, of skin, 1289  
 pulmonary, apical, 458  
   diagnosis, 459  
   evaluation of clinical activity, 462  
   focus, 453, 454  
   hematogenous lesions, 457  
   physical examination, 460  
   prognosis, 463  
   progressive primary lesion, 454  
   roentgenographic examination, 460  
   surgical procedures, 466  
   treatment, 464-6  
     general factors, 466  
     schema for, 465  
 racial factors in, 451  
 "reinfection," 458  
 sex factors in, 451  
 tests, 387, 389  
 vs. actinomycosis, 562  
 vs. coccidioidomycosis, 571, 572  
 vs. histoplasmosis, 567  
 vs. nocardiosis, 566  
 vs. sarcoidosis, 1346  
 vs. sporotrichosis, 567  
 Tuberculous enteritis, 468  
 Tuberculous meningitis, **469-70**  
 Tuberculous pericarditis, 901  
 Tuberculous peritonitis, 468  
 Tuberous sclerosis, 1079  
   adenoma sebaceum in, 1280  
   kidneys in, 1355  
   mental deficiency in, 1131  
 Tularemia, **447-9**  
   skin test, 448  
   vs. sporotrichosis, 567  
 Tumors, **1347-70**  
   adrenal, 1355-6  
   bladder, 1357  
   bone, 1365-9  
   brain, 1084-7  
   eye, 1341  
   gastrointestinal, 1351  
   granulosa cell, of ovary, 1201  
   heart, 1350  
   infratentorial, 1085  
   kidney, 1353-5  
   larynx, 773  
   Tumors, liver, 1352  
     lung, 1350  
     lymph nodes, 992-6  
     mesentery, 689  
     neck, 639  
     ovary, 1358  
     pancreas, 1353  
     parathyroid, 1177  
     peritoneum, 689  
     pituitary, 1151  
     posterior third ventricle, 1086  
     prostate, 1357  
     re megacolon, 674  
     rectum, 684-5  
     retroperitoneum, 1356  
     sacrococcygeal, 685  
     sigmoid, 684-5  
     skin, 1358-62  
     soft tissues, 1362-5  
     spinal cord, 1106  
     stomach, 663  
     supratentorial, 1086  
     testis, 1197, 1357  
       with gynecomastia, 1198  
     tonsils, 757  
     turban, 1362  
     umbilicus, 341  
     uterus, 1358  
     vagina, 1358  
 Turban tumor, 1362  
 Turbidity tests in thyroiditis, 1171  
 Turner's syndrome, 1196, 1198-1200, 1233  
 Turpentine poisoning, 1385  
 Turriccephaly, 1227  
 Tutocaine poisoning, 1386  
 Twins, 304-306  
   conjoined, 306  
   cross-bleeding in utero, 335, 943  
 Tylenol. See *Acetaminophen*.  
 Tympanic membrane, **763**  
   perforation, 763  
 Typhoid bacilli in milk, 122  
 Typhoid fever, **437-42**  
   carrier, 439, 441  
   complications, 440  
   diagnosis, 440  
   epidemiology, 438  
   etiology, 438  
   immunity, 439  
   immunization, 142  
   in children, 439  
   in infants, 440  
   myocarditis in, 893  
   pathogenesis, 439  
   pathology, 439  
   prevention, 441  
   test, 388, 390  
   treatment, 441  
   vs. bacillary dysentery, 436  
 Typhus, epidemic, 553, **555-6**  
   immunization, 142  
   murine, 553, **556**  
   scrub, 553, **557**  
 Typhus fever, 553, **555-6**  
 Typhus infections, general considerations, 553-5  
   tests, 392  
   transmission, 600  
 Tyrosine, and ascorbic acid, in premature, 311  
   in thyroid function, 1163  
   metabolism, defective, 258-61  
 Tyrosinosis, 260  
 Tyrosinuria, 697  
 Ulcerative colitis, 679  
 Ulcerative stomatitis, 491-2  
 Ulcers. See also under specific organs and regions.  
   Curling's, 671  
   duodenal, 671  
   gastric, 671  
   peptic, 671  
   Rokitansky-Cushing, 671  
 Umbilical cord, 30, 340  
   care, 303  
 Umbilicus, **340-42**  
   anomalies, 340  
   diphtheria, 415  
   granuloma, 341  
   hemorrhage from, 341  
   hernia, 341  
   infection, 341  
   lesions, re omphalomesenteric duct, 671  
   polyp, 341  
   tumors, 341  
   types, 340  
 Unconscious patient, examination, **1069**  
 Underfeeding in infant, 130  
 Undernutrition, **352-80**  
 Undulant fever. See *Brucellosis*.  
 Unverricht's myoclonus epilepsy, 1102  
 Upper respiratory tract infections, chronic, **756**  
 Urachal cyst, 340, **1025**  
 Urachus, patent, **1025**  
   persistent, 340  
 Urea, clearance test, 1013  
   formation, 696  
   in urine, 1011  
   nitrogen, blood, 1404  
 Urecholine. See *Bethanechol chloride*.  
 Uremia, 1050-51  
   in acute glomerulonephritis, 1041  
   in nephritis, chronic, 1049, 1050  
   pericarditis in, 901  
 Ureter, diverticulum of, 1027  
 Ureterocele, 1027  
 Ureterovesical obstruction, 1027, 1028  
 Urethane in leukemia, 969  
 Urethra, atresia, 1057  
   calculus in, 1058  
   diverticulum, 1057  
   double, 1057  
   fistula, 1057  
   foreign body in, **1058**  
   malformations, **1057-8**  
   obstruction, **1026, 1028**  
     valvelike, 1057  
   orifice, inflammation, 1058  
   valvelike, 1057  
 Urethritis, 1058  
 Uric acid, blood, 1404  
   in urine, 1020  
   infarcts, 1010  
   plasma level, elevated, 261  
   reabsorption, defective, 261  
   renal, 1007  
 Urinalysis, 146  
 Urinary gonadotropin, 1150  
 Urinary tract, infection, 1028, **1030-34**  
   in brucellosis, 446  
   in newborn, **338**  
   in typhoid fever, 440



- Urinary tract, infection, tests for, 392  
 malformations, **1022-30**  
 obstructions, **1026-30**  
   clinical manifestations, 1028  
   re hyperparathyroidism, 1179-80  
   treatment, 1029
- Urination, frequency, 1011  
 frequent, **1015**  
 in newborn, 30, 1011
- Urine, abnormalities, **1018-22**  
 abnormally colored, 1021  
 acidification, defective, 261  
 Addis count, 1012  
 ammonia in, 1013, 1021  
 bile in, 1022  
 bilirubin in, 702  
 black, 1021  
 blue, 1021  
 characteristics, 1011  
 collection, 203  
 composition, alterations in, **1018-22**  
 concentration test, 1012  
 coproporphyrin in, 697  
 creatinine in, 1014  
 culture, 1033  
 electrolyte losses in, 196  
 excretion, daily, 1011  
   disturbances of, **1014-18**  
 fat in, 1020  
 formation, **1005-10**  
 green, 1021  
 hemoglobin in, 1021  
 in acute glomerulonephritis, 1037  
 in fetus, 1010  
 incontinence, **1015-18**  
   diagnosis, 1017  
   etiology, 1016  
   treatment, 1017  
 indican in, 1020  
 ketones in, 1020  
 melanogen in, 1022  
 nonprotein nitrogen in, 1014  
 normal, **1010-12**  
 pancreatic enzymes in, 720  
 pH, 173  
 protein in, 1012, 1018  
 purple, 1021  
 red, 1021  
   causes, 280  
 retention, **1015**  
   hysterical, 1069  
   tests, 1014  
 specific gravity, 1011, 1012  
 sugar in, 1019-20  
 suppression, 1014  
   in acute glomerulonephritis, 1039, 1041-2  
 urea in, 1014  
 uric acid in, 1020  
 urobilinogen in, 702  
 yellow (bright), 1021
- Urobilin, excretion, 699  
 test, 699
- Urobilinogen, in stool, 702  
 in urine, 702  
 quantitative excretion, 695
- Urticaria, **1318**  
 papular, vs. eczema, 1314
- Urticaria papulosa, **1300**
- Urticaria pigmentosa, **1300**
- Uterus, diseases, **1062**  
 prolapse, 1062
- Uterus, tumors, **1358**
- Uvea, infections, 1339
- Uveitis, 498, 1339
- Uveoparotid fever in sarcoidosis, 1346
- Uvula, elongated, **746**
- VACCINATION. See also *Immunization*.  
 poliomyelitis, 141, 533, 534  
 rabies, 514, 515  
 smallpox, 141, **501-505**  
   encephalitis due to, 551
- Vaccine, bacterial, in asthma, 1324  
 pertussis, 139-40, 141  
 poliomyelitis, 533, 534
- Vaccinia, 504  
 tests, 393
- Vagina, foreign body in, 1060  
 hemorrhage, 1062  
 malformations, **1060**  
 tumors, 1358
- Vaginitis, 1060  
 gonorrheal, 1060  
 herpetic, 492  
 in bacillary dysentery, 436
- Valine, metabolism, defective, 267-8  
 requirements, 101
- Valley fever, **571-3**
- Valsalva, sinus of, rupture, **866**
- Van den Bergh reaction test, 698
- Varamel, 124
- Varicella. See *Chickenpox*.
- Varices, esophageal, 645
- Variola, **499-501**. See also *Smallpox*.  
 major, 499  
 minor, 500
- Varioloid, 500
- Vascular. See also *Blood vessels*.  
 hemophilia, 254, 980  
 nephritis, 1049  
 rings, 877
- Vasopressin, dose, 223
- Vegetables, in children's diet, 129  
 infant feeding, 129
- Veins, cannulation, 199-200
- Vena cava, persistent left superior, with ventricular septal defect, 859
- Venipuncture, 199, 200
- Venous blood, collection, 203
- Venous pressure, 825
- Venous pulse, 823
- Ventilation. See under *Respiration*.
- Ventricle, left, diverticulum, **856**  
 posterior third, tumor, 1086  
 single, **854**  
   with transposition of great vessels, 852
- Ventricular fibrillation, **885**
- Ventricular hypertrophy, left, electrocardiogram in, 829  
 right, 819  
   electrocardiogram in, 828  
   in tetralogy of Fallot, 842-8
- Ventricular puncture, 1071  
 re intracranial pressure, 1084
- Ventricular septal defect, 833-5, **856-9**  
 in tetralogy of Fallot, 842-8  
 multiple, 859  
 with aortic insufficiency, 858  
 with atrial septal defect, 859
- Ventricular septal defect, with coarctation of aorta, 859  
 with endocardial sclerosis, 859  
 with heart block, 859  
 with patent ductus arteriosus, 858  
 with persistent left superior vena cava, 859  
 with pulmonary stenosis, 870  
 with unusual shunts, 858
- Ventriculography, 1072
- Veratrine poisoning, 1393
- Vernal catarrh, 1338
- Vernix caseosa, 29
- Verrucae, **1296**
- Verrucosa cutis, tuberculous, **1289**
- Vertebrae, anomalies, **1233**  
 in gargoylism, 1239
- Vertigo in neurologic disease, 1073
- Vesical calculus, 1055
- Vesical obstruction, 1026, 1028
- Vincent's stomatitis, 491-2
- Viokase. See *Pancreatin*.
- Viral infections, etiologic diagnosis, **384-97**  
 myocarditis in, 893  
 of skin, **1296-7**
- Virus, adenovirus, 746  
 hemadsorption, 747  
 JH, 746, 747  
 "JV-1," 746, 747  
 myxovirus, 747  
 of upper respiratory tract infections, **746-8**  
 tests, 387-94  
 "2060," 746, 747
- Virus pneumonia, **794-8**
- Visceral larval migrans, 574, **578**  
 vs. tropical eosinophilia, 602
- Vision, 65  
 defects, in hysteria, 1068  
   re torticollis, 1265  
 development, 65  
 disturbances, in pertussis, 422  
 examination, in neurologic disease, 1064  
 field of, 1064  
   test, 1330  
 infant, 32  
 loss, in neurologic disease, 1073  
 mirror, 1330  
 school period (6-12 years), 36  
 sight-saving classes, 1343  
 tests, 146, 1330
- Visual features, re intracranial pressure, 1083
- Vital capacity, in respiratory difficulties, 736  
 use in cardiac disease, 838  
 values, 734
- Vitamin A, deficiency, **360-63**  
 effects of, 108  
   in fibrosis of pancreas, 727  
 doses, 362  
 excess, effects of, 108, 363  
 function, 108, 360, 361  
 in celiac disease, 725  
 in hypothyroidism, 1164  
 in infant feeding, 128  
 in keratosis pilaris, 1287  
 in malnutrition in infants, 353  
 in milk, 121  
 metabolism, 107, 109  
 poisoning from, 363  
 re teeth, 623

- Vitamin A, requirements, 107, 108, 111  
sources, 107, 108  
tolerance test, 720
- Vitamin B complex, 109  
deficiency, **363**  
in malnutrition in infants, 353  
re teeth, 623  
requirements, 109-10
- Vitamin B<sub>1</sub>. See *Thiamine*.
- Vitamin B<sub>12</sub>. See *Cyanocobalamin*.
- Vitamin C. See *Ascorbic acid*.
- Vitamin D, deficiency, effects of, 109  
tetany in, **378**, 1111  
excess, effects of, 109  
function, 109  
idiosyncrasy, 1225  
in adolescence, 154  
in celiac disease, 725  
in diet of children, 134  
in hypoparathyroidism, 1176  
in infant feeding, 128  
in lead poisoning, 1377  
in malnutrition in infants, 353  
in milk, 121, 123  
in premature, 310, 311  
in vitamin D-refractory rickets, 1221  
metabolism, 110  
re teeth, 623  
requirements, 107, 109, 110, 111  
sources, 109, 110
- Vitamin D-refractory rickets. See *under Rickets*.
- Vitamin D-resistant rickets, 261
- Vitamin E in nutrition, 111
- Vitamin K, anemia due to, 336  
deficiency, **379**  
effects of, 109  
excess, effects of, 109  
for newborn, 303  
function, 109  
metabolism, 110  
re hemolytic anemia, 953  
re hyperbilirubinemia, 334  
requirements, 109  
sources, 109, 110, 379
- Vitamin P in nutrition, 111
- Vitamins, in celiac disease, 725  
in infant feeding, 128  
in milk, 121  
requirements, **107-11**
- Vitiligo, **1277**
- Vocal nodules, 773
- Voice, changes, 39
- Volvulus of the midgut, 665
- Vomiting, **647-50**  
alkalosis in, 179, 180  
cyclic, 649  
due to cerebral lesions, 648  
due to faulty feeding, 648  
habit, 648  
in adrenal hyperplasia, 1188  
in allergy, gastrointestinal, 1327  
in appendicitis, 677  
in hyperactive infants, 660  
in intussusception, 667
- Vomiting, in neurologic disease, 1074  
in newborn, 315, **330**, 648  
in pyloric stenosis, 659  
in pylorospasm, 660  
nervous, 648  
re infant feeding, 130  
recurrent, 649  
re epilepsy, 649  
toxic, 648  
with rumination, 649
- Vomiting sickness of Jamaica, 711
- Von Economo's disease, 550  
pathology, 548
- Von Gierke's disease, 268-70  
cerebral, 1095  
vs. Werdnig-Hoffmann disease, 1100
- Von Hippel-Lindau's disease, 1080
- Von Hippel's disease, 1359
- Von Recklinghausen's disease, 1079
- Von Willebrand's syndrome, 980
- Vulva, abscess, **1061**  
diphtheria, 415  
malformations, **1060**
- Vulvitis, gangrenous, **1061**
- Vulvovaginitis, **1060**  
herpetic, 492
- WALL-eye. See *Strabismus*.
- War edema, 356
- Warfarin poisoning, 1394
- Warts, 1296
- Wasp sting, 599
- Wassermann test, 478  
falsely positive, 520
- Water, balance, in newborn, 291  
blood content, 1403  
deficit, 175, 185, 187  
in milk, 120, 121, 126  
in milk formulas, 126, 127  
in nutrition, **97**, 99  
losses, abnormal, 195-6  
urinary, 196  
per calories metabolized, 193  
renal reabsorption, defective, 261  
requirements, 97, 99, 100, 193
- Waterhouse-Friderichsen syndrome, 427, 428, **1183-5**  
re unexpected death, 350
- Weaning, 119
- Weber-Christian syndrome, 1279
- Weight, adolescence, 37  
and length, table, 50-51  
annual increments, 14  
birth, 19, 28  
birth to 5 years, **50-51**  
distribution, 11-year-old boys, 20  
5-18 years, **52-5**  
infants, 13, 30, **50-51**  
graph, 45  
prenatal, 13  
preschool period (2-6 years), 33  
school period (6-12 years), 36  
2-13 years, graph, 46
- Weil's disease. See *Leptospirosis*.
- Wenckebach phenomenon, 886
- Werdnig-Hoffmann syndrome, 1085  
inheritance, 239  
vs. glycogen disease, 272
- Whitfield's ointment, 1301
- Whooping cough. See *Pertussis*.
- Widal test, 438, 440
- Wilms' tumor, **1353-4**
- Wilson's disease, 257, 1098
- Witch's milk, 30
- Wolff-Parkinson-White syndrome, 885
- Wolfsbane poisoning, 1390
- Wormseed oil, poisoning, 1386
- Wryneck, 1264
- X CHROMOSOME, 240
- Xanthine, defective reabsorption, 261
- Xanthoma, in diabetes mellitus, 127  
in hyperlipemia, 278  
in nephrosis, 1046  
of skin, **1001-1002**  
with elevated serum cholesterol, 1002  
with normal serum cholesterol, 1001
- Xanthoma disseminatum, 1001
- Xanthomatosis, **1001-1002**
- Xanthuria, simple, 261
- Xeroderma pigmentosum, **1276**
- Xerophthalmia, 361
- Xerostomia, 637
- X-ray injury, **1371-3**  
prevention, 1372
- Xyluluria, 277
- Y CHROMOSOME, 240
- Yellow atrophy of liver, 712
- Yellow fever, **515-17**  
immunization, 142  
transmission, 600
- Young's rule, 208
- ZEPHIRAN. See *Benzalkonium chloride*.
- Zinc, deficiency, effects of, 105  
excess, effects of, 105  
function, 105  
requirements, 105, 107  
sources, 105
- Zinc oxide, ophthalmic, 1331
- Zinc salt, poisoning, 1383
- Zinc stearate pneumonitis, 799
- Zinc stearate powder, poisoning, 1383
- Zinc sulfate in conjunctivitis, 1331
- Zoeller test, 140
- Zoster ophthalmicus, 498
- Zygodactyly, 1231
- Zygomatic process, infection, 766
- Zygote, abnormalities, 234











S.S. 97

Acc. No. 4814

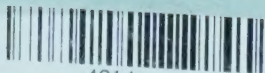
Call No. L-9C; 4 N60

CHECKED  
2008

Please return this publication on or before the last DUE  
DATE stamped below to avoid incurring overdue charges.

**To be issued from :**

<i>Due Date</i>	<i>Return Date</i>	<i>Due Date</i>	<i>Return Date</i>
03 06	01-03-06		



4814  
Textbook of pedi.



